A Randomised Control Study: Post operative analgesic effect of Dexmedetomidine Administration in Wound Infiltration for Abdominal Hysterectomy

Authors

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Introduction
Abdominal hysterectomy is associated with moderate to severe post-operative pain. The post-operative pain not only delays recovery but also can lead to chronic pain. A multimodal approach to pain is the current standard in perioperative pain management. Epidural analgesia may be considered by some to be gold standard for pain management after abdominal surgeries.

Nevertheless, concerns remain regarding complications after neuraxial blocks specifically in older patients. Thus, there is considerable interest in alternative methods of analgesia requiring minimal post-operative monitoring. Post-operative wound infiltration with local anaesthetics is an attractive method because of its simplicity, safety, and low cost. Local anaesthetic infiltration with added adjuvants can improve the quality and duration of analgesia. The added adjuvants are epinephrine, ketorolac, opioids, clonidine, etc.

Dexmedetomidine, a potent $\alpha_2$ adrenoceptor agonist, is approximately eight times more selective towards $\alpha_2$ adrenoceptor than clonidine. When dexmedetomidine is given intravenously, it has a significant opioid sparing effect as well as decreased requirement of anaesthetic agents.

Dexmedetomidine also has been used as an adjunct to local anaesthetics for various nerve blocks. The current study was designed to test the hypothesis that dexmedetomidine when added as an adjuvant to bupivacaine for post-operative wound infiltration after abdominal hysterectomy reduces Diclofenac 1.5mg/kg body weight consumption in first 24 hours of post operative period.

Drugs
1. Dexmedetomidine
An agonist of receptors, adrenergic alpha-2 that is used in clinical medicine for its analgesic and sedative properties.

Structure

![Chemical Structure of Dexmedetomidine](image)

Chemical Formula: $C_{13}H_{16}N_2$
Mol wt.: 200.27 g/mol
Indication: For sedation of initially intubated and mechanically ventilated patients in an intensive care setting, also used in pain relief; anxiety reduction and analgesia.
Mechanism of action
Dexmedetomidine is a specific and selective α2 adrenoceptor agonist. By binding to the presynaptic α2 adrenoceptors, it inhibits the release of norepinephrine, therefore, terminate the propagation of pain signals. Activation of the postsynaptic α2 adrenoceptors inhibits the sympathetic activity thereby decreasing blood pressure and heart rate.

Pharmacodynamics
Dexmedetomidine activates α2-adrenoceptors, and causes the decrease of sympathetic tone, with attenuation of the neuroendocrine and hemodynamic responses to anesthesia and surgery; it reduces anesthetic and opioid requirements; and causes sedation and analgesia.

Pharmacokinetics
- Half-life, elimination: 6 min; 2 hr (terminal)
- Peak plasma: 0.3-1.5 ng/mL
- Protein bound: 94%
- Volume of distribution: 118 L
- Metabolism: Liver, including glucuronidation and CYP2A6
- Metabolites: 3-hydroxy, 3-carboxy, 3-hydroxy N-methyl, 3-carboxy N-methyl, and N-methyl O-glucuronide dexmedetomidine
- Total body clearance: 39 L/hr
- Excretion: Urine (95%); feces (4%)
- Dosage Forms & Strengths injectable solution 100mcg/mL

ICU Sedation
- Load: 1 mcg/kg IV over 10 minutes
- Maintenance 0.2-1.4 mcg/kg/hr IV
- Titrate less frequently than q30 min to prevent hypotension

Fiberoptic Intubation
- Load: 1 mcg/kg IV over 10 minutes
- Maintenance 0.7 mcg/kg/hr IV

Procedural Sedation
- Load: 1 mcg/kg IV over 10 minutes
- Maintenance 0.6 mcg/kg/hr IV titrate to effect (usually 0.2-1 mcg/kg/hr)
- Titrate less frequently than q30 min to prevent hypotension

Adverse Effects
- >10%
- Hypotension (28%)
- 1-10%
- AFib
- Anemia
- Bradycardia
- Fever
- Pleural effusion
- Leukocytosis
- Pulmonary edema

Postmarketing Reports
- Electrocardiogram QT prolonged
- Hypernatremia
- Polyuria
- Acute renal failure
- Respiratory distress syndrome
- Respiratory failure

2. Bupivacaine

Structure

![Chemical Structure of Bupivacaine](image)

Chemical Formula: C18H28N2O

Mol wt: 288.435 g/mol
- Protein binding- 95%
- Half life - 2.7 hours
- Metabolism: liver primarily; CYP450: 3A4 substrate
- Excretion: urine (5% unchanged); Half-life: 3.5h
Mechanism of Action
Inhibits Na ion channels, stabilizing neuronal cell membranes and inhibiting nerve impulse initiation and conduction (amide local anesthetic).

Dosage forms
INJ (0.25%): 2.5 mg per mL; INJ (0.5%): 5 mg per mL; INJ (0.75%): 7.5 mg per mL.

Local Anesthesia [dosing]
Max: 2 mg/kg or 175 mg/dose, 400 mg/24h; Info: onset 2-10min, peak 30-45min, duration 3-6h; some concentrations preservative-free; all conc. available w/ epinephrine 1:200,000.

Regional anesthesia [dosing]
Max: 2 mg/kg or 175 mg/dose, 400 mg/24h; Info: for peripheral and sympathetic nerve blocks and epidural blocks; onset 2-10min, peak 30-45min, duration 3-6h; some concentrations preservative-free; all conc. available w/ epinephrine 1:200,000.

Spinal anesthesia [dosing]
Info: onset <1min, peak 15min, duration 3-6h; some concentrations preservative-free; all conc. available w/ epinephrine 1:200,000.

Absorption
The rate of systemic absorption of local anesthetics is dependent upon the total dose and concentration of drug administered, the route of administration, the vascularity of the administration site, and the presence or absence of epinephrine in the anesthetic solution.

Bupivacaine is a widely used local anesthetic agent. Bupivacaine is often administered by spinal injection prior to total hip arthroplasty. It is also commonly injected into surgical wound sites to reduce pain for up to 20 hours after surgery. In comparison to other local anesthetics it has a long duration of action. It is also the most toxic to the heart when administered in large doses. This problem has led to the use of other long-acting local anaesthetics: ropivacaine and levobupivacaine. Levobupivacaine is a derivative, specifically an enantiomer, of bupivacaine. Systemic absorption of local anesthetics produces effects on the cardiovascular and central nervous systems. At blood concentrations achieved with therapeutic doses, changes in cardiac conduction, excitability, refractoriness, contractility, and peripheral vascular resistance are minimal. However, toxic blood concentrations depress cardiac conduction and excitability, which may lead to atrioventricular block, ventricular arrhythmias and to cardiac arrest, sometimes resulting in fatalities. In addition, myocardial contractility is depressed and peripheral vasodilation occurs, leading to decreased cardiac output and arterial blood pressure. Following systemic absorption, local anesthetics can produce central nervous system stimulation, depression or both.

Aims and Objectives
To compare the effect of local wound infiltration by dexmedetomidine added as an adjuvant to bupivacaine versus bupivacaine alone on postoperative pain after abdominal hysterectomy.

Materials and Methods
After obtaining approval from hospital ethics committee, the present randomised control study was conducted in the postgraduate department of Anaesthesiology and Intensive care, Government Medical College and associated hospitals, Jammu. Sixty women posted for elective abdominal hysterectomy under general anaesthesia between January 2018 and March 2018 belonging to American Society of Anesthesiologists' (ASA) physical status (I or II) aged 18-60 years were selected for the study.


Exclusion criteria: Difficulty in communication
- patients with morbid obesity
- hepatorenal insufficiency
- those receiving adrenoceptor agonists or antagonists before the operation
- history of adverse effects to study drugs
- patients with cardiac failure, rhythm abnormalities
• patients with seizure disorder
• history of drug abuse, opioid dependence
• uncontrolled hypertension
• sepsis
• patients who received any kind of analgesic or sedative in the 24 hour prior to surgery

All patients underwent a pre-anaesthetic checkup on the day before surgery including a detailed history, a thorough physical and systemic examination and relevant demographic characteristics and baseline hemodynamic parameters were recorded. Written informed consent was obtained from each patient for participation in the study.

Routine investigations included hemoglobin, bleeding/clotting time, platelet count, routine urine test, electrocardiograph, serum urea, serum creatinine, serum electrolytes, blood sugar and radiograph chest. The patients were kept fasting for 8 hours preoperatively.

The patients were pre-medicated with oral alprazolam 0.005 mg/kg 8 h before surgery. Patients were randomly allocated into two groups using a computer-generated random number table.

**Group I (control group)** patients received wound infiltration with 30 mL 0.25% bupivacaine at the end of surgery.

**Group II** patients received 30 mL 0.25% bupivacaine with 1 μg/kg dexmedetomidine at the end of surgery.

The person who prepared the study drugs did not participate in the data collection. Anaesthesia was induced with propofol 2-3 mg/kg intravenous (IV). Tracheal intubation was facilitated by vecuronium 0.1 mg/kg IV. Anaesthesia was maintained with isoflurane and 60% nitrous oxide in oxygen. Patients were monitored using Datex Ohmeda GE B40 cardiac monitor. Intraoperative monitoring included electrocardiogram leads II and V5, non-invasive blood pressure at 5 min intervals, oxygen saturation, end-tidal carbon dioxide and nasopharyngeal temperature. Patient's lungs were ventilated by intermittent positive pressure ventilation using a circle system to maintain normocapnia. Heart rate (HR) and mean arterial pressure (MAP) were maintained within 20% of the pre-operative value. Hypotension (MAP <20% of the baseline or <60 mmHg) was treated with infusion of normal saline and if required injection mephentermine 3–6 mg boluses IV. Bradycardia (HR <40 beats/min) was treated with IV atropine 40 μg/kg bolus. All patients received paracetamol 20 mg/kg IV and ondansetron 0.1 mg/kg IV ½ h before the completion of surgery. At the end of surgery, residual neuromuscular block was antagonised with appropriate dose of neostigmine and glycopyrrolate IV. Tracheal extubation was performed on meeting the standard criteria for extubation. Post-operative analgesia was provided with diclofenac 1.5 mg/kg IV every 8 h.

Patients were observed for 24 h after operation in the post-anaesthesia care unit (PACU) by an anaesthesiologist who was not aware of the patient's group assignment. The primary objective was to assess pain at rest and at cough by visual analogue scale.

**VAS Score**

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>no pain</td>
</tr>
<tr>
<td>10</td>
<td>worst imaginable pain</td>
</tr>
</tbody>
</table>

at the time of arrival in the PACU and then at 2, 4, 6, 8, 10 and 12 h after operation. Rescue analgesia was given with diclofenac 75 mg IV in drip on demand or whenever VAS score was ≥4. The number of patients requiring rescue analgesia and total diclofenac consumption during the first 24 h after operation was recorded. The level of sedation was assessed using four-point scale.

**Sedation Scale**

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>awake and oriented</td>
</tr>
<tr>
<td>1</td>
<td>drowsy but responding to commands</td>
</tr>
<tr>
<td>2</td>
<td>sleepy but easy to arouse [by loud command or glabellar tap]</td>
</tr>
<tr>
<td>3</td>
<td>deep sleep, difficult to arouse</td>
</tr>
</tbody>
</table>

The incidence and severity of nausea and vomiting were assessed by 4-point scale.
Categorical scales
0 none
1 mild
2 moderate
3 severe
Metoclopramide 10 mg IV was given for severe nausea or vomiting. Any other adverse effect was also recorded.

Statistical analysis
Sample size was calculated on the basis of previous study. At 95% significance level and 80% power, assuming 30% reduction in Voveron consumption, 27 patients were required in each group. To minimise the effects of data loss, a total of sixty patients were enrolled. The data from the present study were systematically collected, compiled and statistically analysed by Statistical package for the social science for windows. Statistical significance for analgesic requirement was determined by one-way analysis of variance (ANOVA). ASA physical status, sex ratio and need for rescue analgesia in recovery room were analysed using Chi-square test and Fisher's exact test. Comparisons of HR and arterial pressure were made using ANOVA, followed by Student–Neumans–Keul test for in-between group comparisons. Differences were considered statistically significant if P< 0.05.

Observations
In total, 58 patients completed the study out of sixty recruited. Two patients were excluded from the analysis (both underwent extended hysterectomy) as shown in consort chart [Figure 1]. Both groups were similar with respect to patient characteristics, ASA physical status and duration of surgery [Table 1].

Figure 1: Consort diagram
Table 1: Comparison of demographic data of both the group

<table>
<thead>
<tr>
<th>Variables</th>
<th>Mean ±SD</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Group I (n=30)</td>
<td>Group II (n=28)</td>
</tr>
<tr>
<td>Age (Years)</td>
<td>48.4 (35-65)</td>
<td>51.5 (41-66)</td>
</tr>
<tr>
<td>Weight (Kg)</td>
<td>62.8 (11.2)</td>
<td>60.2 (11.3)</td>
</tr>
<tr>
<td>ASA (I : II)</td>
<td>20:10</td>
<td>22:6</td>
</tr>
<tr>
<td>Duration of surgery (min)</td>
<td>90.45 (12.08)</td>
<td>95.25 (13.08)</td>
</tr>
</tbody>
</table>

P>0.05 is not significant. Group I – Control; Group II – Dexmedetomidine wound infiltration; SD – Standard deviation; ASA – American Society of Anesthesiologists

Group II had significantly lower pain scores at rest for first 12 h i.e., at 2, 4, 6, 8, 10 and 12 h [Figure 2] and on cough for 6 h after operation when compared with patients in Group I.

![Figure 2](image)

**Figure 2:** Comparison of visual analogue scale score of both the group at rest

Group I - Control; Group II - Dexmedetomidine wound infiltration

The 24 h diclofenac consumption was also less in Group II when compared with Group I. All the patients in Group I (100%) required diclofenac, while only 14 patients in Group II (50%) required it and this was statistically significant (P < 0.002) [Table 2].

Table 2: Comparison of total diclofenac consumption in both the groups

<table>
<thead>
<tr>
<th>Variables</th>
<th>Mean ±SD</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Group I (n=30)</td>
<td>Group II (n=28)</td>
</tr>
<tr>
<td>Total diclofenac consumption (mg)</td>
<td>75 (2.24)</td>
<td>37.5 (1.1)</td>
</tr>
<tr>
<td>Patients requiring diclofenac</td>
<td>30 (100)</td>
<td>14 (50)</td>
</tr>
</tbody>
</table>

P<0.05 is significant. Group I – Control; Group II – Dexmedetomidine wound infiltration.

Table 3: Comparison of the sedation score in both the groups

<table>
<thead>
<tr>
<th>Sedation score</th>
<th>Group I</th>
<th>Group II</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>27 (90)</td>
<td>26 (92.8)</td>
<td>0.489</td>
</tr>
<tr>
<td>1</td>
<td>3 (10)</td>
<td>2 (7)</td>
<td>0.456</td>
</tr>
<tr>
<td>2</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

P>0.05 is not significant. Data expressed as n (%). Group I – Control; Group II – Dexmedetomidine wound infiltration.
The incidence of post-operative hypotension was negligible in both the groups. No other side effect was recorded in any group. Patients in Group II were more satisfied than those in Group I (satisfaction score, median [interquartile range], 6.00[1] and 8.00[1] for Groups I and II, respectively, P< 0.0001). Intraoperative HR and MAP were comparable among groups.

**Table 4**: Mean baseline heart rate, peripheral oxygen saturation and noninvasive blood pressure of the patients in the two groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group I</th>
<th>Group II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean heart rate</td>
<td>75.75± 7.58</td>
<td>76.95±6.61</td>
</tr>
<tr>
<td>(beats/ minute)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean SpO₂ (%)</td>
<td>98.4 ±0.88</td>
<td>98.2 ±0.83</td>
</tr>
<tr>
<td>Mean SBP (mmHg)</td>
<td>121.35±10.68</td>
<td>123.6±10.65</td>
</tr>
<tr>
<td>Mean DBP (mmHg)</td>
<td>74.9 ± 5.25</td>
<td>74.8 ± 6.66</td>
</tr>
</tbody>
</table>

Mean baseline vital characteristics like heart rate, peripheral oxygen saturation and noninvasive blood pressure of the patients in all the two groups are comparable.

**Discussion**

Various researches done so far has shown good results for the use of dexmedetomidine in IV sedation (Intensive Care Unit and operative patients), spinal, epidural, caudal anaesthesia and Bier's block.

In our study, the demographic profile (age, weight distribution) was comparable in both the groups. The addition of dexmedetomidine to bupivacaine in local wound infiltration prolonged the sensory block and time to first analgesic requirement significantly in a dose dependent manner. It also maintained stable hemodynamics with minimal side-effects. Results of the current study concur with the results obtained by Singh S. *et al.* (2016) who concluded superior pain relief, decreased need of post operative rescue analgesia and lower VAS score when dexmedetomidine was used as an adjuvant to bupivacaine in local wound infiltration.

Our study also concurs with Shukla D. *et al.* who concluded that there was no significant difference in the mean values of heart rate and mean arterial pressures between dexmedetomidine group and plain bupivacaine group without heavy sedation. Our study also had no statistically significant difference in the sedation scores between the two groups.

The results of our study are in contrast to the results obtained by Sunil B.V. *et al.* (2013) who found that the sedation score was significantly higher in dexmedetomidine group as compared to plain bupivacaine group. The possible explanation could be that they had premedicated all the patients with oral diazepam 2 hrs before surgery where as we premedicated all the patients with oral alprazolam 8 hours before surgery.

Peripherally, α2-agonists produce analgesia by reducing the release of norepinephrine and causing α2-receptor-independent inhibitor effect on nerve fiber action potential. Infiltration of dexmedetomidine in surgical wound may be useful to avoid the adverse hemodynamic effects of IV administration while still providing post-operative analgesia. Various animal studies have reported potent antinociceptive effect of dexmedetomidine on peripheral administration along with its safety. Dexmedetomidine enhanced duration of bupivacaine anaesthesia and analgesia of sciatic nerve block in rats without any evidence of histopathological damage to the nerve. In another study, dexmedetomidine added to ropivacaine increased the duration of sciatic nerve blockade in rats, most likely due to the blockade of hyperpolarisation-activated cation current (i.e., a direct effect on the peripheral nerve activity). When dexmedetomidine and clonidine were added to lignocaine for nerve block, it enhanced the local anaesthetic action of lignocaine through peripheral α2A adrenoceptors. In the present study, patients who received dexmedetomidine in wound infiltration with bupivacaine after abdominal hysterectomy had reduced post-operative pain score and diclofenac requirement when compared with the control group. This was similar to few other studies using local infiltration of dexmedetomidine for various surgeries with no delay in psychomotor recovery or increase in post-operative clinically significant adverse effect.
Although this study adds to the current knowledge on dexmedetomidine, the results should be considered taking into consideration the obvious limitations. The population involved the young and otherwise healthy patients and the effect in older patients with cardiovascular comorbidities are yet to be investigated. The main limitation of our study is that we did not compare dexmedetomidine infiltration with IV dexmedetomidine. Further studies are required to see that prolonged analgesic effect of dexmedetomidine infiltration is not due to its intravascular absorption rather due to peripheral effect.

Conclusions
Our report shows that the use of dexmedetomidine as an adjuvant to bupivacaine in local wound infiltration seems to be an attractive option for post operative analgesia with minimal side effects.

Conflicts of Interest
There are no conflicts of interest.

Bibliography


PROFORMA

Date: 
Name: 
W/o, D/o, S/o: 
MRD No.: 
Occupation: 
Address: 
Diagnosis: 
Date of surgery: 
Anaesthesiologist: 

Case No.: 
Age: 
Height (cm): 
Weight (kg): 
Proposed operation: 
Surgeon: 
ASA Grade: 

PREOPERATIVE ASSESSMENT

Chief complaints: 
Medical history: 
Surgical history: 
Drug history: 
Personal history: 
Family history: 
Any significant past history: 

GENERAL PHYSICAL EXAMINATION

Pallor: 
Cyanosis: 
Pulse rate (per minute): 
Any other significant finding: 

Icterus: 
JVP: 
Blood pressure (mmHg): 

SYSTEMIC EXAMINATION

Cardiovascular system: 
Respiratory system: 
Central nervous system: 

INVESTIGATIONS

Blood:

Haemoglobin: 
Bleeding time: 
Clotting time: 
Platelet count: 
Sugar (Fasting): 
Urea: 
Creatinine: 
Sodium: 
Potassium:
SGOT:
SGPT:
Alkaline phosphatase:
PT:
PTI:
INR:

Urine:
  Albumin:
  Sugar:
  RBC:
  Pus cells:

ELECTROCARDIOGRAM (12 leads):

RADIOPHGRAPH CHEST:

CONSENT FOR STUDY

I have read / been briefed on the above project summary and I voluntarily agree to participate in this project. I understand that participation in this study may or may not benefit me. Its general purpose, potential benefits, possible hazards and inconvenience have been explained to my satisfaction. I hereby give my consent for this study.

Name : _______________________

Dated : ______________________

Signature : ____________________