Original Contribution

Effect of acute arterial hypertension on morphine requirements and postsurgical pain

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Abstract

Study objective: The study objective was to establish the impact of acute hypertension on morphine’s requirements after laparoscopic cholecystectomy.

Design: The design was a randomized, simple blinded study.

Setting: The settings were operating room, postoperative recovery area, and first postoperative day.

Patients: There were 50 patients, American Society of Anesthesiologists I-II, aged 18-50 years, undergoing elective laparoscopic cholecystectomy with general anesthesia.

Interventions: Anesthetic management was standardized using propofol for induction, isoflurane for bispectral index (BIS) ranging between 40 and 60, and remifentanil maintained at a constant rate of 0.4 μg kg per minute throughout surgery in all patients. Once intubated, patients were randomly allocated to 1 of 2 groups: hypertensive group: systolic arterial blood pressure was maintained with phenylephrine infusion 20%-30% over baseline; control group: systolic arterial blood pressure was maintained 20%-30% below baseline. All surgical incisions were infiltrated with bupivacaine 0.5%, and every patient received ketorolac 60 mg intravenous. Patient-controlled analgesia with morphine intravenous was used for postoperative analgesia.

Measurements: Pain visual analogue scale scores, arterial blood pressure, and hyperalgesia were assessed at recovery room every 15 minutes during the first 2 postoperative hours and then at 6, 12, and 24 postoperative hours. Cumulative morphine consumption was registered at 2 and 24 postoperative hours.

Main results: The cumulative morphine consumption in the control group was around 18 mg compared with 6 mg in the hypertensive group (P = .019). During the first 75 minutes after surgery, the control group had higher visual analogue scale score pain compared with hypertensive group (P = .005).

Conclusions: The intraoperative acute generation of mild hypertension with phenylephrine reduced postoperative morphine consumption and pain scores after laparoscopic cholecystectomy.

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1. Introduction

A strong relationship between arterial hypertension and decreased sensitivity to painful stimuli was described in animals by Dworkin et al [1] initially and later on in humans
by Zamir and Shuber [2]. This association has also been proven in experimental settings with mechanical and pharmacologic models of acute [3,4] and chronic hypertension [5-7]. Moreover, in human subjects, not only a decreased sensitivity to pain has been described in the context of chronic hypertension [8,9] but also the opposite: increased pain sensitivity associated to chronically low blood pressure has also been repeatedly demonstrated [10,11]. Finally, in normotensive subjects, there is an inverse relationship between arterial pressure and pain thresholds [10,12].

To the best of our knowledge, this subject has only been investigated in the perioperative setting by France [13]. These authors described an inverse relationship between resting systolic blood pressure (SBP) and postsurgical pain after radical prostatectomy. However, the role of acute hypertension in pain modulation has not yet been explored.

The objective of this study was to establish the impact of acute hypertension on postoperative pain perception, expressed as morphine requirements, in patients undergoing laparoscopic cholecystectomy. Our hypothesis was that the generation of pharmacologically induced mild acute hypertension in healthy subjects during surgery reduces morphine requirements after laparoscopic cholecystectomy. In addition, we were interested in investigating the effects of acute mild hypertension on pain scores and hyperalgesia.

2. Materials and methods

After institutional review board approval (School of Medicine, Pontificia Universidad Católica de Chile, reference no. 09-207) and registration at clinicaltrials.gov (NCT01897155), written, informed consent was obtained from 50 American Society of Anesthesiologists I-II patients, aged 18-50 years old, undergoing elective laparoscopic cholecystectomy under general anesthesia. Exclusion criteria were a history of chronic arterial hypertension, a baseline arterial pressure more than 139/89 mm Hg after admission to the hospital (defined as 1 blood pressure measurement taken after 30 minutes of rest in a seated position), chronic pain, drug abuse, any known cerebrovascular disease, obesity (body mass index > 30), use of any analgesic drugs and/or drugs acting on the central nervous system, known pregnancy, or known adverse effects to the study drugs.

Before patients’ arrival to the operating room, their baseline mechanical pain thresholds were established in a delimited area of 3 × 3 cm² in the right central volar forearm using von Frey monofilaments. With the patients’ eyes closed, the von Frey monofilaments were applied at a 90° angle against the skin surface for 1.5 seconds. The mechanical pain threshold was defined as the smallest force perceived as painful by the patient [14]. In the operating room and before anesthesia induction, standard monitors (noninvasive arterial pressure measure in the leg, electrocardiogram [ECG], and pulse oximeter), the bispectral index (BIS) monitor (Aspect A-2000 BIS monitor, version 3.2 XP; Aspect Medical Systems INC, Natick, MA), and a peripheral intravenous (i.v.) line in the left arm were placed. Noninvasive arterial blood pressure, heart rate, and end-tidal isoflurane were automatically registered every 3 minutes and averaged from the induction time until the end of surgery. The patients did not receive any premedication and fasted for at least 8 hours before surgery.

Anesthesia was induced using remifentanil 0.3 μg kg per minute for 3 minutes and propofol 2 mg/kg intravenously. Atracurium 0.5 mg/kg was given to facilitate orotracheal intubation. Mechanical ventilation was adjusted to maintain an end-tidal CO₂ of 30-35 mm Hg. All patients were ventilated with O₂ of 100% throughout the surgery. Anesthesia was maintained with isoflurane with a BIS value target between 40 and 60. Remifentanil was adjusted to a constant rate of 0.4 μg kg per minute throughout surgery in all patients.

Patients were randomly allocated to 1 of 2 groups, assigned by means of a table of random numbers generated by a computer: (a) Hypertension group: the systolic arterial blood pressure was maintained at 20%-30% above baseline using a phenylephrine infusion. The baseline pressure was defined as 1 blood pressure measurement taken in the preoperative setting after 30 minutes of rest in a seated position and before the patient was transported to the operating room. (b) Control group: the systolic arterial blood pressure was maintained at 20%-30% below baseline. This was reached with isoflurane for a BIS value target between 40 and 60 and remifentanil to a constant rate of 0.4 μg kg per minute. For patients whose systolic arterial blood pressure was found to be even lower than the target of 20%-30% below baseline, a phenylephrine infusion was used to raise it to target.

Patients were excluded from both groups if the respective arterial blood pressure ranges were not reached after 10 minutes from intubation, if any patient had ECG ischemia signs (ST-segment depression or elevation and/or T-wave inversion) or any arrhythmia associated with hemodynamic instability.

The anesthesiologist providing the patients’ care did not perform any further patient assessments. Local infiltration of port sites with bupivacaine 0.5% was performed at the beginning of the surgery. Every patient received ketorolac 60 mg i.v., and the intraabdominal pressure secondary to the pneumoperitoneum was 15 mm Hg.

During skin closure, neuromuscular blockade was assessed and antagonized with neostigmine and atropine when necessary. At the end of the surgery, all drugs were discontinued. Airway extubation was performed, when each patient recovered spontaneous ventilation and rejected the tracheal tube.

In the postanesthesia care unit, postoperative pain was initially treated with 3 mg morphine i.v. bolus doses administered by nurses. When the visual analogue scale (VAS) (0, no pain; 10, worst possible pain) was ≤ 4, a morphine patient-controlled analgesia was started (no basal rate infusion, bolus of 1.0 mg, and an 8-minute lockout interval). Ketonolac 30 mg i.v. was administered every 8 hours. No other analgesic drugs were administered.
Pain VAS scores were measured in the postanesthesia care unit every 15 minutes during the first 2 postoperative hours. Thereafter, VAS and mechanical pain thresholds were assessed at 2, 6, 12, and 24 postoperative hours. Cumulative morphine consumption was registered at 2 and 24 postoperative hours.

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

3. Statistical analysis

Using an SD of 4.7 mg [15], a sample size of 22 patients per group was estimated to be needed to detect a minimum difference of 4 mg in postoperative morphine consumption with a power of 80% and an \( \alpha \) level of .05. We enrolled 25 patients per arm to allow for possible dropouts.

We tested normality using the Shapiro-Wilk test and Q-Q plots. Demographic and intraoperative continuous data were compared using unpaired Student t test or Wilcoxon rank sum test as appropriate. Pearson \( \chi^2 \) test or Fisher exact test was used for inferences on proportions. A mixed model for repeated-measures variance analysis implemented with SAS Proc Mixed (SAS Institute Inc, Cary, NC) was used to compare postoperative cumulative morphine consumption, VAS score, and von Frey measurement over time (adjusted for baseline value). We chose the best model based on Akaike’s Information Criterion [16]. In the presence of a significant interaction term or main effect, Bonferroni adjustment for multiple comparisons post hoc analyses was used. Data are expressed as mean (SD) or mean plus bootstrap 95% confidence interval (95% BCI, based on 2000 replications with replacement and Bias corrected and accelerated (BCa) correction) unless otherwise stated. A 2-sided \( P \) value less than .05 was considered significant. Analyses were performed using SAS 9.2 (SAS Institute Inc) and verified using STATA.

4. Results

A total of 50 patients were enrolled in this study. All subjects received their assigned study treatment. No patients were excluded after enrolment, and no patients were lost to follow-up (Fig. 1). Both groups were similar with respect to patient baseline characteristics (Table 1), anesthesia, and postoperative care data (Table 2). All patients reached the target SBP within 10 minutes after intubation. No patients presented ECG changes suggestive of ischemia (ST-segment depression or elevation and/or T-wave inversion) or arrhythmia associated with hemodynamic instability. The mean percentage change in SBP from baseline was 24.7% (95% BCI, 23.6, 26.3) and −24.7% (95% BCI, −26.0, −23.7) for the hypertensive and control group, respectively (\( P \) value < .001, Table 2). During the first 24 postoperative hours, the hemodynamic parameters (SBP, diastolic blood pressure, and heart rate) remained stable and were not different between groups (\( P = .879 \)).

The time course of the postoperative cumulative morphine consumption is shown in Fig. 2. Based on the analysis, the “group × time” interaction was statistically significant (\( P \) value = .019), indicating that the effect of “group (hypertensive vs control)” was not the same across all levels of “time (repeated measures).” The adjusted post hoc analysis showed that, during the first 2 postoperative hours, the difference was not significant but became statistically significant 24 hours after surgery.

The evolution of the VAS score is shown in Fig. 3. The “group × time” interaction was significant (\( P \) value = .006).

Baseline pain thresholds to mechanical stimuli were similar in both groups with mean values of 127.1 g (95% BCI: 90.7, 172.2) in the hypertensive group and 161.0 g (95% BCI: 119.1, 207.7) in the control group (\( P \) value = .277). In the analysis of mechanical pain threshold values, the interaction “group × time” and the main effect “group” were not significant (\( P \) value = .627 and .862, respectively). Within the main effect, “time” was found to be statistically significant (\( P \) value < .001), and the Bonferroni adjustment for multiple comparisons showed that the threshold values decreased significantly during the period 6-12 hours postsurgery, returning to baseline values 24 hours postsurgery (Fig. 4).

5. Discussion

We found that pharmacologically induced mild acute intraoperative hypertension significantly reduced postoperative morphine requirements and pain scores after elective laparoscopic cholecystectomies. In addition, the anesthetic technique used produced acute postoperative hyperalgesia in both groups.

Our study demonstrates the effect of pharmacologically induced mild acute intraoperative hypertension on postoperative analgesia and morphine consumption. These results confirmed the hypothesis that mild intraoperative hypertension was associated with a reduction in pain scores and postoperative morphine consumption when compared with the control group. In accordance with our results, France [13] reported that men with elevated presurgical SBP experienced less postoperative pain after radical prostatectomy; nevertheless, they did not find any difference in postoperative morphine requirements. Our results also agree with previous studies in rats, where acute generation of arterial hypertension increased...
pain thresholds [1,3,4]. In human patients, a strong association between hypertension and decreased pain sensitivity has been reported by different groups [8,17-19] or even with the effects of pharmacologic blood pressure elevation on pain experience [20-22]. In healthy subjects, SBPs at the upper normal limit have also been associated with higher pain thresholds [12].

From our protocol design, it is not possible to distinguish whether the reduction in morphine requirements and pain scores during the postoperative period are due to intraoperative hypertension or by a direct central analgesic effect of phenylephrine.

It has been reported that phenylephrine can stimulate the release of vasopressin in the central nervous system, which might produce an effect on pain modulation [4]. Based on the results of previous studies, which showed that arterial hypertension induced by either administration of phenylephrine or acute mechanical aortic occlusion produced the same increase in pain thresholds [3,4], it is reasonable to speculate that a direct effect of arterial hypertension on pain modulation can probably explain the observed results. On the other hand, it has been demonstrated a central analgesic effect due to the direct action on alpha-2 receptor by clonidine and dexmedetomidine; however, the action of these drugs produces hypotension [23,24], which could reinforce the pain modulation theory by arterial hypertension.

High arterial blood pressure has shown to produce the activation of high-pressure baroreceptors in the carotid sinus-aortic arch regions [1,25]. As a consequence, pain modulatory neurons, particularly those in the nucleus tractus solitaries and the paraventricular hypothalamus, become activated increasing pain threshold from the vasopressinergic

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Baseline characteristics</th>
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<tbody>
<tr>
<td></td>
<td>Group 1</td>
</tr>
<tr>
<td></td>
<td>(hypertension)</td>
</tr>
<tr>
<td>n = 25</td>
<td>n = 25</td>
</tr>
<tr>
<td>Male/female (n)</td>
<td>8/17</td>
</tr>
<tr>
<td>Age (y)</td>
<td>39 (11)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>69 (14)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>164 (9)</td>
</tr>
<tr>
<td>ASA I/II (n)</td>
<td>17/8</td>
</tr>
<tr>
<td>Baseline SBP (mm Hg)</td>
<td>117 (8)</td>
</tr>
<tr>
<td>Baseline DBP (mm Hg)</td>
<td>70 (8)</td>
</tr>
<tr>
<td>Baseline MAP (mm Hg)</td>
<td>83 (11)</td>
</tr>
<tr>
<td>Baseline HR (bpm)</td>
<td>76 (13)</td>
</tr>
</tbody>
</table>

Abbreviations: ASA, American Society of Anesthesiologists; DBP, diastolic blood pressure; MAP, mean arterial pressure; HR, heart rate.

* Values are mean (SD).
effect in the spinal cord [17,26]. Specifically, the experimental stimulation of the nucleus of the solitary tract has a significant antinociceptive effect [27]. This effect is mediated by direct projections to other areas, such as the periaqueductal gray, the nucleus raphe magnus, and the locus coeruleus [28,29]. Other indirect projections from the nucleus of the solitary tract through the thalamus and hypothalamus to the insula, the anterior cingulate, and the somatosensory cortex could also have a further role [29,30].

Acute administration of opioids during the intraoperative period may paradoxically activate \( N \)-methyl-D-aspartate proprioceptive system, leading to postoperative opioid-induced hyperalgesia [31]. The relative high remifentanil infusion scheme used in our study, which is 4 times higher than the reported to produced opioid-induced hyperalgesia in healthy volunteers [32,33], is the most probable explanation for the observed decrease in postoperative pain thresholds in both groups.

Because hyperalgesia was similarly observed in both groups and no evident difference in its magnitude or duration was observed between groups, it is possible to rule out an antihyperalgesic effect of hypertension as a possible mechanism involved in the observed analgesic effect. The administration of ketorolac to all our patients should also be considered in the analysis. There is evidence that the use of nonsteroidal antiinflammatory drugs reduces postoperative hyperalgesia [34,35]; therefore, even when hyperalgesia was present in both groups, the magnitude of this phenomenon was probably decreased by ketorolac administration.

The implications of our results for anesthesia management are not clear yet. It is plausible to argue that the objective arterial blood pressure range for anesthesia maintenance should be reanalyzed. However, it is our opinion that future studies confirming the efficacy and safety of mild intraoperative hypertension as a valid strategy to reduce postoperative

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Table 2  Anesthetic characteristics, hemodynamic parameters, and postoperative care data

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (hypertensive)</th>
<th>Group 2 (control)</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of anesthesia (min) ( ^a )</td>
<td>92.1 (24.6)</td>
<td>87.8 (16.7)</td>
<td>.48</td>
</tr>
<tr>
<td>Duration of surgery (min) ( ^a )</td>
<td>64.8 (25.1)</td>
<td>60.3 (15.2)</td>
<td>.45</td>
</tr>
<tr>
<td>Lactated Ringer solution (mL/kg/h) ( ^a )</td>
<td>5.9 (1.0)</td>
<td>5.5 (0.5)</td>
<td>.10</td>
</tr>
<tr>
<td>Phenylephrine, total dose (( \mu )g/kg) ( ^b )</td>
<td>61.9 (54.5, 70.3)</td>
<td>8.9 (5.8, 14.1)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Isoflurane dose ( ^a )</td>
<td>0.67 (0.15)</td>
<td>0.68 (0.18)</td>
<td>.81</td>
</tr>
<tr>
<td>Change SBP from baseline (%) ( ^b )</td>
<td>24.7 (23.6, 26.3)</td>
<td>-24.7 (-26.0, -23.7)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Change DBP from baseline (%) ( ^b )</td>
<td>20.8 (16.2, 26.0)</td>
<td>-26.2 (-30.0, -22.2)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Change MAP from baseline (%) ( ^b )</td>
<td>21.5 (17.2, 26.1)</td>
<td>-28.1 (-31.4, -24.5)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Change HR from baseline (%) ( ^b )</td>
<td>-21 (-27.0, -13.7)</td>
<td>-23.7 (-26.6, -20.3)</td>
<td>.97</td>
</tr>
<tr>
<td>Extubation time (/min)</td>
<td>10.6 (3.7)</td>
<td>9.0 (2.6)</td>
<td>.08</td>
</tr>
<tr>
<td>PONV (n)</td>
<td>10</td>
<td>9</td>
<td>.77</td>
</tr>
</tbody>
</table>

Abbreviation: PONV, postoperative nausea and vomiting.
\( ^a \) Values are mean (SD).
\( ^b \) Values are mean (95% BCI).

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Fig. 2  Postoperative cumulative morphine consumption. Values are presented as mean (95% bCI). The interaction “group × time” was significant (\( P \) value = .019). *\( P \) value < .05 after Bonferroni adjustment for multiple comparisons.
pain are needed before any recommendation can be given. In the meantime, our results suggest that studies assessing postoperative pain should better report intraoperative arterial blood pressure management in their protocols’ designs.

One limitation of our study is that we did not control for family history of hypertension. Some studies have reported a significant reduction in pain sensitivity in otherwise healthy people with a familiar history of hypertension [36-39]. The potential confounding effect of this factor should be considered but is probably minimized from the random allocation of patients to both groups.

Studies analyzing the influence of sex on the relationship between hypertension and hyperalgesia have shown conflicting results [40]. Because in our study patient of both sexes was evenly distributed in both groups, a potential confounding effect of this variable is most probably negligible. We did not explore the effect of this variable on postoperative pain and morphine consumption because our study was not powered enough to for this type of analysis.

In conclusion, the intraoperative acute generation of mild hypertension with phenylephrine significantly reduced postoperative morphine consumption and pain scores after laparoscopic cholecystectomy. Although our results suggest that mild hypertension might be a novel strategy to reduce postoperative pain, more studies are needed to support our findings.

References


