Background and Aims: The primary measure of efficacy of any analgesic regimen is pain relief, but it is important to measure dynamic pain relief rather than pain relief at rest. Epidural analgesia is an effective technique for postoperative analgesia. The drug combinations given therein (local anesthetics with adjuvants such as opioids/alpha-2 agonists), however, remain a personal choice. The aim of this study was to evaluate dynamic pain scores in patients receiving different epidural analgesia regimens for postoperative pain relief after elective gynecological surgery used in our institution.

Material and Methods: One hundred eighty-seven patients enrolled in this study received postoperatively either bupivacaine 0.125% + morphine 0.1 mg/mL (group BM) or bupivacaine 0.125% + fentanyl 2 μg/mL (group BF) or bupivacaine 0.125% + clonidine 1 μg/mL (group C1) or bupivacaine 0.125% + clonidine 2 μg/mL (group C2) by continuous epidural infusion @ 5 mL/h. Differences in dynamic pain scores (on coughing and mobilization), pain scores at rest, sensory and motor blockade, sedation scores, dry mouth, pruritus, nausea, and vomiting were recorded. Also duration of postoperative analgesia, epidural top-ups, requirement of rescue analgesic, and patient satisfaction were determined. All observations were carried out at 1, 2, 4, 8, and 12 h after surgery and then at 8 am, 12 noon, 4 pm, 8 pm on subsequent postoperative day till removal of epidural catheter (after 96 h).

Results: There was no difference in demographic or hemodynamic profile among the four groups (P > 0.05). There was no statistically significant difference in pain scores at rest among the four groups but dynamic pain scores were found to be better in group C2 as compared to group BM, BF, and C1 at most of the time intervals although not statistically significant (P > 0.05). Requirement of rescue analgesics was lower in group BM and group C2 as compared to group BF and C1 (P < 0.01). Incidence of pruritus was 43.5% in group BM and 19% in group BF, while no patients in group C1 or C2 had pruritus. Mean postoperative nausea and vomiting (PONV) scores were higher in group BM and group BF as compared to group C1 and C2 (P < 0.001). Mean sedation scores were comparable in all four groups. Incidence of dry mouth was 22% in group C2 as compared to 11% in group C1, while no patients in group BM or BF had dry mouth. Patients in group C2 were more satisfied as compared to other three groups.

Conclusions: Combination of clonidine 2 μg/mL to 0.125% bupivacaine @ 5 mL/h in combined spinal epidural provides better postoperative analgesia as compared to combination of bupivacaine with opioids with greater patient satisfaction and significantly reduced side effects.

Keywords: Bupivacaine, clonidine, combined spinal epidural, fentanyl, gynecological surgery, morphine, postoperative pain
Introduction

Patients undergoing gynecological surgery experience significant postoperative pain that may persist for several days after surgery. Despite current pain management guidelines, postoperative pain often remains under-treated.\(^1\)\(^2\) Effective postoperative pain management leads to earlier mobilization and reduction in the immediate complications: infectious, neurological, cardiovascular, and thrombo-embolic sequelae caused by immobility. This shortens hospital stay, reduces hospital costs, increases patient satisfaction, and leads to early postoperative rehabilitation.\(^3\)\(^4\) The primary measure of efficacy of any analgesic regimen is pain relief. It is important to realize that pain scores are commonly measured at rest and this results in failure to identify those techniques that allow patients to move and cough effectively, that is, techniques that provide dynamic pain relief.\(^5\) The quest is thus always on for a postoperative pain relief technique that provides effective dynamic pain relief. Epidural analgesia with continuous infusion of the analgesic drugs through the epidural catheter is widely regarded as a superior technique in providing prolonged duration of postoperative pain relief after elective gynecological surgery. The drug combinations given therein (local anesthetics with adjuvants such as opioids/alpha-2 agonists), however, remain a personal choice.

It is a known fact that the solution to the problem of inadequacy of postoperative pain management does not actually lie in the acquisition of expensive medication or development and use of new techniques, but rather in the optimal utilization of already available drugs, techniques, facilities, and establishment of formal pain management services.\(^6\) This study was planned to identify which of the many postoperative epidural drug regimens used in our institution provided the most effective dynamic pain relief.

Material and Methods

One hundred eighty-seven patients aged between 18 and 60 years, American Society of Anesthesiologists (ASA) physical status I and II, scheduled to undergo elective gynecological surgeries under combined spinal epidural (CSE) anesthesia were included in this prospective observational study after approval from the Institutional Ethical Committee. The study was registered with Clinical Trials Registry of India (CTRI/2016/04/006800) [Registered on: 05/04/2016]. Written informed consent was taken from all the patients. Patients, who refused CSE, were ASA III and IV, had any contraindication to regional anesthesia or history of drug allergy, had contraindications to any of analgesic drugs, and had history of chronic use of opioids, nonsteroidal anti-inflammatory drugs, or corticosteroids were excluded from the study. Patients who were unable to understand the study protocol or unable to communicate and patients in whom CSE was inadequate for conduct of surgery were also excluded.

After adequate fasting patients were premedicated with oral diazepam 0.1 mg/kg night before surgery. Patients were made familiar with 11 cm numerical pain rating score (NRS). On arrival to the operating room, pulse oximeter probe, electrocardiography leads, and noninvasive blood pressure cuff were attached and readings recorded. An intravenous (IV) catheter was placed and adequate preloading was done. Under all aseptic precautions, epidural space was identified and using the needle through needle technique, spinal anesthesia was induced with 2.5 to 3 mL of 0.5% hyperbaric bupivacaine, followed by insertion of epidural catheter. Level of T6 was established and confirmed with loss of sensation to pin prick before the start of surgery. Depending on the duration of surgery, if required, epidural anesthesia was administered with a bolus of 0.5% bupivacaine. Vitals were monitored continuously intraoperatively. At the end of surgery, a single epidural bolus of 5 mL of the drug to be given in infusion later was administered, followed by the start of epidural infusion (local anesthetic with adjuvants) for postoperative pain relief. Patients were initially monitored in the post anesthesia care unit and then shifted to gynecological postoperative ward. All observations and interventions were made by anesthesiology resident as per routine practice of acute pain management services.

Demographic data including patient’s age, height, weight, and type of surgery were noted. A note was made of drugs and modalities used for epidural analgesia. The various drug combinations being routinely used in the hospital for providing postoperative pain relief after elective gynecological surgeries include bupivacaine with morphine, bupivacaine with fentanyl, and bupivacaine with clonidine.

All patients were monitored postoperatively and decrease in systolic blood pressure (SBP) to <90 mm Hg or >20% below baseline was treated with IV ephedrine 6 mg as required. Bradycardia of <50 beats per minute was treated with IV atropine 0.6 mg. Degree of pain was observed using the NRS-11 score at rest, on coughing and on movement from lying down to sitting position except when the patient was sleeping or sitting comfortably; then NRS scores were taken to be ≤3. Each patient was presented with a 11-cm long line and there were numerical values starting from 0 to 10 on that scale and they were told that the left end (zero) represented no pain and the right end (ten) represented the worst pain imaginable. Rescue analgesia was administered if the patient had pain and demands analgesia, but not at a predetermined trigger value of
NRS score. If the patients complained of pain, epidural drug bolus was given according to the treating anesthesiologist’s instructions. If the patients still complained of pain even after two epidural boluses, each given after half hour interval, systemic analgesics (diclofenac sodium 75 mg intramuscularly) were administered. The total number of epidural boluses and total amount of systemic analgesics consumed postoperatively were noted. The time of first analgesic request after stopping the epidural infusion/last epidural bolus was also recorded. The time (in hours) from the removal of the epidural catheter to the time of first analgesic request in the postoperative period was recorded as the duration of postoperative analgesia. Sedation was evaluated using a four-point ordinal scale (1 = wide awake and alert, 2 = awake but drowsy, responding to verbal stimulus, 3 = arousable, responding to physical stimulus, 4 = not arousable, not responding to physical stimulus). Sensory block was assessed by pin prick in the midaxillary line. Duration of sensory block was defined as the time from epidural injection of drug (bolus of analgesic solution used subsequently) till regression of anesthesia below T12 dermatome. Lower limb motor blockade was graded according to modified Bromage scale. Duration of motor blockade was defined as the time from epidural injection of drug (bolus of analgesic solution used subsequently) till Bromage scale reached one. Postoperative nausea and vomiting (PONV) was assessed with a four-point scale (0 = none, 1 = nausea, 2 = retching/dry vomiting, and 3 = vomiting). Inj. Ondansetron 6 mg IV was given as a rescue antiemetic when the patient had PONV score ≥2. After removal of epidural catheter (after 96 h), patients were asked to score their level of satisfaction with regards to postoperative pain relief on a four-point patient satisfaction score (1 = extremely satisfied, 2 = satisfied, 3 = dissatisfied, and 4 = extremely dissatisfied). Other associated side effects such as respiratory depression (respiratory rate <8 breaths/min or SpO₂ <94%), dry mouth (on a binary scale, yes/no), pruritus (on a binary scale, yes/no), and urinary retention (on a binary scale, yes/no) were also observed. All observations were carried out at 1, 2, 4, 8, and 12 h after surgery and then at 8 am, 12 noon, 4 pm, and 8 pm on subsequent postoperative day till removal of epidural catheter (after 96 h).

**Objectives**

The primary objective was to study dynamic pain scores in patients receiving different epidural analgesia regimens for postoperative pain relief after elective gynecological surgery. The secondary objectives were to study the difference in following parameters between different epidural analgesia regimens – pain scores at rest, hemodynamic parameters, side effects of drugs used, level of sensory blockade, degree of motor blockade, total analgesia requirement postoperatively, duration of analgesia after removal of epidural catheter, and difference in patient satisfaction scores.

**Sample size**

Assuming that four epidural analgesic regimens are commonly used for postoperative pain relief in our institution, at least 30 patients in each group were required to demonstrate a clinically significant difference of >2 in NRS scores with a significance level of 0.05, a power of 90%, and sample size calculated was 120. Assuming a 30% drop out rate, 150 patients had to be taken, but finally we recruited 187 patients for the study.

**Statistical analysis**

The data were compiled, tabulated, and statistically analyzed using SPSS version 20 (IBM Corp.: Armonk, NY, United States of America). Analysis of variance was used for analysis of continuous variables, such as duration of analgesia, differences in the mean NRS scores, heart rate (HR), blood pressure (BP), and relative risk. If the F value was significant and variance was homogeneous, Bonferroni multiple comparison test was used to assess the differences between the individual groups; otherwise, Tamhane’s T2 test was used. Chi-square test was used for categorical variables, such as incidence of respiratory depression and pruritus. For analysis of variables with nonparametric distributions, such as PONV scores, level of sedation, and patient satisfaction scores, Kruskal–Wallis test was used. Results of continuous data were presented as mean ± standard deviation (SD). Probability values <0.05 were considered significant.

**Results**

A total of 187 patients were enrolled and none of the patients were excluded from the study. The following drug combinations were identified as being routinely used for providing postoperative pain relief after elective gynecological surgeries, and for purposes of analysis four groups were formed, as this was an observational study. Drugs were given epidurally as infusions through a disposable elastomeric infusion pump (Fornia®) with a preset rate @ 5 mL/h.

- 0.125% bupivacaine with 2 μg/mL fentanyl – Group BM
- 0.125% bupivacaine with 0.1 mg/mL morphine – Group BF
- 0.125% bupivacaine with 1 μg/mL clonidine – Group C1
- 0.125% bupivacaine with 2 μg/mL clonidine – Group C2.

The groups were comparable with regards to demographic data (age, height, and weight) as shown in Table 1. The types of surgeries are depicted in Figure 1. There was no statistically significant difference in the hemodynamic profile (HR, SBP, and diastolic blood pressure (DBP)) of the patients as shown in Figures 2-4 of the four groups: BF, BM, C1, and C2.
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Table 1: Demographic profile among groups BF, C1, C2, and BM

|                | Group BF (n=48) | Group C2 (n=46) | Group C1 (n=47) | Group BM (n=46) | BF vs. C2 vs. C1 vs. BM |
|----------------|-----------------|-----------------|-----------------|-----------------|-------------------------|
| Age (years)    | 40.48±12.4      | 40.37±9.88      | 41.04±9.66      | 41.85±10.57     | 0.909                   |
| Weight (kg)    | 56.56±3.44      | 56.80±4.96      | 53.66±4.49      | 56.70±4.69      | 0.994                   |
| Height (cm)    | 155.94±3.78     | 155.41±4.98     | 154.49±3.84     | 155.74±3.84     | 0.337                   |

Figure 1: Types of surgery

Figure 2: Mean heart rate among groups BF, C2, C1, and BM

Figure 3: Mean systolic blood pressure among groups BF, C2, C1, and BM

Figure 4: Mean diastolic blood pressure among groups BF, C2, C1, and BM

NRS scores at rest
There was no statistically significant difference in mean NRS scores at rest among the four groups [Figure 5 and Table 2] at any of the time intervals till the removal of epidural catheter (P > 0.05).

NRS scores on coughing
Dynamic pain scores on coughing were found to be significantly higher in Group BF (P < 0.05) as compared to Groups C2, C1, and BM at 2, 4, 8, and 12 h on the day of surgery and it was comparable with the three groups C2, C1, and BM on first, second, and third postoperative days at all time intervals [Figure 6 and Table 3]. The mean NRS scores were comparable between groups C2 and C1, between groups C2 and BM, and between groups C1 and BM throughout the study. However, NRS scores were lower in group C2 as compared to groups C1 and BM at all time points (P > 0.05).

NRS scores on mobilization (from lying to sitting)
Similar to the NRS scores on coughing, dynamic pain scores on mobilization were also found to be significantly higher in Group BF (P < 0.05) as compared to group C2, group C1, and group BM at 2, 4, 8, and 12 h on the day of surgery and it was comparable with groups C2, C1, and BM on first, second, and third postoperative days at all time intervals [Figure 7 and Table 4]. The mean NRS scores were comparable between groups C2 and C1, between groups C2 and BM, and between groups C1 and BM throughout the study. However, NRS scores were lower in group C2 as compared to groups C1 and BM at all time points (P > 0.05).

Side effects
PONV scores were significantly higher (P < 0.05) in both groups BM as well as group BF as compared to C2 and C1 at all the time points on the day of surgery and till 12 hours in the afternoon on first postoperative day and were comparable (P > 0.05) after that till the removal of catheter [Figure 8 and Table 5]. Among the opioids, the scores were significantly higher (P < 0.05) in group BM as compared to group BF on the day of surgery and were comparable after that till the stoppage of infusion and were comparable between groups C2 and C1 throughout the study. Incidence of vomiting is shown in Table 6. A total of 37% patients in group BM and 16.7% of the patients in group BF required antiemetics, while none of the patients either in group C1 or group C2 required any antiemetics [Table 6]. The incidence of pruritus [Table 6] was significantly higher in group BM (43.5%) as compared to group BF (19%), while no patients in group C1 or C2 had pruritus at any time point (P < 0.001). The incidence of dry mouth [Table 6] was significantly higher in group C2 (22%) as
Table 2: Mean NRS scores at rest among groups BF, C1, C2, and BM

| NRS scores at rest | Mean±SD | P |
|--------------------|---------|---|
|                     | Group BF (n=48) | Group C2 (n=46) | Group C1 (n=47) | Group BM (n=46) | BF vs C2 vs C1 vs BM | BF vs BM | BF vs C1 | C2 vs BM | C2 vs C1 | C1 vs BM |
| 0 h                 | 0.29±0.46 | 0.24±0.43       | 0.23±0.43       | 0.22±0.42       | 0.855 | 0.936 | 0.917 | 0.841 | 1.000 | 0.995 | 0.998 |
| 1 h                 | 0.92±0.45 | 0.87±0.45       | 0.91±0.46       | 0.89±0.43       | 0.952 | 0.957 | 1.000 | 0.993 | 0.962 | 0.996 | 0.994 |
| 2 h                 | 1.4±0.49  | 1.35±0.48       | 1.36±0.49       | 1.37±0.49       | 0.970 | 0.964 | 0.986 | 0.994 | 0.999 | 0.997 | 1.000 |
| 4 h                 | 1.92±0.43 | 1.85±0.47       | 1.89±0.52       | 1.76±0.56       | 0.589 | 0.051 | 0.064 | 0.053 | 0.971 | 0.837 | 0.574 |
| 8 h                 | 2.58±0.58 | 2.41±0.54       | 2.51±0.58       | 2.39±0.58       | 0.331 | 0.472 | 0.925 | 0.363 | 0.843 | 0.998 | 0.744 |
| 12 h                | 2.71±0.58 | 2.63±0.57       | 2.68±0.63       | 2.65±0.57       | 0.925 | 0.918 | 0.996 | 0.967 | 0.976 | 0.998 | 0.995 |
| 8 am POD1           | 2.98±0.78 | 2.76±0.67       | 2.96±0.66       | 2.91±0.72       | 0.449 | 0.449 | 0.999 | 0.970 | 0.545 | 0.735 | 0.991 |
| 12 noon POD1        | 2.79±0.62 | 2.78±0.63       | 2.85±0.62       | 2.87±0.54       | 0.871 | 1.000 | 0.964 | 0.924 | 0.948 | 0.901 | 0.999 |
| 4 pm POD1           | 2.87±0.81 | 2.74±0.71       | 2.87±0.82       | 2.93±0.83       | 0.686 | 0.842 | 1.000 | 0.984 | 0.851 | 0.642 | 0.982 |
| 8 pm POD1           | 3.00±0.74 | 2.98±0.72       | 3.11±0.67       | 3.15±0.67       | 0.576 | 0.999 | 0.880 | 0.717 | 0.813 | 0.632 | 0.989 |
| 8 am POD2           | 3.12±0.87 | 3.00±0.63       | 3.19±0.85       | 3.22±0.81       | 0.563 | 0.872 | 0.977 | 0.943 | 0.654 | 0.559 | 0.999 |
| 12 noon POD2        | 2.75±0.79 | 2.67±0.73       | 2.83±0.79       | 2.83±0.78       | 0.740 | 0.965 | 0.959 | 0.965 | 0.768 | 0.783 | 1.000 |
| 4 pm POD2           | 2.50±0.68 | 2.43±0.69       | 2.57±0.71       | 2.57±0.65       | 0.742 | 0.967 | 0.952 | 0.967 | 0.760 | 0.798 | 1.000 |
| 8 pm POD2           | 2.71±0.92 | 2.59±0.88       | 2.62±0.97       | 2.72±0.96       | 0.877 | 0.922 | 0.964 | 1.000 | 0.999 | 0.908 | 0.955 |
| 8 am POD3           | 2.46±0.85 | 2.35±0.77       | 2.45±0.83       | 2.57±0.83       | 0.656 | 0.915 | 1.000 | 0.922 | 0.938 | 0.583 | 0.899 |
| 12 noon POD3        | 2.50±0.68 | 2.46±0.72       | 2.43±0.65       | 2.52±0.69       | 0.907 | 0.990 | 0.952 | 0.999 | 0.996 | 0.969 | 0.906 |
| 4 pm POD3           | 2.25±0.86 | 2.13±0.78       | 2.15±0.72       | 2.22±0.84       | 0.874 | 0.888 | 0.928 | 0.997 | 1.000 | 0.954 | 0.977 |
| 8 pm POD3           | 1.96±0.85 | 1.85±0.84       | 1.85±0.75       | 1.85±0.84       | 0.889 | 0.915 | 0.920 | 0.915 | 1.000 | 1.000 | 1.000 |
| Mean NRS            | 2.32±0.69 | 2.23±0.65       | 2.30±0.67       | 2.31±0.68       | 0.886 | 0.741 | 0.984 | 0.996 | 0.626 | 0.712 | 0.998 |

Figure 5: Comparison of NRS scores at rest among groups BF, C2, C1, and BM

Figure 6: Comparison of NRS scores on coughing among groups BF, C2, C1, and BM

Figure 7: Comparison of NRS scores on mobilization among groups BF, C2, C1, and BM

Figure 8: Comparison of PONV scores of patients among groups BF, C2, C1, and BM

compared to group C1 (11%), while no patients in group BF or BM had dry mouth (P < 0.001). There was no statistically significant difference in mean sedation scores among the four groups [Figure 9] at any point of time throughout the study period (P > 0.05). In the group BF and C1, all patients were awake after 4 h, while in group C2 and BM all patients were awake after 8 h, till then maximum sedation score reached was 2, i.e., patients were only mildly sedated and drowsiness did not interfere with measurement of pain. None of the patients in any group had any episode of respiratory depression (respiratory rate <8/min) at any time point or any episode of fall in SpO₂ (P > 0.05).

There was no statistically significant difference in the mean duration of sensory block, the duration or degree of motor blockade [Table 7] among four groups throughout the study period (P > 0.05). None of the patients in four groups had grade 3 motor blockade after 2 h on the day of surgery till the end of the study.

There was a statistically significant difference in requirement of rescue analgesics [Table 8] among the four groups BF, C2, C1, and BM (P < 0.05). The requirement of systemic analgesics was significantly higher in group BF as compared to groups C2, C1, and BM (P < 0.05) and no significant
difference requirement of rescue analgesics between groups C2 and C1 and between groups C2 and BM ($P > 0.05$). The requirement of rescue analgesics was significantly higher in group C1 as compared to group BM ($P < 0.05$). Regarding the mean duration of postoperative analgesia [Table 8], there was statistically significant difference among the four groups BF, C2, C1, and BM ($P < 0.05$). There was a significant difference between groups BF and C2; BF and C1; BF and BM; C2 and BM; and between C1 and BM ($P < 0.01$). Groups C2 and C1 were comparable to each other with respect to duration of postoperative analgesia ($P > 0.05$). Majority of the patients were extremely satisfied in group C2 as compared to satisfied in groups BF, BM, and C1 ($P < 0.01$) [Table 9].
The primary measure of efficacy of any analgesic regimen is pain relief. Many studies of postoperative analgesia rely on the measurement of pain scores at rest and surrogate measures, such as respiratory spirometry. However, instead of high-quality postoperative analgesia at rest, a more important postoperative outcome measure is the ability to breathe deeply and to tolerate physiotherapy with minimum discomfort, which is dynamic pain relief. We tried to evaluate which of the many analgesic regimens being used at our institution provided the best dynamic pain relief with minimum side effects. On literature search, we were unable to find any published data comparing postoperative epidural infusion of morphine with fentanyl with two different doses of clonidine for dynamic pain relief after elective gynecological surgeries under CSE.

Our study has demonstrated that dynamic pain scores were significantly higher in patients receiving epidural fentanyl with bupivacaine as compared to morphine with bupivacaine and clonidine with bupivacaine at most of the time intervals on the day of surgery and thereafter were comparable till end of study period. Although the NRS scores were comparable

### Discussion

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#### Table 5: PONV scores among groups BF, C1, C2, and BM

| Side effect | BF (n=48) | C1 (n=47) | C2 (n=46) | BM (n=46) | P |
|-------------|-----------|-----------|-----------|-----------|---|
| PONV (%)    | 11 (23%)  | 1 (2%)    | 4 (8.5%)  | 20 (43.4%)| <0.001 |
| Pruritus (%)| 9 (19%)   | 0         | 0         | 0         | <0.001 |
| Dry mouth (%)| 0       | 10 (22%)  | 5 (11%)   | 0         | <0.001 |
| Total antiemetic requirement in 96 h (8 mg) | 8 (16.7%) | 0 | 0 | 17 (37%) | <0.001 |

#### Table 6: Incidence of side effects among groups BF, C1, C2, and BM

| Side effect | BF (n=48) | C1 (n=47) | C2 (n=46) | BM (n=46) | P |
|-------------|-----------|-----------|-----------|-----------|---|
| PONV (%)    | 11         | 1         | 4         | 20        | <0.001 |
| Pruritus (%)| 9          | 0         | 0         | 0         | <0.001 |
| Dry mouth (%)| 0       | 10        | 5         | 0         | <0.001 |
| Total antiemetic requirement in 96 h (8 mg) | 8         | 0         | 0         | 17        | <0.001 |

#### Table 7: Duration of sensory block and motor block

| Duration | Mean±SD | BF vs C2 vs C1 vs BM | P |
|----------|---------|----------------------|---|
| Sensory block (min) | 152.32±8.86 | 168.98±7.68 | 162.27±23.39 | 156.78±10.28 | 0.392 | 0.397 | 0.317 | 0.886 | 0.898 | 0.546 | 0.814 |
| Motor block (min) | 210.33±32.37 | 230.47±33.23 | 224.71±35.22 | 218.45±31.42 | 0.346 | 0.321 | 0.303 | 0.812 | 0.962 | 0.426 | 0.889 |
between the clonidine groups, the analgesia provided by clonidine @ 10 μg/mL was better than that provided by clonidine @ 5 μg/mL at all time points. The mean duration of postoperative analgesia was shortest in group BF and longest in group BM, and correspondingly, the minimum requirement of rescue analgesia was in morphine group. This is to be expected on the basis of drug pharmacokinetics as morphine is much longer acting drug than fentanyl. The analgesia provided by epidural infusion of morphine with bupivacaine was comparable to the analgesia provided by epidural infusion of clonidine. Clonidine produced a dose-dependent increase in duration of postoperative analgesia and provided comparable analgesia to morphine at a dose of 10 μg/mL.

Our results were similar to those of Vukovic et al.,[9] who investigated the quality and duration of analgesic and hemodynamic effects of clonidine when used as an additional analgesic for postoperative epidural analgesia in major vascular surgery. The authors concluded that clonidine added to morphine provided significantly better pain scores after starting the epidural infusion and longest-lasting analgesia following the discontinuation of infusion. The dosage of morphine used in their study was the same as ours and dose of clonidine was slightly higher. Jain et al.[10] used similar doses of epidural clonidine (1 and 2 μg/mL) but with 4 mL of patient-controlled epidural analgesia (PCEA) morphine (0.1 mg/mL) in 0.1% bupivacaine per delivery. Although they demonstrated that there was no statistically significant difference between the mean NRS scores and categorical rating scale scores for pain at rest, on coughing, or during mobilization from the supine to sitting at any time between the groups, number of patients in clonidine groups requiring rescue analgesia was, however, significantly less as compared with nonclonidine group. Also, because the side-effects were less with clonidine 1 μg/mL, the authors concluded that the optimal epidural clonidine concentration in morphine (0.1 mg/mL) and bupivacaine (0.1%) solution after lower abdominal surgery is 1.0 μg/mL. We, in our study, have observed that although NRS scores were comparable in the two clonidine groups, they were consistently lower in group C2. Thus, the optimal dose of clonidine is 2 μg/mL rather than 1 μg/mL. The difference in the results of the two studies is probably because Jain et al. had used clonidine with morphine in addition to bupivacaine.

Consistent with our results, Mogensen et al.[11] concluded that addition of clonidine to low-dose epidural infusion of bupivacaine and morphine provides better dynamic pain relief. Likewise, Gupta et al.[12] concluded that the addition of clonidine significantly increases the duration of postoperative analgesia and reduced the requirement of rescue analgesia as compared with nonclonidine group.

Few authors have reported results different from ours. Fischer et al.[13] compared continuous postoperative epidural infusion of fentanyl with bupivacaine and morphine with bupivacaine and observed that mean postoperative VAS scores were higher with fentanyl though not significant (P > 0.05). Probably the analgesia provided by fentanyl was found to be comparable to morphine because the dose of fentanyl they used was very high (50 μg/h) as compared to our study (10 μg/h). Giovanni Cucchiaro et al.[14] concluded in their study that the VAS scores and amount of rescue medication in groups receiving epidurally administered combination of bupivacaine–clonidine or bupivacaine–fentanyl are equivalent to those receiving combination of bupivacaine–fentanyl–clonidine in patients undergoing the Nuss procedure. The smaller doses of clonidine and a large concentration of fentanyl used by them probably made the pain relief produced by fentanyl comparable to that produced by clonidine. Bajwa et al.[15] demonstrated

### Table 8: Requirement of rescue analgesics and duration of postoperative analgesia

|                        | Group BF (n=48) | Group C2 (n=46) | Group C1 (n=47) | Group BM (n=46) | P               |
|------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Total no. of           | 2.96±0.29       | 2.48±0.51       | 2.83±0.380      | 2.35±0.48       | <0.001          |
| epidural top-ups       |                 |                 |                 |                 |                 |
| Total amount of        |                 |                 |                 |                 |                 |
| systemic analgesics (mg)| 198.75±36.23    | 138.75±27.23    | 141.75±28.1     | 99.75±59.2      | <0.001          |
| Duration of            | 4.15±0.64       | 8.54±0.78       | 6.80±1.33       | 14.57±2.55      | <0.001          |
| postoperative          |                 |                 |                 |                 |                 |
| analgesia (h)          |                 |                 |                 |                 |                 |

### Table 9: Patient satisfaction score

|                        | Group BF (n=48) | Group C2 (n=46) | Group C1 (n=47) | Group BM (n=46) | P               |
|------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Satisfaction score     | 2.06±0.522      | 1.15±0.363      | 1.61±0.585      | 1.87±0.58       | <0.001          |
that there was no statistically significant difference in the analgesic properties of clonidine and fentanyl. These results were probably due to high dose of fentanyl delivered by bolus, both alone and along with clonidine. Karnawat et al.\textsuperscript{16} analyzed the effect of epidural bupivacaine, bupivacaine with fentanyl, and bupivacaine with clonidine and concluded that bupivacaine–fentanyl and bupivacaine–clonidine provided equivalent postoperative epidural analgesia in patients undergoing hip surgery.

Morphine and fentanyl are known to have no effect on BP or HR and rhythm at therapeutic doses.\textsuperscript{17} Neuraxial clonidine, however, reduces BP by inhibiting preganglionic sympathetic neural activity in spinal cord.\textsuperscript{18} In our study, there was no significant variation in mean HR or mean SBP and DBP among four groups at all time points. Similar to our observations, Vukovic et al.\textsuperscript{9}, Jain et al.\textsuperscript{10} Bajwa et al.\textsuperscript{15} and Karnawat et al.\textsuperscript{16} also demonstrated that there was no statistically significant difference in hemodynamic parameters at any time point between groups with the use of epidural clonidine. On the contrary, Paech et al.\textsuperscript{19} concluded that clonidine produced a dose-dependent decrease in BP and HR and an increase in the vasopressor requirement ($P < 0.01$), probably due to the high dose of clonidine used as compared to a lower dose used in our study.

Pure antinociception without side effects has long been an elusive goal.\textsuperscript{20,21} In the present study, the mean PONV scores were significantly higher in opioid groups as compared to clonidine group and among the two opioids groups, the incidence was significantly higher in group BM as compared to BF. Also requirement of antiemetics was maximum in group BM and lowest in group C2. It has been previously documented in the literature that clonidine has an antiemetic effect.\textsuperscript{22}

Similar to our observations, Paech et al.\textsuperscript{19} also concluded that there was no significant difference in the incidence of nausea and vomiting with different doses of clonidine. Karnawat et al.,\textsuperscript{16} Giovanni Cucchario et al.,\textsuperscript{14} and Bajwa et al.\textsuperscript{15} have also reported significantly less vomiting with the use of clonidine. Jain et al.,\textsuperscript{10} however, observed that the incidence of nausea and vomiting in clonidine group was not statistically significant as compared to nonclonidine group. Presumably, because all their patients received PCEA morphine that contributed to nausea and vomiting.

The most common side effect of neuraxial opioids is pruritus. As expected, in our study, the incidence of pruritus was highest in group BM as compared to group BF, while no patients in clonidine group had pruritus at any time point. Fischer et al.\textsuperscript{13} have reported a lower incidence of pruritus with fentanyl as compared to morphine. The incidence of pruritus due to fentanyl in their study is comparable to ours (22% vs 19%) in spite of the authors using five times the amount of fentanyl that we used. This shows that the incidence of itching is not related to the dose of fentanyl used neuraxially as has already been well documented in the literature.\textsuperscript{23,24} Vukovic et al.,\textsuperscript{9} Karnawat et al.,\textsuperscript{16} and Giovanni Cucchario et al.\textsuperscript{14} found that no patient who received only clonidine experienced any episode of pruritus.

Sedation is a well-known side effect of clonidine when used for regional anesthesia and also occurs following intrathecal and epidural opioids administration. In the present study, there was no statistically significant difference in mean sedation scores among the four groups. Similar to our results, Vukovic et al.,\textsuperscript{9} Fischer et al.,\textsuperscript{13} and Giovanni Cucchario et al.,\textsuperscript{14} who have compared various combinations of epidural opioids with each other or with clonidine, have observed no significant difference in the sedation scores among the different groups. Bajwa et al.\textsuperscript{15} observed that the incidence of sedation was significantly higher with fentanyl as compared to clonidine or combination of clonidine and fentanyl. A significantly more degree of sedation with high dose of epidural clonidine reported by Karnawat et al.\textsuperscript{16} confirms that sedation caused by clonidine is dose-dependent and lower doses as used in our study are safe. Jain et al.,\textsuperscript{10} while using doses of clonidine similar to ours, reported more sedation with clonidine, probably because clonidine infusion was combined with morphine in all groups. Another side effect of clonidine is the decrease in salivary outflow leading to a sensation of dry mouth, reported frequently in the literatures (Gupta et al.\textsuperscript{12} and Bajwa et al.\textsuperscript{15}).

In our study, there was no significant difference in degree of motor and sensory blockade among four groups throughout the study period. Because motor and sensor blockade is primarily a function of LA, these results are a consequence of reduced concentration of LA being used for epidural analgesia in the studies mentioned (Fischer et al.,\textsuperscript{13} Paech et al.,\textsuperscript{19} Mogensen et al.,\textsuperscript{11} Bajwa et al.,\textsuperscript{15} Karnawat et al.,\textsuperscript{16} and Jain et al.\textsuperscript{10}).

Our study demonstrated that patients were extremely satisfied in group C2 as compared to satisfied in groups BF, BM, and C1. The NRS scores were comparable between group C2 and BM. Also, the duration of analgesia was longer and requirement of rescue analgesics were less in group BM. In spite of this, patient satisfaction was better in group C2 due to significantly reduced incidence of major side effects such as pruritus and PONV.

Our study had few limitations, the most important being that it is an observational study. In observational studies,
the assignment of subjects to groups is observed rather than manipulated and there enters a probability of selection bias. The initial anesthesiologists managing the infusion and subsequent evaluators were not blinded, and this could have produced a potential bias. All the patients in our study were given epidural infusion at a fixed rate, so it would have resulted in some patients with inadequate pain relief or marked side effects.

**Conclusion**

We conclude that the addition of clonidine 2 μg/mL to 0.125% bupivacaine @ 5 mL/h in patients undergoing elective gynecological surgery under CSE anesthesia provides better postoperative dynamic pain relief, decreases the postoperative analgesic requirement, and provides greater patient satisfaction, with significantly reduced side effects.

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**Conflicts of interest**

There are no conflicts of interest.

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