Effect of Induced Acute Mild Arterial Hypertension on Postoperative Analgesic Requirements After Laparoscopic Ovarian Cystectomy: A Randomized Double Blinded Study

Atef K Salama* and Nasr M Abdalla**

Abstract

Objective: To evaluate the effectiveness of inducing acute hypertension during laparoscopic ovarian cystectomy on postoperative nalbuphine analgesic requirements.

Methods: This randomized clinical trial involved 90 women scheduled for elective laparoscopic ovarian cystectomy in the department of obstetrics and gynecology, Cairo University. Patients were randomly allocated into one of two treatment groups. The Hypertension group had their systolic arterial blood pressure raised and maintained at 20-30% above baseline using ephedrine increments. In the Control Group, the systolic arterial blood pressure was maintained at 20-30% below baseline under the effect of increments of 25 µg fentanyl. The patients were observed in the post-anesthesia care unit for 24 hours to assess the total postoperative nalbuphine consumption, VAS score for pain, hemodynamics and postoperative nausea and vomiting.

Results: The total dose of nalbuphine used in the hypertension group was significantly lower than that in the control group (p <0.001). The VAS score was significantly lower in the hypertension group on arrival to PACU and during the period between 1 and 6 hours postoperatively.

Conclusion: This study demonstrates that pharmacologically induced mild acute intraoperative hypertension significantly reduces postoperative nalbuphine consumption and pain scores following laparoscopic ovarian cystectomy. Trial registration in Pan African Clinical Trial Registry: identification number for the registry is PACTR201508001247179

Key words: analgesia, hypertension, laparoscopic ovarian cystectomy

Introduction

The goals of laparoscopic procedures are to minimize tissue trauma, improve cosmetic results and reduce postoperative pain which consequently decreases hospital stay. Recovery of the patient’s full function is enhanced by good quality postoperative analgesia1. Opioids are commonly used postoperative analgesics2, however, they have many undesirable effects. Nalbuphine, an opioid agonist-antagonist was produced to provide analgesia without these undesirable side effects3.

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Understanding the pathophysiology of pain is a key for optimal management of postoperative pain. In fact, pathophysiology of pain perception involves complex mechanisms and several pathways. In healthy individuals, the cardiovascular control system shares numerous central and peripheral neurotransmitters, anatomic nuclei and projections with the antinociceptive systems.

Several animal studies described the association between acute or chronic hypertension with behavioral hypoalgesia. For example, the responses of two types of dorsal horn neurons involved in nociceptive transmission were more delayed and less intense in spontaneously hypertensive rats compared to Wistar-Kyoto rats.

In humans, the same hypertension-associated hypoalgesia have been reported in response to different painful stimuli. That is, in acute pain models, blood pressure correlates negatively with the perception of the intensity of painful stimuli and positively with the pain threshold.

In healthy normotensive individuals, raised resting blood pressure has been shown to be associated with hypoalgesia. Likewise, presurgical resting systolic BP is inversely associated with acute postsurgical pain intensity.

Many studies reported inverse associations between blood pressure and prevalence of chronic low back pain, headache and migraine. Some studies suggested that hypoalgesia may precede hypertension in normotensive persons with a family history of hypertension.

This study was designed to evaluate the effectiveness of inducing acute hypertension during laparoscopic ovarian cystectomy on postoperative nalbuphine analgesic requirements.

**Methods**

This randomized clinical trial involved 90 women scheduled for elective laparoscopic ovarian cystectomy in the department of obstetrics and gynecology, Cairo University during the period from August 2015 to November 2015. All patients were 20-50 years with physical status I-II according to the American Society of Anesthesiologists (ASA) classification. The study was approved by the institutional review board of Cairo University. A written informed consent was obtained from each participant. The trial was registered in Pan African Trial Registry with identification number for the registry is PACTR201508001247179.

Exclusion criteria were history of chronic hypertension, a baseline arterial pressure ≥140/90 mmHg after admission to the hospital, chronic pain, drug abuse, any known cerebrovascular disease, obesity (body mass index ≥35), use of any analgesic drugs and/or drugs acting on the central nervous system, known pregnancy, or known adverse effects to the study drugs.

The patients did not receive any premedication and fasted for at least 8 hours before surgery. In the operating room and before induction of anesthesia, standard monitors (noninvasive arterial pressure measure, electrocardiogram [ECG], and pulse oximeter) were applied. Arterial blood pressure and heart rate were automatically registered every 3 minutes. Anesthesia was induced using fentanyl 2 μg/kg and propofol 2 mg/kg intravenously. Atracurium 0.5 mg/kg was given to facilitate orotracheal intubation. Mechanical ventilation was adjusted to maintain the end-tidal CO₂ at 30-35 mm Hg. All patients were ventilated with 100% O₂ throughout surgery. Anesthesia was maintained with isoflurane 1%.

Using a table of random numbers generated by a computer, patients were randomly allocated into one of two treatment groups. In the Hypertension Group, the systolic arterial blood pressure was raised and maintained at 20-30% above baseline using ephedrine increments of 3 mg every 5 minutes starting immediately after intubation. The baseline pressure is defined as one blood pressure measurement taken in the preoperative setting after 30 minutes of rest in a seated position and before the patient is transported to the operating room. In the Control Group, the systolic arterial blood pressure was maintained at 20-30% below baseline under the effect of increments of 25 μg fentanyl. For patients whose systolic arterial blood pressure was found to be lower than the target of 20-30% below baseline, an ephedrine bolus of 3-5 mg was used to raise it to target.
Local infiltration of port sites with bupivacaine 0.5% was performed at the beginning of surgery. Every patient received ketorolac 60 mg IV, after induction of anesthesia as a preemptive analgesia and the intra-abdominal pressure secondary to the pneumoperitoneum was maintained at 15 mm Hg after primary trocar insertion. During skin closure, neuromuscular blockade was assessed and antagonized with neostigmine and atropine. Airway extubation was performed when the patient recovered spontaneous ventilation and became fully awake.

In both groups, patients were excluded if the targeted arterial blood pressure range was not reached until 10 minutes after intubation and if ECG showed signs of ischemia (ST-segment depression or elevation and/or T-wave inversion) or any arrhythmia associated with hemodynamic instability. The patient was treated accordingly.

In the post-anesthesia care unit (PACU), Visual Analog Score (VAS) for pain were assessed every 15 minutes during the first 2 postoperative hours, then after 2, 6, 12, and 24 postoperative hours. Postoperative pain (VAS is ≥4) was treated with 5 mg nalbuphine IV bolus doses. When VAS was <4 a nalbuphine IV patient controlled analgesia (no base rate, 1 mg bolus, lockout 10 minutes) was started. Ketorolac 30 mg IV was administered every 8 hours. Cumulative nalbuphine consumption was registered.

Patients, medical staff (nurse, anesthesiologist, and surgeon), and investigators performing the postoperative assessments were blinded to group allocation during the entire study period.

The primary outcome measure was the total postoperative nalbuphine consumption. The secondary outcome measures were VAS score, hemodynamics and postoperative nausea and vomiting.

**Statistical Analysis**

A previous study found that intraoperative induction of acute mild hypertension reduced postoperative analgesic requirements 2 hours postoperatively by 3 mg with a pooled SD of 5 mg. Based on these results, a sample size of 45 cases in each group is required to elicit the difference at an alpha level of 0.05 and a power of the study of 80%.

Statistical analysis of the data was performed using IBM® SPSS® Statistics version 22 (IBM® Corp., Armonk, NY). Numerical variables were presented as mean and standard deviation or median and range as appropriate. Qualitative data were expressed as frequency and percentage. The intergroup differences were compared using the independent-samples student t-test or Mann-Whitney test as appropriate. Chi-square test (Fisher’s exact test) was used to examine the relation between qualitative variables. All tests were two-sided. A p-value <0.05 was considered statistically significant.

### Table 1

Baseline characteristics of the two studied groups

<table>
<thead>
<tr>
<th></th>
<th>Hypertension Group (n = 45)</th>
<th>Control Group (n = 45)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>28.6 ± 5.1</td>
<td>29.4 ± 5.0</td>
<td>0.430</td>
</tr>
<tr>
<td>BMI</td>
<td>25.4 ± 2.2</td>
<td>25.6 ± 2.0</td>
<td>0.699</td>
</tr>
<tr>
<td>Duration of anesthesia</td>
<td>91.6 ± 9.3</td>
<td>92.3 ± 10.0</td>
<td>0.727</td>
</tr>
<tr>
<td>Duration of surgery</td>
<td>79.8 ± 8.7</td>
<td>79.7 ± 9.2</td>
<td>0.972</td>
</tr>
<tr>
<td>SBP Baseline</td>
<td>120.5 ± 2.7</td>
<td>122.2 ± 2.6</td>
<td>0.004</td>
</tr>
<tr>
<td>DBP baseline</td>
<td>76.9 ± 2.3</td>
<td>76.7 ± 2.6</td>
<td>0.637</td>
</tr>
<tr>
<td>HR baseline</td>
<td>73 ± 4</td>
<td>74 ± 4</td>
<td>0.401</td>
</tr>
<tr>
<td>Total dose of ephedrine</td>
<td>30.0 (18.0-45.0)</td>
<td>0.0 (0.0-9.0)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Data as mean ± SD or median (range)
Results

The two groups were comparable in age, BMI, duration of anesthesia and surgery. There was no significant difference between the two groups in diastolic blood pressure and heart rate. Systolic blood pressure was statistically higher in the control group \((p = 0.004)\), however the blood pressure values were within the clinically accepted range. Within the control group, 17 patients needed a small dose (3-9 mg) of ephedrine for adjustment of blood pressure.

Figures 2 and 3 show the intraoperative systolic and diastolic blood pressure levels. In the hypertension group the systolic blood pressure was elevated by 22.6 ± 1.0\% (range: 21.1 ± 23.8\%). In the control group, systolic blood pressure was decreased by 22.1 ± 0.05\% (range: 21.1 ± 22.9\%) relative to the baseline values. Heart rate showed mild changes throughout the intraoperative period (Fig. 4).
Fig. 2
Changes of systolic blood pressure (SBP) during the intraoperative period

* Significant difference between the two groups (p < 0.05), Data are presented as mean ± SD

Fig. 3
Changes of diastolic blood pressure (DBP) during the intraoperative period

* Significant difference between the two groups (p < 0.05), Data are presented as mean ± SD
During the postoperative period, the total dose of nalbuphine used in the hypertension group was significantly lower than that in the control group (p < 0.001). The VAS score for pain was significantly lower in the hypertension group on arrival to PACU and during the period between 1 and 6 hours postoperatively (Table 2).

**Discussion**

This study demonstrates that pharmacologically induced mild acute intraoperative hypertension significantly reduces postoperative nalbuphine consumption and pain scores following laparoscopic ovarian cystectomy. These results confirm the

**Table 2**

<table>
<thead>
<tr>
<th>Time</th>
<th>Hypertension Group (n = 45)</th>
<th>Control Group (n = 45)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>On Arrival to PACU</td>
<td>4 (3-5)</td>
<td>5 (3-5)</td>
<td>0.002</td>
</tr>
<tr>
<td>30 min</td>
<td>3 (2-3)</td>
<td>3 (2-3)</td>
<td>0.441</td>
</tr>
<tr>
<td>1 hour</td>
<td>2 (2-3)</td>
<td>3 (2-3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>2 hours</td>
<td>1 (1-2)</td>
<td>2 (2-3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>6 hours</td>
<td>0 (0-2)</td>
<td>1 (1-2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>12 hours</td>
<td>0 (0-1)</td>
<td>0 (0-1)</td>
<td>0.075</td>
</tr>
<tr>
<td>24 hours</td>
<td>0 (0-1)</td>
<td>0 (0-1)</td>
<td>0.042</td>
</tr>
<tr>
<td>Total dose of Nalbuphine (mg)</td>
<td>28.0 (23.0-32.0)</td>
<td>43.0 (35.0-46.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PONV</td>
<td>3 (6.7%)</td>
<td>16 (35.6)</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

Data presented as median (range) or No. (%)  
PONV: postoperative nausea and vomiting
hypertension-associated hypoalgesia theory previously suggested by Ghione6.

These findings support results of a previous study by Delfino et al.21 in patients undergoing laparoscopic cholecystectomy. The authors reported significant reduction of pain scores and morphine consumption after intraoperative induction of mild hypertension. Similarly, in men recovering from radical prostatectomy, France and Katz14 have reported that postsurgical pain ratings were inversely related to resting systolic blood pressure obtained from patient records collected at the time of admission to the hospital.

Many investigators have reported lower sensitivity to pain in hypertensive patients.22-24 This phenomenon was also observed in normotensive humans under the effect of pharmacologic elevation of blood pressure25,26 or acute mechanical aortic occlusion27.

Mechanisms underlying hypertension-associated hypoalgesia remain unclear. Some studies in animals and humans suggested a role for endogenous opioids28-31. Other investigators found the same association between blood pressure and pain after pharmacological block of opioid systems7,32-34. The increased pain threshold and reduced perception of painful stimuli may be mediated by a central activity through the inhibitory descending pathways15. Noradrenergic systems might contribute to regulatory interactions between cardiovascular system and pain perception.

The results of the current study and previous studies in normotensive individuals suggest a direct effect of arterial hypertension on pain modulation. High arterial blood pressure has shown to activate high-pressure baroreceptors in the carotid sinus-aortic arch regions5,35. Consequently, pain modulatory neurons become activated and increase the pain threshold from the vasopressinergic effect in the spinal cord6,37.

We can conclude that in cases of day surgery and minimally invasive procedures like laparoscopic ovarian cystectomy, postoperative analgesia can be potentiated through induction of mild acute intraoperative hypertension without increasing opioid consumption. This can enhance more rapid discharge and regaining normal activity in these cases.

Acknowledgement

Non declared.

List of abbreviations

References

BRIDION—**for optimal neuromuscular blockade management and improved recovery**

**Predictable and complete reversal**

- 98% of BRIDION patients recovered to a TOF ratio of 0.9 from reappearance of T₁ ¹ within 5 minutes ²
- 97% of BRIDION patients recovered to a TOF ratio of 0.9 from 1 to 2 PTCs ³ within 5 minutes ²

**Rapid reversal**

- BRIDION rapidly reversed patients from reappearance of T₂ ⁴ in 1.4 minutes ²
- BRIDION rapidly reversed patients from 1 to 2 PTCs ¹ in 2.7 minutes ³

**BRIDION is indicated for the reversal of neuromuscular blockade induced by rocuronium or vecuronium. In children and adolescents (aged 2-17 years), BRIDION is only recommended for routine reversal of moderate rocuronium-induced neuromuscular blockade.**

**Important safety information**

BRIDION is not recommended in patients with severe renal impairment. Studies in patients with hepatic impairment have not been conducted and, therefore, patients with severe hepatic impairment should be treated with great caution. Caution should be exercised when administering BRIDION to pregnant women as no clinical data on exposed pregnancies are available.

BRIDION has not been investigated in patients receiving rocuronium or vecuronium in the intensive care unit (ICU) setting.

Neuromuscular blockade is required within 24 hours of BRIDION administration, a nondepolarizing neuromuscular blocking agent should be used instead of rocuronium or vecuronium. The most commonly reported adverse reactions were dysgeusia (metal or bitter taste) and anaphylactic reactions (miosis, coughing, vomiting, or urticaria on the eyelid or neck). Patients treated with BRIDION, a few cases of awareness were reported. The relation to BRIDION was uncertain. In a few individuals, allergic-like reactions (ie, flushing, erythematous rash) following BRIDION were reported. Clinicians should be prepared for the possibility of allergic reactions and take the necessary precautions. In a trial of patients with a history of pulmonary complications, bronchospasm was reported in 2 patients and a causal relationship could not be fully excluded.

Volunteer studies have demonstrated a slight (11%–22%) and transient (<36 minutes) prolongation of the prothrombin time/activated partial thromboplastin time (PT/ aPTT) with BRIDION; however, clinical studies have demonstrated no clinically relevant effect on pre- or postoperative bleeding complications with BRIDION alone or in combination with anticoagulants. As BRIDION has demonstrated an in vitro pharmacodynamic interaction with anticoagulants, caution should be exercised. In patients on anticoagulants for a pre-existing or cardiac condition. This pharmacodynamic interaction is not clinically relevant for patients receiving routine postoperative prophylactic anticoagulation. Although formal interaction studies have not been conducted, no drug interactions were observed in clinical trials. Preclinical data suggest that clinically significant drug interactions are unlikely with the possible exception of terfenadine, histamine, and hormonal contraceptives.

1* Train-of-four
2* Posttetanic count
3* Second twitch

**REFERENCES:**
1. BRIDION Summary of Product Characteristics (SPC).

Please see summary of product characteristics for full prescribing information.

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