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Original Research Article

Postoperative Analgesic Requirements in Patients Receiving Intraoperative Dexmedetomidine Infusion

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ABSTRACT

Background: Newer alpha-2 agonist dexmedetomidine is implied with analgesic, sedative, central sympatholytic and anesthetic actions. We conducted a case-control study to analyze the efficacy of intraoperatively administered dexmedetomidine on its postoperative analgesic and opioid sparing effects.
Methods: A sample of 109 adult patients undergoing elective mastectomy were divided into cases and controls. The intervention group received intraoperative dexmedetomidine infusion at standard dosage. Postoperative analgesic efficacy of dexmedetomidine was monitored with respect to mean Visual Analogue Scale (VAS) score, time to first dose of tramadol and mean dose of tramadol received.
Results: Time to first dose of tramadol was significantly more (9.40 +/- 2.81 vs 5.48 +/- 1.10 hours, $p<0.001$) and mean number of doses of tramadol less in cases group 1.63 +/- 0.64 vs 3.60 +/- 0.49, $p<0.001$).
Conclusion: Intraoperatively administered dexmedetomidine offers significant opioid sparing effect and reduced pain scores with fluctuation in pulse rate and blood pressure, however within physiological limits.

Key Words: Dexmedetomidine, anesthesia, analgesia
Key Message: Intraoperatively administered dexmedetomidine offers significant analgesic and opioid sparing effects into the 24 hour postoperative period.

INTRODUCTION

Pain is a common complaint among individuals following most surgical interventions. Prevention and treatment of postoperative pain is a major challenge in the postoperative care. Postoperative pain plays an important role in the early mobilization and well-being of surgical patients. Failure to relieve pain is morally and ethically unacceptable. Adequate pain relief is a basic human right. Poorly managed acute pain that might occur following surgery can produce pathophysiologic processes in both the peripheral and the central nervous systems (CNS) that have detrimental acute and chronic effects. The attenuation of perioperative pathophysiology that occurs during surgery through reduction of nociceptive inputs to the CNS and optimization of perioperative analgesia may decrease complications and facilitate

recovery during the immediate postoperative period.

Initially, the pathophysiology and treatment of postoperative pain and neuropathic pain have been considered separate and distinct. Opioids, NSAIDs and local anesthetics were used for acute pain, and anticonvulsants and tricyclic antidepressants for chronic pain. Cardinal features of neuropathic pain, like allodynia and hyperalgesia, are also present after trauma and surgery. [1,2] Postoperative pain responses are comprised of nociceptive/ inflammatory and neuropathic/ neurogenic components. Conventional analgesics, such as opioids and NSAIDs, often fail to treat the later components. However, it has been demonstrated that α2 receptor agonists are able to manage the neuropathic/ neurogenic components successfully. [3]

Pre-emptive analgesia is defined as an antinociceptive treatment that prevents the establishment of altered central processing of afferent inputs, which amplifies postoperative pain. It is a treatment that is initiated before, and is operational during the surgical procedure. It results in reduced pain intensity and lower analgesic requirement, even after the analgesic effects of preemptive agent is worn-off. [4]

Dexmedetomidine is a potent and highly selective α_2 receptor agonist with sympatholytic, sedative, amnestic and analgesic properties. It is the most recently developed and commercialized agent in this pharmacological class. It provides 'conscious sedation' analgesia without respiratory depression. It has an opioid sparing effect. The Food and Drug Administration approved dexmedetomidine in the United States in 1999 for use in humans for short term sedation/analgesia in the intensive care unit (ICU).

This study investigates the postoperative analgesic action and opioid sparing effect of dexmedetomidine administered intraoperatively at a loading dose of 1μ/kg over 10 minutes followed by 0.2μ/kg/hr infusion, in patients undergoing mastectomy

MATERIALS AND METHODS

This study was conducted after obtaining approval of Institutional Ethics Committee and written patient consent. The study design was observational conducted over a period of 12 months. Inclusion criteria was American Society of Anaesthesiologists (ASA) class I and II patients, aged between 25 -60 years undergoing elective mastectomy. Patients with known hypersensitivity to dexmedetomidine**,** heart block/dysrrhythmia, difficulty in comprehending visual analogue scale, chronic liver disease, chronic kidney disease, pregnancy, drug therapy with sympathomimetics, sympatholytic or anticholinergic drugs, chronic analgesic users (more than 1 month) and anticipated duration of surgery more than 3hrs were excluded.

Sample size was calculated using method in similar pilot study. [5] With a β error 5%, attributing power of 95%, the calculated sample size was 50 each in either group. After preanesthetic check up, 109 patients to undergo elective mastectomy was allocated into two groups, A and B. Even number was taken as cases and odd number was taken as controls (57-cases and 52 - controls). These patients were to receive either a loading dose of dexmedetomidine 1μg/kg over 10 minutes, followed by a continuous infusion at a rate of 0.2μg/kg/h or same volume of 0.9% saline infusion intravenously. The patients were educated about VAS pain score and briefed about the study design. After overnight fasting, all patients were premedicated with midazolam 0.02mg/kg, metoclopramide 10mg and morphine 0.1mg/kg on the morning of

surgery. They were monitored with ASA standard monitors intraoperatively. Both groups were induced with intravenous thiopentone sodium 5mg/kg, lignocaine 1.5mg/kg and intubated under neuromuscular blockade with succinylcholine 1.5mg/kg. Anesthesia was maintained with isoflurane, N2O, O2 and top up doses of vecuronium. After induction of anaesthesia, a resident trainee anesthesiologist, who was not one of the observers, prepared solutions containing either dexmedetomidine or 0.9% saline. Dexmedetomidine was supplied in 2ml ampoules in a concentration of 100µg/ml, which was diluted with 98ml normal saline to a final concentration of 2µg/ml. The saline solution was prepared in a similar fashion. After induction of anaesthesia Group A (cases n=57) received a loading dose of dexmedetomidine 1µg/kg over 10 minutes, followed by a continuous infusion at a rate of 0.2µg/kg/h. Group B (controls, n=52) received same volume of 0.9% saline infusion. The infusion was discontinued at the end of surgery. Heart rate less than 50/min were treated with injection atropine 0.6mg intravenously. Blood pressure below 20% of the base line value was managed by reducing the inspired concentration of isoflurane. At the end of surgery after ensuring adequate reversal, patients were extubated and shifted to recovery room. During their stay in the recovery room and in the post operative ward, heart rate, blood pressure, respiratory rate, saturation, pain score and sedation score were assessed at intervals of 15min, 30 min, 45 min, 1, 2, 3, 6, 12, 24 hour period. Hypoxia, SpO_2 less than 94% was corrected with supplementary oxygen postoperatively. When the VAS score was more than 3, the patients were given rescue doses of injection tramadol 50mg intravenously. The time for the first dose of tramadol and total dose of tramadol required over 24 hr periods was recorded.

OBSERVATIONS AND RESULTS

The observations made were entered in microsoft excel spreadsheet and analysed using Statistical Program for Social Sciences (SPSS) software version 18. The data were expressed in its frequency, percentage, mean and standard deviation. To find the associations and comparisons between different parameters, nonparametric test, Chi square (X^2) test was used. Student's t test was used to compare mean values between two groups for parametric data whereas Mann Whitney U test was employed to compare nonparametric data between two groups. For all statistical evaluations, a two-tailed probability of value, < 0.05 was considered significant.

Mean age (in years) of cases (n=57) were 47.39 (SD=7.01) and of controls (n=52) were 49.44 (SD=7.79). Mean weight (in kgs) of cases were 55.81 (SD=4.62) and of controls were 54.19 (SD=3.64). Mean duration of surgery (in hours) of cases were 1.87 (SD= 0.36) and that of controls were 1.82 (SD=0.368). There was no significant difference in comparability between either groups with regard to age, weight and duration of surgery [t= -1.45, p= 0.15; t =2.03, p= 0.05; and t= 0.63, p= 0.52 respectively]. Among cases (n=57) 26 patients (45.61%) belonged to ASA class I and 31 (54.38%) belonged to ASA class II. In control group (n=52); 25 patients (48.07%) belonged to ASA class I and 27 (51.92%) belonged to ASA class II [X^2=0.016; p=0.89].

Number of doses of analgesic tramadol administered in cases (1.63 +/- 0.64) was significantly lower than that among controls (3.6 +/- 0.49). Time of first analgesic administration was found to be significantly delayed by 3.9 hours in the intervention group compared to control group (t=9.68, p<0.001) **[Table 1]**

Table 1- Comparison of number of doses of tramadol and time to first dose of tramadol in cases and controls

Number of doses of tramadol administered				
Groups	***Mean***	***SD***	***T***	***p***
Cases (n=57)	1.63	0.64	-17.92	<0.001
Controls (n=52)	3.60	0.49		
Time to first dose of tramadol (in hours)				
Groups	***Mean***	***SD***	***T***	***p***
Cases (n=57)	9.40	2.81	9.68	<0.001
Controls (n=52)	5.48	1.16		

The mean intraoperative and postoperative pulse rates were significantly lower among cases compared to controls (p<0.001). The mean systolic blood pressures was significantly lower among cases at 45, 60, 75 and 90 min intra operatively and mean diastolic blood pressure was also found to be reduced in cases significantly at 30, 45, 60 and 90 min compared to controls. The mean systolic blood pressure was significantly lower in cases at 0, 15, 30 min and 3rd, 6th and 12th hour. The mean diastolic blood pressure was also reduced significantly in cases at 0, 15, 30 min and 1st, 2nd, 3rd, 6th, 12th and 24 hrs compared to control group postoperatively. The mean respiratory rates were significantly lower in intervention group compared to control group at post operative time intervals of zero, 15, 30, 45 minutes and 2nd and 3rd hour. The SpO_2 measurement showed significant difference in mean SpO_2 values in 0, 15, 45 min, 1 and 24 hrs with a p value of < 0.05.

The mean postoperative sedation score among cases (1.10±0.135) was found to be significantly higher compared to controls (0.87±0.148) [t value=8.60, mean difference=0.234, p<0.001] **(Figure 1).** The mean VAS score was found to be significantly lower among cases (0.6 ± 0.21) compared to mean score among control group (1.21±0.31) (**Figure 2).**

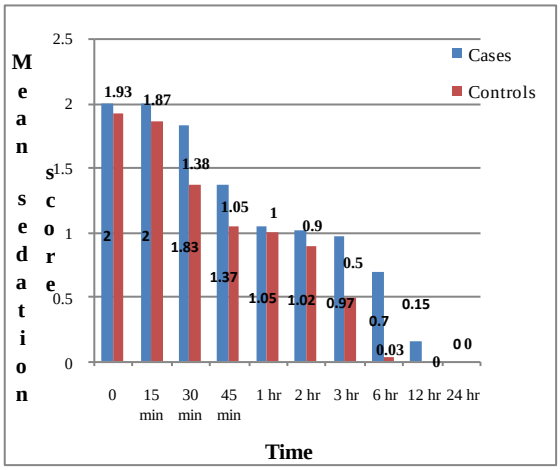

Figure 1. Comparison of mean postoperative sedation score

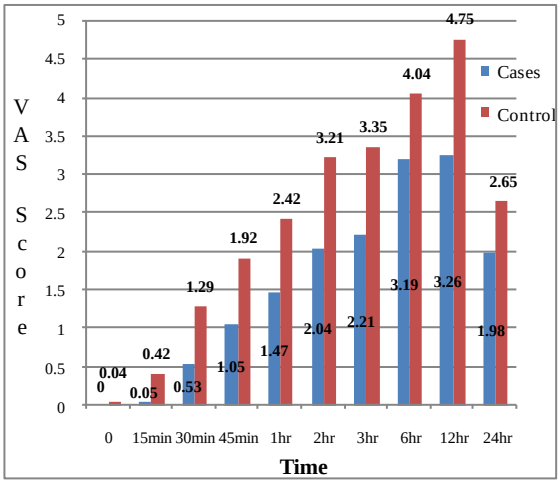

Figure 2. Comparison of mean postoperative VAS score

(The percentage of patients in the study group with pain (VAS) score >3 at 2 hr, 3hr, 6hr, 12hr and 24 hr were found to be significantly lower compared to control group.)

DISCUSSION

Prevention and treatment of perioperative pain is a major challenge in postoperative care. Postoperative pain management plays an important role in the early mobilization and well being of surgical patients. Poor postoperative pain control results in patient dissatisfaction with the surgical experience, and has adverse psychological consequences. It also

contributes to pathophysiologic processes, in both the peripheral and central nervous systems, which have the potential to produce chronicity [6] and increase the incidence of persistent postoperative pain conditions. Opioid analgesics, with their well known side effects, represent a cornerstone in postoperative pain control. Testing new analgesics as well as combination of analgesics in order to reduce the need for opioids is a key area in acute pain research. The Joint Commission on Accreditation of Healthcare Organizations has declared that "pain is the fifth vital sign".

Surgery produces biphasic insult on the human body. Tissue trauma during surgery and inflammatory process in the post surgical period produce noxious stimuli. Together they sensitize pain pathway. This occur both at the peripheral and central level. It is well documented that inadequate pain relief is deleterious, and can lead to a number of complications in the post operative period. Therefore the pain of surgery must be relieved totally. Despite awareness regarding the beneficial effects of pain relief in the postoperative period, many patients do not receive adequate analgesia. Transduction, transmission, perception and modulation are classically described in the processing of nociception. Multimodal analgesic technique, an approach for balanced analgesia aims reduction in postoperative pain by targeting one or more of these pathways of nociception, thereby reducing the side effects of either. Better management of pain in the PACU setting will likely improve patient satisfaction and facilitate shorter PACU stays.

Dexmedetomidine has eight times more affinity than clonidine for adrenoceptors (α_2: α_1 ratio 1600: 1). Activation of presynaptic α_2 receptors in sympathetic nerve endings inhibits release of noradrenaline. Stimulation of postsynaptic receptors by α_2 agonists in the CNS leads to inhibition of sympathetic activity, decreases in blood pressure and heart rate, and sedation, while binding of agonists to α_2 adrenoceptors in the spinal cord produces analgesia. Peripheral α_2 receptors in blood vessels mediate vascular smooth muscle contraction. Rapid injection of potent α_2 agonist can result in transient hypertension. It is rapidly and extensively distributed to tissues with a distribution half-life of 5 min and elimination half-life of 2–3 hrs. Dexmedetomidine provides analgesia by acting on α_2 receptors within the locus caeruleus and spinal cord. [7] A2 agonists have analgesic effect when injected intrathecally or epidurally. [8] When dexmedetomidine is injected into the epidural space, it rapidly diffuses into the CSF. The effects on blood pressure are seen in 5 to 20 minutes. The primary site of analgesic action is spinal cord. [9]

Either group in our study was comparable with regard to age, weight, ASA class and mean duration of surgery. Number of doses of analgesic tramadol administered postoperatively in cases (1.63 +/- 0.64) was significantly lower than that among controls (3.6 +/- 0.49). The mean VAS score was found to be significantly lower among cases (0.6 ± 0.21) compared to mean score among control group (1.21±0.31) **(Figure 2).** Time of first analgesic administration was also significantly delayed by 3.9 hours in the intervention group compared to control group ($t=9.68$, $p<0.001$). Statistically significant hemodynamic variations were produced by dexmedetomidine in the intervention group. However, all these were within the physiological milieu and did not require any specific therapeutic intervention. The mean postoperative sedation score among cases (1.10±0.135) was found to be significantly higher compared to controls (0.87±0.148) [t value=8.60, mean difference=0.234, $p<0.001$] **(Figure 1).**

The results of our study indicate that intravenously administered dexmedetomidine intraoperatively provides lasting postoperative analgesia. Mastectomy was chosen as surgical procedure for the ease of standardization. Our study consolidates the findings of previous similar studies, pertaining to reduced postoperative pain and opioid sparing effects of dexmedetomidine; yet stand unique from other studies as the opioid we studied was tramadol. Tramadol is the preferred opioid for postoperative use in our setting where PACUs are managed by nursing staff instead of qualified anesthesiologist, considering the present exigencies of work in this field. Analgesic action and side effects of tramadol vary considerably from morphine and fentanyl used in previous studies.

Aho MS *et al* [10] conducted a double-blind randomized controlled study on 96 women undergoing laparoscopic tubal ligation using intravenous dexmedetomidine either 0.2 or 0.4 µg/kg, 60 µg/kg oxycodone, or 250 µg/kg diclofenac for postoperative pain. They found that only 33% of the patients receiving either oxycodone or the higher dose of dexmedetomidine required analgesic supplementation with morphine. The study concluded that after laparoscopic tubal ligation, intravenous dexmedetomidine relieves pain and reduces opioid drug requirement.

Burcu *et al* [11] did a prospective randomized double-blind and placebo-controlled dose ranging study to evaluate the effect of dexmedetomidine on recovery after laparoscopic bariatric surgery in 80 ASA II-III morbidly obese patients. They used dexmedetomidine infusions of 0.2, 0.4, 0.8µg/kg/hour. They found that the length of PACU stay was significantly reduced in the dexmedetomidine groups (81 ± 31 verses 104 ± 33 minutes; $p<0.05$). The dose of rescue fentanyl required in the PACU was less in the dexmedetomidine group versus control group. The percentage of patients requiring antiemetic therapy was also reduced in the dexmedetomidine group. Authors concluded that intraoperative infusion of dexmedetomidine (0.2-0.8 µg/kg/hr) decreases fentanyl use, antiemetic therapy and length of stay in PACU.

Gurbet A *et al* [12] conducted a prospective randomized double-blind placebo controlled study in 50 women undergoing total abdominal hysterectomy using dexmedetomidine 1 µg/kg/hr as loading dose during induction of anaesthesia followed by continuous infusion at 0.5 µg/kg/hr. They found that dexmedetomidine group consumed less morphine in the PACU and in the ward ($p<0.05$). Authors concluded that continuous intravenous infusion of dexmedetomidine during abdominal surgery provide postoperative analgesia and reduces morphine requirements without increasing adverse effects.

Unlugenc H *et al* [13] studied the effect of pre-anaesthetic administration of 1 µg/kg dexmedetomidine as single intravenous dose on postoperative pain scores and morphine consumption in 60 patients undergoing abdominal surgery and found that cumulative morphine consumption was lower in dexmedetomidine group at 6, 12 and 24 hrs ($p<0.05$). They concluded that a single intravenous dose of dexmedetomidine 1 µg/kg given 10 minutes before induction of anaesthesia reduced postoperative morphine consumption without affecting postoperative recovery time.

Further modification in the method of administration of dexmedetomidine was contemplated by Abdelmageed WM *et al.* [14] The authors studued the effect of dexmedetomidine 1 µg/kg intravenously 30 minutes before the anticipated end of surgery in obstructive sleep apnea syndrome patients undergoing uvulopalatopharyngo-

plasty and found that dexmedetomidine group required 52.7% less morphine during the first 24 hours postoperatively. Time to first analgesic request was longer. This study provides valid evidence to the rational use of dexmedetomidine in a specific group of patients susceptible to opioid induced respiratory depression. Further studies consolidated this evidence. [15]

Studies conducted with dose variation using a higher maintenance dose of dexmedetomidine, in patients undergoing open gynaecological abdominal surgery, also demonstrates the opioid sparing effect with no added side effects. [16]

The hemodynamic effects of dexmedetomidine have been studied since its introduction. [17] The pharmacological effects of dexmedetomidine on cardiovascular system like bradycardia and hypotension are established. However, these effects have been used to demote the hemodynamic perturbations during endotracheal intubation in various studies attaining statistical significance. [18]

In this study intraoperative use of dexmedetomidine has significant analgesic effect among mastectomy patients as reflected by reduction of the mean number of doses of tramadol and significantly delayed first analgesic administration among the intervention group. The present study showed 44.44 % reduction in total tramadol use in postoperative period in patients receiving dexmedetomidine compared to control group. Results show intra operative dexmedetomidine infusion reduced the postoperative analgesic requirements, prolonged the time for first rescue analgesic and reduced pain scores. The hemodynamic changes in the case group were significant however, within physiological limits.

Apart from its analgesic role the present day uses of dexmedetomidine are - in intensive care unit as a short-term sedative lasting up to 24 hours, [19,20,21] as a premedicant, [22] attenuate the hemodynamic response to endotracheal intubation and postoperative extubation, [23,24,25,26,27] additive in regional anesthesia, [28,29] maintenance of anesthesia, [30,31,32,33] sedation for monitored anesthesia care, [34,35,36,37,38] and treatment of withdrawal of narcotics, benzodiazepines, alcohol, and recreational drugs. [39]

Strengths of this study are well matched cases and control group; selection of standardised surgical procedure mastectomy; and sample size matching power analysis requirements. A few limitations to mention are - apart from hemodynamic perturbations other side effects of dexmedetomidine were not analysed; moreover, variable length of mastectomy incision in each procedure may have confounded the results.

Dexmedetomidine is an invaluable addition to our practice, allowing sedation, analgesia and anxiolysis. Controlling the hemodynamic fluctuations could improve the quality of perioperative period making it less distressing for the anaesthesiologist to use it.

CONCLUSION

After analysing the results it is concluded that intra operative dexmedetomidine infusion at a loading dose of 1µg/kg over 10 minutes, followed by 0.2µg/kg/hr infusion reduces the postoperative analgesic requirement and prolongs the time for first rescue analgesic with significant yet physiological hemodynamic variation.

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