



ORIGINAL INVESTIGATION

Comparison between intravenous and intrathecal clonidine for postoperative analgesia of patients submitted to laparoscopic cholecystectomy: randomized clinical trial

Christiane Rodrigues da Silva ^{a,*}, Cinthya Iamile Fritzz Brandão de Oliveira^{b,c},
Juscimar Carneiro Nunes^{c,d,e}

^a Hospital Universitário Getúlio Vargas (HUGV), Programa de Pós-Graduação em Cirurgia (PPGRACI), Manaus, AM, Brazil

^b Universidade Federal do Amazonas, Instituto de Ciências Biológicas, Departamento de Farmacologia, Manaus, AM, Brazil

^c Universidade Federal do Amazonas, Programa de Pós-Graduação em Cirurgia (PPGRACI), Manaus, AM, Brazil

^d Universidade Federal do Amazonas (UFAM), Faculdade de Medicina, Anestesiologia, Manaus, AM, Brazil

^e Universidade do Estado do Amazonas (UEA), Manaus, AM, Brazil

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Abstract

Introduction and objectives: Alpha2 adrenergic agonists, such as clonidine, are used as adjuvants during anesthesia due to their analgesic, sedative, and cardiovascular effects. The objective of the present study was to compare the effect of clonidine administered intravenously and intrathecally on the postoperative pain score of patients undergoing laparoscopic cholecystectomy, according to the route of administration and postoperative opioid consumption.

Methods: This randomized clinical trial, blind to patients and evaluator, assessed 60 patients, candidates for elective laparoscopic cholecystectomy under standardized general anesthesia techniques. Patients were randomly allocated into three groups (20 in each group): Control Group (CG), Intrathecal Clonidine Group (ITCG), and Intravenous Clonidine Group (IVCG). The primary outcome was the comparison of pain, Blood Pressure (BP) and Heart Rate (HR) scores among groups. The secondary outcome was report of adverse effects such as bradycardia, hypotension and sedation, and the need for rescue medication.

Results: The mean age was 37.2 ± 8.2 years, and the mean body mass was 28.3 ± 3.6 kg.m⁻². Regarding HR ($p = 0.003$) and pain ($p = 0.027$), patients in ITCG and CG showed a different profile over time, with CG showing higher consumption of morphine as rescue medication ($p = 0.005$).

* Corresponding author.

E-mail: christianesilva.hugv@ebserh.gov.br (C.R. Silva).

Conclusion: The administration of intrathecal and intravenous clonidine in low doses can reduce hemodynamic parameters and decrease postoperative requirement of analgesics. Further studies should investigate the ideal dose and method.

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Introduction

Cholelithiasis affects approximately 10% of the general population and acute cholecystitis is its most frequent complication occurring in 15% to 26% of cases.¹ The laparoscopic approach provides minimally invasive surgery benefits but promotes pathophysiological changes which can challenge anesthesia and postoperative pain management treatment,¹⁻³ with a risk of postoperative pain similar to open surgery.^{4,5}

Postoperative pain can be divided into parietal, visceral and referred shoulder pain that results from diaphragmatic stimulation by Carbon Dioxide (CO₂) in the abdomen and irritation of the phrenic nerve,^{6,7} that delays patient recovery, extends hospitalization, and increases morbidity and costs.^{5,8} The pain reaches its maximum intensity in the initial 4–12 hours and declines in 2–6 days.⁴

Multimodal analgesia, with the association of adjuvants, seeks to reduce postoperative pain, opioid requirements and adverse effects.^{9,10} Using α_2 adrenergic agonist drugs, such as clonidine, provides analgesia and sedation, and is associated with greater intra and postoperative hemodynamic stability.¹¹⁻¹³

The present study assessed the effect of intravenous and intrathecal clonidine on the postoperative pain score of patients submitted to laparoscopic cholecystectomy at Hospital Universitário Getúlio Vargas/Federal University of Amazonas (HUGV/UFAM), as a function of the route of administration and analgesia requirements postoperatively.

Methods

Ethical aspects

The study was approved by the Ethics Committee of the Universidade Federal do Amazonas/UFAM (CAAE: 70099417.7.0000.5020, resolution nº2.146429) on June 29, 2017, and the informed consent was obtained from participants (Resolution 466/2012).¹⁴ The study followed CONSORT guidelines and was registered at the Brazilian Registry of Clinical Trials (ReBEC) ([http://www.ensaiosclinicos.gov.br/rg/RBR-33vyhm/v1/](http://www ensaiosclinicos.gov.br/rg/RBR-33vyhm/v1/)).

Eligibility criteria

We included in the study patients to be submitted to elective laparoscopic cholecystectomy, from both genders, between 18 and 50 years of age, presenting BMI < 35 kg.m⁻², and with physical status classification I or II according to the American Society of Anesthesiologists (ASA).¹⁵

Exclusion criteria

We excluded from the study pregnant patients, breastfeeding patients, patients from the indigenous population or patients with difficulty to understand the Visual Analogue Scale (VAS) and the Faces Pain Scale (FPS),^{16,17} that were used for collecting data.

Variables assessed

The primary outcome was measurement of pre- and postoperative pain scores, Blood Pressure (BP) and Heart Rate (HR), and the secondary outcome was the occurrence of adverse effects and the requirement for rescue medication.

Statistical analysis

The sample of the study was calculated pondering the frequency of patients in the hospital, the margin of error of 0.05 (α) and power of 80%. A total of 60 patients was estimated for the final analysis, and they were allocated into three blocks of 20 patients. The normal distribution of data was checked by the Kolmogorov Smirnov test and the variables were described according to their distribution, by absolute and relative values. Quantitative variables were compared using ANOVA, Kruskal Wallis and Mann-Whitney tests. Pearson's Chi-square and Fischer's Exact tests were used for analyzing the association among categorical variables, and the Spearman test for correlations. The Generalized Estimation Equations model and post hoc Minimal Significant Difference test ($p < 0.05$) were used to compare variables (primary outcome) among groups over time.

Design and participants

A phase IV randomized, single center, patient- and evaluator-blinded, factorial, and with 1:1 allocation rate clinical trial was performed with patients submitted to laparoscopic cholecystectomy from October 2, 2017 to March 7, 2018, at HUGV/UFAM, Manaus – AM (tertiary center).

Procedures

Patients were instructed on VAS and FPS in the preoperative period. They were allocated by a drawing procedure, that used opaque, sealed, and 1 to 60 sequentially numbered envelopes, into three blocks (with 20 possibilities of being drawn), by a collaborator that was blind regarding the sequence envelopes, and responsible for collecting data in the postoperative period. The anesthesiologist received the

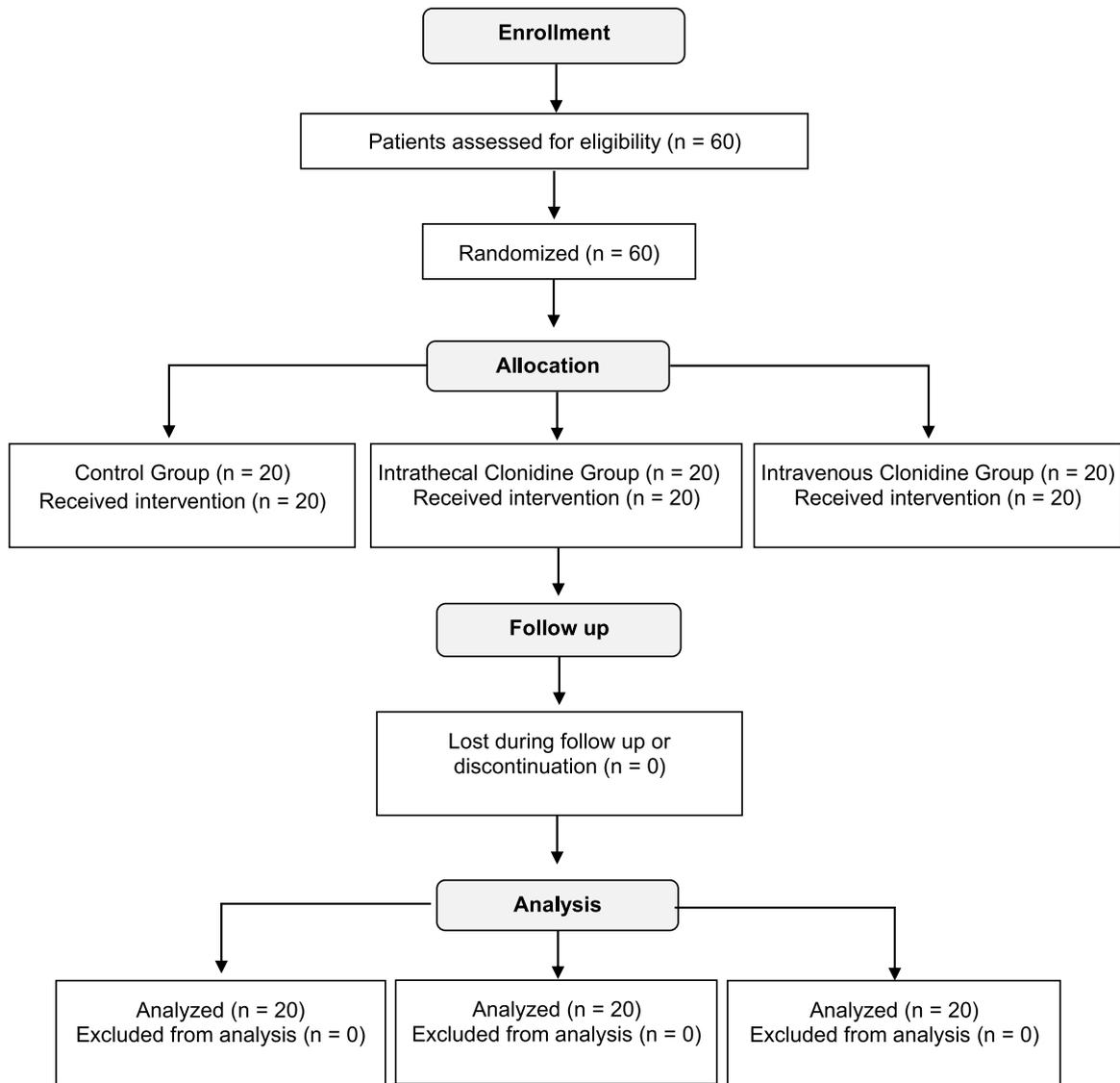


Figure 1 CONSORT flowchart of participants of the study (n = 60).

envelope determining the intervention to be adopted and performed the procedure, which was not informed to the patient. Therefore, 60 patients were allocated into 3 groups: Control (CG), Intrathecal Clonidine (ITCG) and Intravenous Clonidine (IVCG).

The anesthesiologist responsible for the anesthesia prepared the medication in the operating room and administered it after the onset of the sedative and sleep-inducing effects promoted by intravenous (IV) midazolam (0.2 to 0.3 mg.kg⁻¹). Standard anesthesia was performed with propofol (2.5 mg.kg⁻¹), remifentanyl (0.2–0.3 µg.kg⁻¹. min⁻¹), rocuronium (0.3–0.6 mg.kg⁻¹) and sevoflurane (CAM = 1.5% to 2%). All patients were submitted to standardized anesthetic techniques; ITCG participants received intrathecal clonidine (1.0 µg.kg⁻¹); and IVCG participants received intravenous clonidine (2.0 µg.kg⁻¹) before anesthetic induction.

At the end of the surgery, all participants received intravenous doses of tramadol (2.0 mg.kg⁻¹), dipyron (30 mg.kg⁻¹), tenoxicam (40 mg), and subcutaneous infil-

tration of bupivacaine (0.25%) at the site of the trocar insertion. Laparoscopy surgery was performed using a four-port technique and intra-abdominal pressure was maintained between 12 and 14 mmHg during the procedure.

In case of moderate or severe postoperative pain (visual pain scale score ≥ 4), patients received morphine (0.05 to 0.1 mg.kg⁻¹) as rescue medication. Vital parameters and pain scores were recorded after awakening from anesthesia and at 6, 12 and 24 hours after the end of surgery.

Results

A total 60 patients were randomly enrolled. No patients were withdrawn from the study before completion for not complying with eligibility or follow-up criteria. Each group remained with 20 patients (Fig. 1).

Patients presented mean age of 37.2 ± 8.3 years (20 to 50 years) and the majority were female (80.0%) (Table 1). The

Table 1 Demographic and anthropometric variables of patients submitted to laparoscopic cholecystectomy at HUGV/UFAM according to study groups (n = 60).

Variables	Total sample n (%)	Group		
		Control n = 20	IT Clonidine n = 20	IV Clonidine n = 20
Demographic				
Age (years)	37.2 ± 8.3	37.9 ± 8.1	35.6 ± 8.1	38.2 ± 8.2
Gender, n (%)				
Male	12 (20.0)	2 (10.0)	2 (10.0)	8 (40.0)
Female	48 (80.0)	18 (90.0)	18 (90.0)	12 (60.0)
Anthropometric				
Weight (kg)	70.5 ± 11.9	70.5 ± 8.3	67.8 ± 11.4	73.3 ± 12.7
Height (m)	1.6 ± 0.1	1.6 ± 0.1	1.6 ± 0.1	1.6 ± 0.1
Body Mass Index (kg.m ⁻²)	28.1 ± 4.4	28.0 ± 3.4	27.4 ± 4.5	29.0 ± 5.3

Source: Preanesthetic assessment sheet from HUGV/UFAM, Manaus-AM (2017).

Table 2 Clinical and surgical variables of patients and adverse effects referred by patients submitted to laparoscopic cholecystectomy at HUGV/UFAM (n = 60), according to control, Intrathecal Clonidine (IT) e Intravenous Clonidine (IV) groups.

Variable	Total sample n (%)	Group			p
		Control (n = 20) n (%)	IT Clonidine (n = 20) n (%)	IV Clonidine (n = 20) n (%)	
Clinical and surgical					
ASA					0.490 ^a
I	42 (70.0)	12 (60.0)	15 (75.0)	15 (75.0)	
II	18 (30.0)	8 (40.0)	5 (25.0)	5 (25.0)	
Surgery time (minutes)	169.1 ± 41.3	156.3 ± 36.9	168.5 ± 37.0	182.5 ± 47.0	0.132 ^b
Morphine use (N/Y)					0.005 ^a
Not used	37 (61.7)	7 (35.0)	17 (85.0)	13 (65.0)	
Used	23 (38.3)	13 (65.0)	3 (15.0)	7 (35.0)	
Morphine doses (median e II)	0 (0–5)	5 (0–8)	0 (0–0)	0 (0–4)	0.001 ^d
Adverse effects					
Nausea and vomiting					0.241 ^a
No	40 (66.7)	11 (55.0)	13 (65.0)	16 (80.0)	
Yes	20 (33.3)	9 (45.0)	7 (35.0)	4 (20.0)	
Skin Rash					0.999 ^c
No	59 (98.3)	20 (100.0)	20 (100.0)	19 (95.0)	
Yes	1 (1.7)	0 (0.0)	0 (0.0)	1 (5.0)	
Tachycardia					0.999 ^c
No	59 (98.3)	19 (95.0)	20 (100.0)	20 (100.0)	
Yes	1 (1.7)	1 (5.0)	0 (0.0)	0 (0.0)	
Headache					0.999 ^c
No	58 (96.7)	19 (95.0)	19 (95.0)	20 (100.0)	
Yes	2 (3.3)	1 (5.0)	1 (5.0)	0 (0.0)	

Source: Protocol for Postoperative pain assessment (2017). ASA, Physical Status Classification of the American Society of Anesthesiologists; II, Interquartile Interval.

^a Pearson's *Chi*-square test.

^b ANOVA.

^c Fischer's exact test.

^d Kruskal Wallis test.

study revealed that 70% of patients were ASA I, the surgery lasted close to 3 hours, and no related complications were reported. Higher morphine consumption was observed in the CG ($p = 0.005$), with more doses ($p = 0.001$), compared to the other groups (Table 2).

At 12 hours after surgery IVCG patients showed lower DBP values than CG and ITCG, and at 24 hours, IVCG patients showed higher DBP values than ITCG ($p = 0.035$). At the end of the procedure, HR of patients in the CG was higher than in the other groups ($p = 0.043$), and HR was lower after 6

Table 3 Comparison of clinical parameters of patients submitted to laparoscopic cholecystectomy at HUGV/UFAM (n = 60), along study times (0 h, 6 h, 12 h, and 24 h), and according to group studied (Control [C], Intrathecal [IT], Clonidine, and Intravenous [IV] clonidine).

Variables	Group			p		
	Control (n = 20)	IT Clonidine (n = 20)	IV Clonidine (n = 20)	Group	Time	Group vs. Time
SAP (mmHg)				0.122	0.193	0.054
Baseline	121.3 ± 1.7	120.1 ± 3.4	120.6 ± 2.6			
0 h	126.6 ± 3.2	120.1 ± 3.7	118.7 ± 2.7			
6 h	121.0 ± 2.9	125.6 ± 3.4	117.4 ± 3.0			
12 h	121.3 ± 3.3	122.1 ± 3.1	111.4 ± 2.8			
24 h	119.0 ± 2.2	127.9 ± 4.5	115.9 ± 4.1			
DAP (mmHg)				0.035	0.086	0.370
Baseline	76.8 ± 1.3	76.8 ± 3.0	76.8 ± 2.0			
0 h	74.5 ± 3.8	75.1 ± 2.5	71.2 ± 2.6			
6 h	75.8 ± 2.6	77.8 ± 2.6	71.2 ± 2.3			
12 h	75.1* ± 2.3	76.2* ± 2.8	67.4** ± 1.8			
24 h	77.0 ± 2.5	80.3* ± 3.4	70.5** ± 2.5			
MAP (mmHg)				0.051	0.106	0.171
Baseline	91.2 ± 1.2	90.9 ± 2.9	91.1 ± 1.9			
0 h	91.8 ± 3.3	90.1 ± 2.6	87.0 ± 2.5			
6 h	90.8 ± 2.5	93.7 ± 2.7	86.6 ± 2.3			
12 h	90.5 ± 2.4	91.5 ± 2.8	82.0 ± 2.1			
24 h	91.0 ± 2.2	96.2 ± 3.6	85.6 ± 3.0			
HR (bpm)				0.043	0.001	0.003
Baseline	70.0 ^a ± 2.4	72.3 ± 2.5	73.4 ± 2.7			
0 h	87.9 ^{ab} ± 2.7	74.7 ^{**} ± 3.4	73.4 ^{***a} ± 2.3			
6 h	79.3 ^c ± 3.6	72.2 ± 2.0	72.7 ^a ± 2.4			
12 h	75.6 ^{a,c} ± 2.4	72.5 ± 1.9	69.3 ^b ± 2.7			
24 h	76.7 ^c ± 2.2	72.8 ± 2.7	70.0 ± 3.0			
Pain (pain score)				0.632	< 0.001	0.027
0 h	4.9 ^a ± 0.7	2.4 ^a ± 0.7	3.4 ^a ± 0.8			
6 h	1.8 ^b ± 0.4	2.1 ^a ± 0.6	1.4 ^b ± 0.4			
12 h	0.5 ^c ± 0.2	1.4 ^{a,b} ± 0.4	0.9 ^{b,c} ± 0.3			
24 h	0.4 ^c ± 0.2	0.8 ^b ± 0.3	0.6 ^c ± 0.2			

Source: Protocol of Postoperative Assessment (2017).

General Estimating Equations and Post Hoc Minimal Significant Difference, represented according to Tukey (different signs and different letters = statistically significant difference between groups and between times, respectively).

DAP, Diastolic Arterial Pressure; SAP, Systolic Arterial Pressure; MAP, Mean Arterial Pressure; HR, Heart Rate.

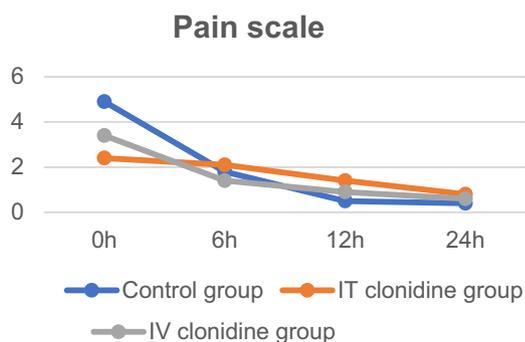


Figure 2 Scores for pain scale assessment over time (0 h, 6 h, 12 h, and 24 h) for patients submitted to laparoscopic cholecystectomy at HUGV/UFAM (n = 60).

hours in the IVCG ($p < 0.001$). In the CG, the pain score immediately after the procedure was higher than the pain scores reported at the other times. For IVCG, the pain score at time 0 was higher than the pain scores reported after 6 and 24 hours ($p < 0.001$) (Table 3). Regarding pain scores ($p = 0.027$) (Fig. 2) and HR ($p = 0.003$) (Fig. 3), the groups depicted a different behavior over time, with lower results in the CG and IVCG, respectively.

The median and interquartile interval of pain scores were higher among patients presenting nausea and vomiting (6.0 [5.0–8.8] vs. 1.0 [0.0–3.8]) ($p < 0.001$) and requiring morphine (6.0 [5.0–10.0] vs. 0.0 [0.0–2.5]) ($p < 0.001$; Mann-Whitney) (52.2% vs. 21.6%) ($p = 0.015$; Pearson's Chi-Square).

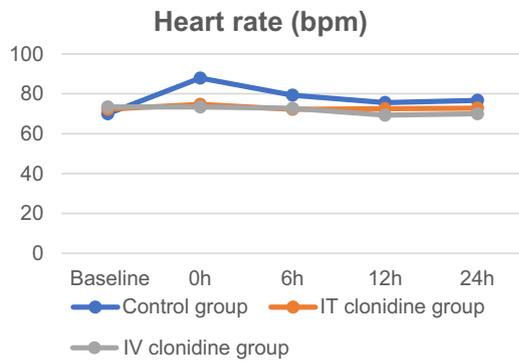


Figure 3 Heart rate over time (0 h, 6 h, 12 h, and 24 h) for patients submitted to laparoscopic cholecystectomy at HUGV/UFAM (n = 60).

Discussion

Clonidine is an α_2 adrenergic receptor, with central action on postoperative analgesia and hemodynamics.¹⁰⁻¹² This study compared the effects of the intrathecal and intravenous administration of clonidine as a component of a multimodal therapeutic strategy to reduce opioid requirements in the post-operative.¹⁸

The analysis of demographic and anthropometric variables showed that the three study groups were comparable. As the surgery was performed as an elective procedure in asymptomatic patients, the physical condition of the patients and the surgical time did not influence intergroup results. As described by Yilmaz et al.,⁵ patients submitted to emergency procedures or presenting complicated surgery may experience increase in postoperative pain due to complications of the surgical technique and increased surgical time.

Patients who received clonidine required less morphine than patients of the control group, and showed reduction in the cumulative dose and less consumption of analgesics in the perioperative period, similar to the results reported by Samantaray et al.,¹⁸ Bharti et al.,¹⁹ and Ahmed et al.²⁰ According to the systematic review and meta-analysis by Zhang et al.,²¹ clonidine promoted decrease in opioid requirements intraoperatively, lower nausea and vomiting incidence, less surgical stress response, and hemodynamic stability.^{22,23}

In the present study, a decrease in BP and HR values was observed in the clonidine groups in agreement with the studies by Anjum et al.,¹³ Singh et al.,²² Sahajananda and Rao,²³ and Kamble et al.²⁴ On the other hand, patients of the IVCG and ITCG groups showed similar results for hemodynamic variables, with no superiority of one administration route over the other.

The limitations of the study were the reduced size of the sample, investigation of associated use of antihypertensive drugs, and assessment of secondary events that can influence VAS responses, such as anxiety. The study demonstrated that intravenous and intrathecal clonidine administration is safe, shows no significant adverse effects, and facilitates a multimodal action strategy for pain management in laparoscopic cholecystectomy.

Conclusion

The administration of intrathecal and intravenous clonidine in low doses is safe and effective, promotes hemodynamic stability, and reduces the requirement for analgesics in patients submitted to laparoscopic cholecystectomy. Future studies are recommended to determine ideal doses and methods, drug associations, and other factors in the response to pain.

Collaborators

Thatiana Lúcia de Alcântara Vieira; Luciana da Silva De Armond; Luciane Moral da Silva Pereira; Renê Alves Moura Cavalcanti; Júlio Adriano da Rocha Carvalho; Brígida Thaine Fernandes Cabral; Juan Eduardo Rios; Matheus Moura Catique; Mylla Christie de Oliveira Paschoalino; Gustavo Rodrigues da Silva; Felicien Vásquez.

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Conflicts of interest

The authors declare no conflicts of interest.

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