

# Evaluation of postoperative analgesia with intraperitoneal ropivacaine instillation in videolaparoscopic cholecystectomy

## *Avaliação da analgesia pós-operatória com instilação de ropivacaína intraperitoneal em colecistectomia videolaparoscópica*

Thiago Lucena César de Albuquerque<sup>1</sup>, Monique Ferro Bezerra<sup>1</sup>, Cíntia Cibelly Paz Zuzu Schots<sup>1</sup>, Ana Karla Arraes Von Sohsten<sup>2</sup>, Jane Auxiliadora Amorim<sup>2</sup>, Otávio Damázio Filho<sup>2</sup>

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### ABSTRACT

**BACKGROUND AND OBJECTIVES:** This study aimed at evaluating postoperative analgesia with ropivacaine instillation inside the peritoneal cavity in videolaparoscopic cholecystectomy.

**METHODS:** This is a randomized clinical trial with 60 patients. The intervention group (RP, n = 30) received 0.5% ropivacaine instillation in right and left subdiaphragmatic regions and in gallbladder bed in equal volumes of 10 mL. The control group (SS, n = 30) received 0.9% saline solution instillation. Patients of both groups received multimodal analgesia. Scores of abdominal pain and referred pain in shoulder were evaluated at emergence and after 1, 2, 4, 12 and 24 hours, in addition to the need for rescue analgesia, opioid consumption and adverse events, considering statistically significant  $p < 0.05$ .

**RESULTS:** There has been no statistical difference between groups with regard to demographic data and anesthetic-surgical time. The intervention group had lower and statistically significant pain scores as compared to control group at emergence ( $p = 0.001$ ), 1 ( $p = 0.019$ ) and 2 ( $p = 0.04$ ) postoperative hours, in addition to lower opioid consumption at emergence ( $p = 0.022$ ) and in total in the first 24 hours ( $p = 0.001$ ). Time for first request for rescue analgesia was longer in the intervention group ( $p = 0.001$ ).

**CONCLUSION:** Ropivacaine instillation inside the peritoneal cavity has decreased pain scores in the first 2 hours and postoperative opioid consumption.

**Keywords:** Analgesia, Laparoscopic cholecystectomy, Local anesthetics, Postoperative pain, Ropivacaine.

### RESUMO

**JUSTIFICATIVA E OBJETIVOS:** O objetivo deste estudo foi avaliar a analgesia pós-operatória com instilação de solução de ropivacaína dentro da cavidade peritoneal em colecistectomia videolaparoscópica.

**MÉTODOS:** Trata-se de um ensaio clínico randomizado com 60 pacientes. No grupo intervenção (RP, n=30) foi realizada instilação de solução de ropivacaína a 0,5% nas regiões subdiaphragmáticas direita e esquerda e no leito da vesícula biliar em iguais volumes de 10 mL. No grupo controle (SF, n=30) foi realizada instilação de solução fisiológica a 0,9%. Os pacientes de ambos os grupos receberam analgesia multimodal. No período pós-operatório foram avaliados os escores de dor abdominal e referida no ombro ao despertar e após 1, 2, 4, 6, 12 e 24 horas, além da necessidade de analgesia de resgate, consumo de opioide e eventos adversos. Foi considerado estatisticamente significativo o valor de  $p < 0,05$ .

**RESULTADOS:** Não houve diferença estatística entre os grupos em relação a dados demográficos e tempo anestésico-cirúrgico. O grupo intervenção apresentou escores de dor menores e estatisticamente significativos comparado ao grupo controle ao despertar ( $p = 0,001$ ), com 1 hora ( $p = 0,019$ ) e 2 horas ( $p = 0,04$ ) de pós-operatório, bem como menor consumo de opioide ao despertar ( $p = 0,022$ ) e no total nas primeiras 24 horas ( $p = 0,001$ ). O tempo para necessidade da primeira analgesia de resgate foi maior no grupo intervenção ( $p = 0,001$ ).

**CONCLUSÃO:** A instilação de ropivacaína dentro da cavidade peritoneal reduziu os escores de dor nas primeiras duas horas e o consumo de opioide no pós-operatório.

**Descritores:** Analgesia, Anestésicos locais, Colecistectomia laparoscópica, Dor pós-operatória, Ropivacaína.

### INTRODUCTION

Videolaparoscopic cholecystectomy (VC) is the golden standard for gallbladder removal and the laparoscopic procedure more performed worldwide<sup>1</sup>. According to Datasus, 58,663 surgeries were performed in Brazil in 2014<sup>2</sup>.

For being a minimally invasive procedure, laparoscopy induces the wrong perception that it is also minimally painful; however pain has been mentioned as major complaint and a reason for delayed postoperative recovery.

Post-VC pain has three components: incisional, visceral and

1. Universidade de Pernambuco, Recife, PE, Brasil.

2. Hospital da Restauração, Hospital Getúlio Vargas, Hospital Universitário Oswaldo Cruz, Recife, PE, Brasil.

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#### Correspondence to:

Rua Arnóbio Marques, 310 - Santo Amaro

50100-130 Recife, PE, Brasil.

E-mail: moniqueferro@msn.com

referred, the latter in general in the shoulder<sup>3</sup>. In addition to discomfort and postoperative physiological repercussions, such as respiratory restriction, tachycardia and hypertension, pain delays early ambulation and hospital discharge<sup>4,5</sup>.

Multimodal analgesia has been used to minimize post-VC pain, including the perioperative use of non-steroid anti-inflammatory drugs (NSAIDs), opioids, N-methyl D-aspartate receptor inhibitors (NMDA), anticonvulsants and local anesthetic infiltration in the surgical wound. In this context, intraperitoneal ropivacaine instillation has been suggested by some authors as a feasible and easy resource to control post-videolaparoscopic cholecystectomy pain<sup>6-9</sup>.

This study aimed at evaluating postoperative analgesia with intraperitoneal ropivacaine instillation for VC.

## METHODS

Participated in this analytical, randomized and double-blind study 60 patients of both genders, aged 18 years or above, physical status ASA I, II and III, according to the American Society of Anesthesiology, submitted to elective VC under balanced general anesthesia in the *Hospital Universitário Oswaldo Cruz* (HUOC), Recife, PE, between July and September 2015. Exclusion criteria were patients weighing less than 50kg, with acute pancreatitis, preoperative abdominal or shoulder pain, being treated for chronic pain, in antiepileptic therapy, alcohol or drug addicts, with liver or kidney dysfunction, allergy or sensitivity to drugs used in this study, cognitive deficiency, pregnant or breastfeeding women and when the surgical technique had to be changed to conventional.

During preanesthetic evaluation and after signing the Free and Informed Consent Term (FICT), patients were divided in two groups of 30 individuals: Group RP (intervention), who received intraperitoneal instillation of 30mL of 0.5% ropivacaine, and Group SS (control) who received 30mL of 0.9% saline solution. This was a convenience sample, considering the approximate number of available patients in the service in one time unit. We decided to use a minimum of 30 patients per group to allow the use of parametric tests.

All patients had venous access assured with 18G or 20G catheter, were hydrated with crystalloid solution with volume defined at the anesthesiologist's judgment, were monitored with cardioscope, pulse oximeter, noninvasive blood pressure and capnograph and were sedated with intravenous midazolam (0.04mg/kg). After pre-oxygenation, anesthesia was induced with intravenous remifentanyl (0,3µg/kg/min), lidocaine (1.5mg/kg), propofol (2mg/kg) and rocuronium (0.6mg/kg). All patients received parecoxib (40mg) and cefazolin (2g) before surgical incision. To prevent nausea and vomiting, patients have received dexamethasone (4mg) after anesthetic induction and ondansetron (8mg) at surgery completion.

Anesthesia was maintained with 1.5-2.5 CAM sevoflurane and remifentanyl (0.1 to 0.3µg/kg/min). Ventilation was controlled and  $P_{ET}CO_2$  levels were maintained between 30 and 40 mmHg. In the beginning of the surgical procedure, all patients received infiltration of 20mL of 0.25% ropivacaine

at trocars insertion site, being 6mL in the umbilical incision, 6mL in the epigastric incision and 4mL in both working portals. Surgery was performed by the technique consisting in the umbilical insertion of a 10mm trocar in the epigastric region and two 5mm trocars in the right abdomen. Pneumoperitoneum was assured with non-moistened and non-heated  $CO_2$ , maintaining abdominal pressure between 12 and 14 mmHg. After gallbladder resection, however before its removal from the abdominal cavity, 0.5% ropivacaine (group RP) or 0.9% saline solution (group SS) were instilled inside the peritoneum in three volumes of 10mL each in a total of 30mL. First instillation was administered in right subdiaphragmatic region, the second in the gallbladder bed and the third in left subdiaphragmatic region. Patients remained in Trendelenburg position for 5 minutes after instillation.

All patients received dipirone (30mg/kg) immediately after gallbladder removal from its anatomic bed and at surgery completion residual neuromuscular block was reverted with intravenous neostigmine (0.04mg/kg) and atropine (0.02mg/kg). Patients were referred to the post-anesthetic recovery unit (PACU) and afterward to the general surgery ward. Pain intensity was evaluated with the visual analog scale (VAS) at anesthetic emergence and at 1, 2, 4, 6, 12 and 24 postoperative hours, where zero meant no pain and 10 "the worst pain" felt by the patient.

Postoperative analgesia was maintained with dipirone (30mg/kg) every 6h and ketoprofen (100mg) every 12 hours, both by venous route, in the first 24 hours, due to easy availability of these drugs in the surgical ward. Patients referring abdominal or shoulder pain with VAS score equal to or higher than 4 in the PACU received intravenous morphine until reaching VAS equal to or less than 3, and in the ward, they received intravenous tramadol. In this period, nausea, vomiting, dizziness, signs and symptoms of acute intoxication by local anesthetics were looked for.

## Statistical analysis

Parametric and non-parametric tests were used for statistical analysis according to necessary model assumptions. ANOVA analysis of parametric variance, non-parametric Kruskal-Wallis analysis of variance and Friedman non-parametric analysis of variance for corresponding data were used. Chi-square and Fisher Exact tests were used for independence tests between pairs of randomized variables, considering statistically significant  $p < 0.05$ .

This study was approved by the institution's Ethics Committee (CAAE: 45524115.7.0000.5192) and complied with ethic criteria of the Declaration of Helsinki (2008).

## RESULTS

Sample was made up of 60 patients. There were no statistically significant differences between groups with regard to gender, age, physical status (ASA) and surgical time (Table 1). Patients' age has varied from 23 to 75 years, being 86.7% females and 98% ASA I and II. Surgical time has varied from 49.8 to 119.7 minutes.

**Table 1.** Clinical characteristics of sample and surgical time

	Group SS (n=30)	Group RP (n=30)	p value
Age (years)*	42.5±13.9	48.9±14.5	0.086 <sup>†</sup>
Gender (n)			
Female	24	28	0.254 <sup>†</sup>
Male	6	2	
Physical status (n)			
ASA I	17	19	0.598 <sup>†</sup>
ASA II	12	11	0.266 <sup>†</sup>
ASA III	1	0	
Surgical time (min)*	87.7 ± 32	78.8 ± 29	

ASA = American Society of Anesthesiology, Group SS = 0.9% saline solution; Group RP = ropivacaine. \*Values in mean± standard deviation; n=number; † = Student t test; ‡ = Fisher Exact test.

At abdominal pain evaluation, lower and statistically significant pain scores were found in the group RP at emergence (2.33 ± 2.97 vs. Group SS 4.83±3.10; p=0.001), in the first hour (2.70±2.26 vs. Group SS 3.77±1.56; p=0.019) and in the second hour (1.47±1.61 vs. Group SS 2.53±1.33; p=0.004). There were no statistically significant differences between groups in pain scores evaluated at 4, 6, 12 and 24 postoperative hours (Table 2).

**Table 2.** Abdominal pain scores in the first 24 postoperative hours

Time (hour)	Group SS (n=30)	Group RP (n=30)	p value*
Emergence	4.83±3.10	2.33±2.97	0.001
1h	3.77±1.56	2.70±2.26	0.019
2h	2.53±1.33	1.47±1.61	0.004
4h	1.47±1.67	0.93±1.25	0.084
6h	0.97±1.77	0.47±0.86	0.085
12h	0.33±1.32	0.30±0.59	0.450
24h	0.40±1.30	0.23±0.62	0.265

Group SS = 0.9% saline solutions; Group RP = ropivacaine. Values in mean ±standard deviation; n = number of patients; \* Student t test.

Six group RP patients have referred shoulder pain until the second postoperative hour, while 10 group SS patients had this complaint, among them seven in the 2<sup>nd</sup> hour, 2 in the 4<sup>th</sup> hour and just one in the 24<sup>th</sup> hour. Referred shoulder pain was more frequent in the first two postoperative hours without significant difference between groups (Table 3). For the analysis of 4, 6, 12 and 24 hours after emergence, because values of one group were equal zero, it was not possible to test equality of variances or means.

**Table 3.** Referred shoulder pain scores in the first two postoperative hours

Time (hour)	Group SS (n=30)	Group RP (n=30)	p value*
Emergence	0.30±1.64	0.30±1.64	0.500
1h	0.47±1.61	0.20±0.76	0.208
2h	0.37±1.25	0.17±0.53	0.211

Group SS = 0.9% saline solutions; Group RP = ropivacaine. Values in mean ±standard deviation; n = number of patients; \* Student t test.

Opioid consumption was higher and statistically significant for the Group SS in two moments: at emergence (0.0540±0.03 vs group RP 0.0304±0.05; p=0.022) and when total consumption was calculated for 24 postoperative hours (0.0639±0.04 vs group RP 0.0301±0.04; p=0.001). There has been no opioid consumption after the 4<sup>th</sup> postoperative hour for both groups (Table 4).

**Table 4.** Opioid consumption (mg/kg) in the first two postoperative hours

Time (hour)	Group SS (n=30)	Group RP (n=30)	p value
Emergence	0.0540±0.03	0.0304±0.05	0.022*
1h	0.0127±0.02	0.0077±0.01	0.171*
2h	0.0006	0.0000	- †
Consumo total	0.0639±0.04	0.0301±0.04	0.001*

Group SS = 0.9% saline solution; Group RP = ropivacaine. Values in mean±standard deviation; n = number of patients; \* Student t test; † = because one group had values equal zero, it was not possible to test equality of variances or equality of means.

Rescue analgesia was less requested by the group RP (15 patients vs SS 25 patients; p=0.006). In addition, mean time in minutes for the first rescue analgesia was shorter for group SS (7.32±9.34 min vs RP 23.67±20.66 min; p=0.0001).

With regard to postoperative adverse events, there has been no dependence association between having received ropivacaine instillation and the incidence of nausea and vomiting (p=1.000) or of dizziness (p=0.670). There have been no cases with symptoms of tongue numbness, perioral paresthesia, visual blur, tinnitus or seizure in both groups. Surgery time had no linear correlation with any other variable evaluated in this study. So, surgical time has not influenced the evaluation of postoperative pain, opioid consumption or adverse events

## DISCUSSION

Our results confirm literature findings about analgesic effects of intraperitoneal ropivacaine instillation in VC surgeries<sup>6-8,10,11</sup>. In our study, patients receiving intraperitoneal 150mg of 0.5% ropivacaine at surgery completion, had significant decrease in abdominal pain scores up to two postoperative hours and time for first rescue analgesia was longer as compared to patients receiving 0.9% saline solution instillation. Moreover, total morphine consumption and morphine consumption at emergence were lower for group RP. For remaining evaluations, there has been no significant difference between groups in pain scores and morphine consumption. Kucuk et al.<sup>10</sup> have evaluated 80 patients and compared intraperitoneal instillation of bupivacaine (100mg at 0.5%), ropivacaine (100mg at 0.5% and 150mg at 0.75%), both with epinephrine, and saline solution. Similarly to our study, solution was instilled in right and left subdiaphragmatic spaces and in gallbladder bed at surgery completion. Morphine consumption in the first 24 hours, administered by patient-controlled analgesia (PCA), was significantly higher in the group SS. Lowest pain score was observed in the group RP receiving

150mg of 0.75% ropivacaine.

These authors have obtained morphine consumption decrease in all time intervals evaluated in the first 24h, while in our study there has been decrease only at emergence and in total consumption. This difference might be due to several factors present in the study<sup>10</sup>, among them the use of epinephrine which might have delayed local anesthetic absorption; the different multimodal analgesia (fentanyl at anesthetic induction and sodium diclofenac after intubation) and opioid administration via PCA. PCA is the ideal method to adequately administer opioids and measure their consumption, as compared to the administration of analgesics according to demand by a trained team, as performed in our study.

Cha et al.<sup>6</sup> have studied visceral, parietal and referred shoulder pain in VC in 80 patients comparing surgical incision infiltration and intraperitoneal ropivacaine nebulization to the administration of the same volume of saline solution. Visceral pain was significantly lower in the groups receiving intraperitoneal ropivacaine, with additive effect to the surgical wound infiltration, and have decreased abdominal pain scores in up to 8 postoperative hours. Differently from our study, preemptive ropivacaine nebulization at beginning of procedure may justify the longer postoperative pain scores reduction period. Pappas-Gogos et al.<sup>8</sup> in a study with 120 patients, have compared ropivacaine (40mL at 0.2%) instillation and saline solution instillation at VC beginning and completion. Similarly to Cha et al.<sup>6</sup>, these authors have observed that local anesthetic instillation in the beginning of cholecystectomy was able to decrease pain scores in up to 48 postoperative hours as compared to instillation at procedure completion. So, in our study, ropivacaine instillation at surgery completion may be seen as a factor responsible for pain scores reduction only until the 2<sup>nd</sup> postoperative hour.

Among pain components in this type of surgery, visceral pain is often mentioned as the most severe and the peak of highest discomfort is especially referred in the first two hours after emergence<sup>6,7,11</sup>. Intraperitoneal ropivacaine instillation seems to be a promising method within the multimodal context of analgesia for VC procedures, however, new studies may clarify the ideal moment to instill this local anesthetic drug and time of postoperative analgesia obtained with this method. In our study, instillation at procedure completion has not interfered with surgical time and was a simple, fast and safe method to decrease pain in the period it is referred as more severe. Limitations of this study may be variation among pain scores

examiners, administration technique of postoperative rescue opioids and the lack of measurement of ropivacaine plasma concentration, although no adverse effects were reported.

## CONCLUSION

Intraperitoneal ropivacaine instillation at elective videolaparoscopy cholecystectomy completion as compared to saline solution instillation, has significantly decreased abdominal pain scores and morphine consumption in the first postoperative hours, in addition to delaying the request for first rescue analgesia, without evidences of adverse effects. So, it is a safe and easy practice to provide further comfort to patients in the period where the incidence of postoperative visceral pain is higher.

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