Intraperitoneal Analgesia for Laparoscopic Cholecystectomy: Use of Bupivacaine with and Without Dexmedetomidine as Adjuvant

Dr. Mohamad Ommid, Ummer Ali, Shahzada Gani, Shaheeda Akhter, Nuzhat ul Islam, Saba Ahad, Anka Amin, Humera Manzoor
Department of Anaesthesiology, Government Medical College Srinagar, J&K-190010, India

Abstract: Intraperitoneal instillation of local anaesthetic agents alone or in combination with opioids, \( \propto \)-2 agonists such as dexmedetomidine have been found to reduce post operative pain following laparoscopic cholecystectomy. The purpose of this study was to assess the analgesic effect of the intraperitoneal administration of intraperitoneal dexmedetomidine combined with bupivacaine and intraperitoneal bupivacaine alone in patients undergoing laparoscopic cholecystectomy. One hundred patients of (ASA) physical status I-II of both sexes, aged between 18 to 60 years, equally divided into two groups, randomly allocated to one of the groups using a table of randomization, Group B \((n = 50)\): Intraperitoneal bupivacaine 30 ml 0.25% +5 ml normal saline (NS), Group BD \((n = 50)\): Intraperitoneal bupivacaine 30 ml 0.25% + dexmedetomidine1 u g/kg (diluted in 5 ml NS). Visual analogue scale was recorded half and hours, 1, 2, 4, 6 and 24 hours postoperatively. Incidence of postoperative nausea and vomiting (PONV) was also recorded. In addition, supplementary analgesics and antiemetic consumption were assessed. Statistical analysis was performed using Microsoft (MS) Office Excel Software with the Student’s \( t \)-test and Chi-square test (level of significance \( P = 0.05 \)). Pain intensity, as well as postoperative supplementary medications were significantly lower in Group BD, \((2.12 \pm 0.91)\) as compared to Group B \((4.21 \pm 1.15)\). Time to first request of analgesia (min) was longest \((132 \pm 20)\), \((60 \pm 19)\) and total analgesic consumption (mg) was lowest \((48 \pm 18)\), \((182 \pm 80)\) in Group BD than Group B. Intraperitoneal instillation of dexmedetomidine in combination with bupivacaine is an effective method for management of postoperative pain after laparoscopic cholecystectomy. It significantly reduced supplementary postoperative analgesic and antiemetic medication.

Keywords: Bupivacaine, Dexmedetomidine, Laparoscopic cholecystectomy, intraperitoneal injection, post operative pain.

INTRODUCTION

Surgical procedures are characterized by incisional damage to skin and various other tissues, application of thermal and chemical stimuli to wound and often prolonged traction and manipulation of somatic and visceral structures. Nociceptive pain is often regarded as the key feature of acute post operative pain. Besides inflammatory, visceral and neuropathic pain mechanisms may contribute to the pain occurring during the post-operative period [1].

The economic and health impact of cholelithiasis is significant due to high morbidity. Since the introduction of laparoscopic cholecystectomy in early 90s, which is considered a safe treatment for cholelithiasis, many studies have demonstrated safety, feasibility and cost effectiveness of laparoscopic cholecystectomy as a day care procedure[2].

Currently, the standard treatment for acute post-operative pain is the use of systemic opioids. Opioids bind to specific receptors located throughout the central nervous system and other tissues. Unfortunately, opioids are not without complications. Drowsiness, nausea, vomiting, ileus, urinary retention and pruritus, are all side effects of opioids. These side effects can lead to longer lengths of stays and poor patient outcomes [3,4].

Another approach to control post-operative pain and limit post-operative opioid usage is local anesthetic wound infiltration prior to wound closure. Injecting local anesthetics prior to surgical incision into the surgical wound has been more extensively studied. The results in this area are mixed with several studies showing significant pain reduction [5-7].

Intraperitoneal instillation of local anesthetic agents alone or in combination with opioids, \( \propto \)-2 agonists such as dexmedetomidine have been found to reduce post operative pain following laparoscopic cholecystectomy. The purpose of this study was to assess the analgesic effect of the intraperitoneal administration of intraperitoneal dexmedetomidine combined with bupivacaine and intraperitoneal bupivacaine alone in patients undergoing laparoscopic cholecystectomy. One hundred patients of (ASA) physical status I-II of both sexes, aged between 18 to 60 years, equally divided into two groups, randomly allocated to one of the groups using a table of randomization, Group B \((n = 50)\): Intraperitoneal bupivacaine 30 ml 0.25% +5 ml normal saline (NS), Group BD \((n = 50)\): Intraperitoneal bupivacaine 30 ml 0.25% + dexmedetomidine1 u g/kg (diluted in 5 ml NS). Visual analogue scale was recorded half and hours, 1, 2, 4, 6 and 24 hours postoperatively. Incidence of postoperative nausea and vomiting (PONV) was also recorded. In addition, supplementary analgesics and antiemetic consumption were assessed. Statistical analysis was performed using Microsoft (MS) Office Excel Software with the Student’s \( t \)-test and Chi-square test (level of significance \( P = 0.05 \)). Pain intensity, as well as postoperative supplementary medications were significantly lower in Group BD, \((2.12 \pm 0.91)\) as compared to Group B \((4.21 \pm 1.15)\). Time to first request of analgesia (min) was longest \((132 \pm 20)\), \((60 \pm 19)\) and total analgesic consumption (mg) was lowest \((48 \pm 18)\), \((182 \pm 80)\) in Group BD than Group B. Intraperitoneal instillation of dexmedetomidine in combination with bupivacaine is an effective method for management of postoperative pain after laparoscopic cholecystectomy. It significantly reduced supplementary postoperative analgesic and antiemetic medication.

Keywords: Bupivacaine, Dexmedetomidine, Laparoscopic cholecystectomy, intraperitoneal injection, post operative pain.
agonists such as clonidine and dexmedetomidine have been found to reduce postoperative pain following laparoscopic cholecystectomy [8-11]. After laparoscopic cholecystectomy patients complain more of visceral pain as a result of stretching of the intraabdominal cavity, peritoneal inflammation and phrenic nerve irritation caused by residual carbon dioxide in the peritoneal cavity, whereas after open cholecystectomy the type of pain results mostly in parietal pain [12]. Postoperative abdominal pain usually occurs during the first 24 hours, while shoulder pain most commonly appears the second day after laparoscopic cholecystectomy. Intrapерitoneal (IP) administration of some aroscopic surgery. Some authors suggest that intraperitoneal instillation of drugs for pain relief is effective if used before creation of pneumoperitoneum [13]. While others conclude that intraperitoneal drug administration is effective at the end of the surgery applied through a trocar [14].

METHODS
The present study was conducted at the SMHS Hospital which is one of the associated hospitals of Government Medical College Srinagar. After obtaining approval from competent authorities of the government medical college Srinagar, One hundred patients of (ASA) physical status I-II of both sexes, aged between 18 to 60 years, equally divided in to two groups, Group B (n=50), and group BD (n=50), undergoing laparoscopic cholecystectomies were included in this prospective double blinded study. Patient who were allergic to local anesthetic and study drugs, patients with acute cholecystitis, patients with severe cardiac, pulmonary, and neurological diseases, those in whom procedure had to be converted to open cholecystectomy were excluded from the study. After getting approval from Institutional Ethical Committee, written informed consent was obtained from all the patients before surgery.

Patients were randomly divided into two groups of 50 patients each by computer generated random table number. Group B (n=50): Intrapерitoneal bupivacaine 30 ml 0.25% +5 ml normal saline (NS), and Group BD (n=50): Intrapерitoneal bupivacaine 30 ml 0.25% + dexmedetomidine1µ g/kg (diluted in 5 ml NS). The study drug solution was prepared by an anesthesiologist who was blinded to study protocol and was not involved for intra operative data collection. The surgeon and resident anesthetist were also be blinded to the treatment regimen. All patients were admitted prior to the day of the surgery, and fasting of 6 hour was ensured. On arrival to the operation theatre, the baseline systemic blood pressure, heart rate, peripheral oxygen saturation (SpO2) and ECG were recorded. After establishing the intravenous line, lactate Ringer solution was started and they were pre medicated with ondansetron (0.1-0.3)mg/kg), glycopyrrolate (10 µg/kg), 15 min before induction of anesthesia.

After pre oxygenation for 3 min, anesthesia was induced with propofol (2 mg/kg) till loss of verbal command and tracheal intubation was facilitated with vecuronium 0.1 mg/kg. Anaesthesia was maintained with 60% nitrous oxide in oxygen and isoflurane dial concentration was titrated to achieve a systolic blood pressure 30% below the baseline values. Patients were mechanically ventilated to maintain the end tidal concentration (EtCO₂) between 30 and 35 mm Hg. Intraoperatively, the heart rate, arterial blood pressure, ECG, EtCO₂ and peripheral pulse oximetry (SpO2) were monitored and recorded at 5 min intervals till end of surgery.

Hypotension/hypertension was defined as fall/rise in systolic blood pressure of >20% from the baseline values and bradycardia/tachycardia was defined as fall/rise in pulse rate of >20% from the baseline values. Haemodynamic fluctuations were to be managed accordingly. Patients were placed in 15-20° reverse Trendelenberg’s position with the left side tilt position. During laparoscopy, intra-abdominal pressure was maintained 12-14 mm Hg. The CO₂ was removed carefully by annual compression of the abdomen at the end of the procedure with open trocar.

At the end of the surgery, the study solution was given intraperitoneally before removal of trocar in Trendelenberg’s position, into the hepato-diaphragmatic pace, on gall bladder bed and near and above hepatoduodenal ligament. The neuro-muscular blockade was antagonized with neostigmine 0.05 mg/kg and glycopyrrolate 0.01 mg/kg and trachea was extubated. The nasogastric tube was removed, and the patient was shifted to post-anesthesia care unit (PACU).

All patients stayed in PACU for 24 h after the end of surgery. The primary outcome variable was to compare pain (visual analogue scale [VAS]) score. The Secondary outcome included time to the first request of analgesia in the post-operative period, total dose of analgesic used in 24 h period (post-operative) and any adverse/side effects.

The intensity of post-operative pain was recorded for all the patients using VAS score at 0.5, 1, 2, 4, 6, 12, 24 h after surgery and over all VAS score (mean of all VAS scores). All the study patients were instructed about the use of the VAS score before induction of anesthesia (VAS score 0 - no pain, VAS score 10 - worst possible pain). Patients who reported VAS 3 or >3 were given diclofenac 75 mg intramuscularly as rescue analgesia. Patients were also observed for post-operative nausea and vomiting. Patients who suffered nausea or vomiting were given ondansetron 4 mg IV. Time to the first request of analgesia (considering the extubation as time 0), total dose of analgesia and adverse or side effects over 24 h postoperatively were noted.
A total sample size of 100 patients (n = 50 each for two groups) was calculated using Power and Sample size calculator (PS version 3.0.0.34), assuming 30% improvement in pain scores with error of 0.05 and power of 80%. To obtain a 100 study sample size, a total of 115 patients were included; but 15 patients were excluded on the basis of exclusion criteria.

Statistical analysis was performed using Microsoft (MS) Office Excel Software (Microsoft Microsoft Excel, Redmond, Washington: Microsoft 2003, Computer software). Results were expressed as mean ± standard deviation, number and percentage (%).

Data were analyzed using post hoc analysis method. Normally distributed data were assessed using unpaired Student’s t-test (for comparison of parameters among groups). Comparison was carried out using Chi-square test with a P value reported at 95% confidence level. Level of significance used was P = 0.05.

RESULTS

There was no significant difference with respect to age, sex, weight, height, ASA physical status, duration of surgery and anaesthesia time [Table 1].

Visual analogue scale at different time intervals were statistically significantly lower at all times in Group BD than Group B fig. 1. Furthermore, overall VAS in 24 h was also significantly lower in Group BD (1.80 ± 0.36) than Group B (3.01 ± 0.48) [Table 2].

### Table-1: Demographic characteristic of patients in study groups (Mean±SD)

<table>
<thead>
<tr>
<th>VARIABLES</th>
<th>GROUP B (N=45)</th>
<th>GROUP BD (N=45)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>42.5±16.259</td>
<td>49.8±14.896</td>
<td>0.649*</td>
</tr>
<tr>
<td>SEX: MALE/FEMALES</td>
<td>41/9</td>
<td>38/12</td>
<td>0.83*</td>
</tr>
<tr>
<td>WEIGHT (KG)</td>
<td>61.50±8.87</td>
<td>62.50±10.99</td>
<td>0.82*</td>
</tr>
<tr>
<td>HEIGHT</td>
<td>166.3±4.610</td>
<td>166.1±4.407</td>
<td>0.264*</td>
</tr>
<tr>
<td>ASA I/II</td>
<td>42/08</td>
<td>39/11</td>
<td>0.23*</td>
</tr>
<tr>
<td>DURATION OF SURGERY (min)</td>
<td>62.55±12.927</td>
<td>55.69±10.049</td>
<td>0.562*</td>
</tr>
<tr>
<td>Duration of anaesthesia (min)</td>
<td>74±10.30</td>
<td>70±11.05</td>
<td>0.685*</td>
</tr>
</tbody>
</table>

ASA American society of Anaesthesiology, SD standard deviation, * Level of significance

### Table-2: Post-operative over all VAS score & analgesic requirements (Mean±SD)

<table>
<thead>
<tr>
<th>variable</th>
<th>GROUP B (N=50)</th>
<th>GROUP BD (N=50)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Over all VAS over 24h post operatively</td>
<td>4.50±1.50</td>
<td>1.73±0.83</td>
<td>0.003</td>
</tr>
<tr>
<td>Time to request for first analgesia in post operative period (min)</td>
<td>60±3.54</td>
<td>132±7.6</td>
<td>0.0030</td>
</tr>
<tr>
<td>Total dose of analgesia in 24 h (mg)</td>
<td>182±8.34</td>
<td>48±2.97</td>
<td>0.0021</td>
</tr>
</tbody>
</table>

In our study, among group B patients, nausea/vomiting was found in 11 patients out of 50 patients and 4 patients out of 50 patients in groups BD that is comparable to a study done by Bhakamees et al. [19].

In our study, the incidence of shoulder pain was significantly low in groups BD compared to group B. We found that in group B 30 patients out of 50 patients and in groups BD, 4 patients out of 50 patients had postoperative shoulder pain that is comparable to the study done by Ahmed et al. [18].

CONCLUSION
We concluded that intraperitoneal instillation of dexmedetomidine with bupivacaine provides prolonged duration of analgesia and require less number of rescue analgesic doses compared to bupivacaine alone in patients undergoing laparoscopic surgery without any significant side effects.

REFERENCES
2. Dr Ayaz Gul, Dr Ahmad Fayaz. Laparoscopic cholecystectomy: Effect of intraperitoneal


Table 3: Post-operative adverse/side effects in the study group

<table>
<thead>
<tr>
<th>Variable</th>
<th>GROUP B (N=50)</th>
<th>GROUP BD (N=50)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>05</td>
<td>02</td>
</tr>
<tr>
<td>Vomiting</td>
<td>06</td>
<td>02</td>
</tr>
<tr>
<td>Shoulder pain</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>Pruritis</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Regarding the adverse/side effects the analysis showed that adverse events were not statistically significantly different in all the two study groups (P = 0.3013) [Table 3].

DISCUSSION
Post-operative pain after laparoscopic cholecystectomy consists of three components, visceral, parietal and referred shoulder pain distinguishable from each other in the intensity, latency and duration[15]. Previous studies [16] suggest that predominant cause of pain is parietal but in contrast many other studies emphasized that in early convalescent period, major portion is occupied by visceral pain because as compared to small incisions and limited trauma to the abdominal wall, the surgical manipulation and tissue destruction in visceral organs is much more [17].

Mean pain scores were significantly lower in the group BD when compared to group B during the entire duration of the study. There was statistically significant difference in VAS pain score at 6, 8, 12, 18, 24 hours after surgery in group BD (2.12±0.93) compared to group B (4.21±1.66) up to 24 hours. Similar results were observed with study done by Ahmed, et al. [18] who compared the antinociceptive effect of dexmedetomidine or mepridine with bupivacaine to bupivacaine alone intraperitoneally after the laparoscopic gynecological surgery found that intraperitoneal instillation of mepridine or dexmedetomidine in combination with bupivacaine significantly decreases VAS score.

Bhakamees, et al.[19] evaluated the patients who received dexmedetomidine and found that they had less VAS score as compared to placebo in the postoperative period. Ahmed Mostafa, et al.[20] observed that the patients who received intraperitoneal levobupivacaine instillation had profound postoperative analgesia. Usha Shukla, et al.[21]. Intraperitoneal instillation of bupivacaine in combination with dexmedetomidine is superior to bupivacaine alone and may be better than bupivacaine with tramadol.

Time to requirement of first dose rescue analgesia was longer in the group BD (128 ± 20 min) as compared to Group B (118 ± 22 min). Total diclofenac consumption was also lowest in Group BD (45 ± 15 mg) than Group B (85 ± 35) [Table 2].

Arain et al.[22] studied the efficacy of dexmedetomidine and morphine for postoperative analgesia after a major surgery. Bhattacharjee et al.[23] concluded that dexmedetomidine improves intra and post operative hemodynamic stability during laparoscopic surgeries without prolongation of recovery and similar results were obtained by Bakamees et al.[19].

Available online: http://saspublisher.com/sjams/

1. Instillation of bupivacaine on mean postoperative Intiyaz Khan opic scores. Professional med j 2014;21(4):593-600

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