ORIGINAL ARTICLE

Comparative study between epidural ketamine and morphine in patients submitted to mastectomy*

Estudo comparativo entre cetamina e morfina peridural em pacientes submetidas à mastectomia

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ABSTRACT

BACKGROUND AND OBJECTIVES: This study aimed at comparing epidural thoracic S(+) ketamine and morphine, both associated to ropivacaine, for mastectomy procedures.
METHODS: This is a prospective study with 26 patients aged between 18 and 70 years, submitted to mastectomy, who were divided into two equal groups. Group M (morphine) patients have received 12 mL of 0.75% ropivacaine associated to 2 mg preservative-free morphine; Group K (ketamine) patients have received 12 mL of 0.75% ropivacaine associated to 50 mg of preservative-free S(+) ketamine. We have evaluated hemodynamic parameters, need for vasopressors, drugs for sedation, pain visual analog scale in the first 24 hours, analgesic and antiemetic consumption, and incidence of nausea and vomiting.
RESULTS: There has been no statistical difference between groups in demographics, systolic and diastolic blood pressure, amount of local anesthetics or need for vasopressors. The ketamine group has demanded more midazolam to control sedation (p = 0.0005). This group had lower pain scores at post-anesthetic care unit discharge (p = 0.0018), 12 hours after procedure (p = 0.0001) and 24 hours later (p = 0.0094). The Morphine Group had higher pain scores at post-anesthetic care unit, 12 and 24 postoperative hours, and has demanded more postoperative analgesics (dipirone, p = 0.0009) and antiemetics (metoclopramide, p = 0.0032).
CONCLUSION: It has been observed that S(+) ketamine in the evaluated dose was hemodynamically safe and effective, with better performance to control postoperative pain, generating less analgesic consumption as well as lower incidence of nausea and vomiting.
Keywords: Analgesia, Epidural anesthesia, Ketamine, Mastectomy.

RESUMO

JUSTIFICATIVA E OBJETIVOS: O objetivo deste estudo foi comparar a S(+) cetamina em relação à morfina associada à ropivacaína por via peridural torácica em operações de mastectomia.
MÉTODOS: Estudo prospectivo com 26 pacientes com idade entre 18 e 70 anos submetidas à mastectomia, divididas em dois grupos de igual tamanho. As pacientes do Grupo M (morfina) receberam 12 mL de ropivacaína a 0,75% associadas a 2 mg de morfina sem conservantes e as pacientes do Grupo C (cetamina) receberam 12 mL de ropivacaína a 0,75% associadas a 50 mg de S(+) cetamina sem conservantes. Foram avaliados os parâmetros hemodinâmicos, a necessidade de vasopressores, os fármacos para sedação, a escala analógica visual de dor nas primeiras 24 horas, consumo de analgésicos, de antieméticos e incidência de náuseas e vômitos.
RESULTADOS: Não houve diferença estatística entre os grupos em relação a dados demográficos, níveis de pressão arterial sistólica e diastólica, quantidade de anestésico local utilizado ou necessidade de vasopressores. O GC demandou maior uso de midazolam para controle da sedação (p = 0,0005). Este grupo apresentou menores escores de dor ao serem avaliados na alta da sala de recuperação pós-anestésica (p = 0,0018), após 12 horas do procedimento (p = 0,0001) e após 24 horas (p = 0,0094). O Grupo Morfina apresentou maiores escores de dor na sala de recuperação pós-anestésica, após 12 e 24 horas, demandando maior uso de analgésicos no pós-operatório (dipirona, p = 0,0009) assim como antieméticos (metoclopramida, p = 0,0032).
CONCLUSÃO: Observou-se que a S(+) cetamina na dose avaliada foi segura e eficaz do ponto de vista hemodinâmico, apresentando melhor desempenho no controle de dor pós-operatória gerando menor consumo de analgésicos; assim como menor incidência de náuseas e vômitos.
Descritores: Analgesia, Anestesia peridural, Cetamina, Mastectomia.

INTRODUCTION

Regional anesthesia is a safe and low cost technique, with the advantage of offering intraoperative hemodynamic stability and prolonging postoperative analgesia. Effective postoperative pain management significantly decreases autonomic, neuroendocrine and somatic responses triggered by surgical trauma[1], which generates major impact on perioperative morbidity and mortality

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decrease. For breast cancer, upper thoracic epidural anesthesia has been used in different centers as anesthetic technique to replace general anesthesia.

In parallel to the development of regional anesthetic techniques, studies were carried out aiming at improving its quality and prolonging analgesia. Initially, opioids were associated to local anesthetics. Currently, new adjuvants have been used, even as single drug for regional blocks, among them N-methyl-d-aspartate (NMDA) receptor inhibitors which have ketamine as their primary representative[2,3], with analgesic properties by inhibiting NMDA, activating monoaminergic descending inhibitory system, activating opioid and cholinergic receptors, in addition to blocking sodium channels similarly to local anesthetics[4-6].

Several studies have evaluated the effect of this drug on neuraxis[6,7], but none of them has analyzed its effect on upper thoracic epidural space, where cardioaccelerator sympathetic branches emerge[8]. Many fear the addition of drugs to this region due to possible local interaction of ketamine with cardioaccelerator fibers with possible direct cardiovascular stimulating effect of sympathetic nervous system[9], and possible neurotoxicity. Different administration routes have been used in clinical trials carried out with racemic ketamine or its levogyrous component, in low doses, isolated or associated to other drugs[10].

Racemic ketamine and its levogyrous derivative, even without preservative, may be associated to spinal neurotoxicity, so they should not be administered by subarachnoid route, especially in high doses[11-15], although chlorobutanol (preservative) is considered the primary responsible[16,17]. There are evidences that continuous subarachnoid ketamine infusion is related to histopathological findings of spinal cord vacuolization[18,19]. Conversely, there are studies with epidural sacral racemic ketamine[20] or S(+) ketamine[16,21] in children, or lumbar epidural in adults[22,23] which have not reported neurotoxicity, being preservative-free ketamine especially recommended[24,25]. Authors[12], in editorial, have called the attention to the promising use of epidural racemic ketamine associated to other analgesic agents.

In light of the above, this study aimed at comparing perioperative analgesic quality of S(+) ketamine and morphine, associated to ropivacaine, by upper epidural route in thoracic breast cancer surgeries and at confirming its safety.

METHODS

Participated in this analytical, interventional, clinical, prospective, randomized and double-blind study 26 female patients aged from 18 to 70 years, physical status ASA I and II, submitted to mastectomy under thoracic epidural anesthesia. All patients were operated on at the Base Hospital, Federal District (HBDF) between January 2009 and December 2010 and have signed the Free and Informed Consent Term (FICT).

Exclusion criteria were patients refusing to be submitted to the procedure and those with contraindications for epidural puncture, such as puncture site infection, uncorrected hypovolemia, coagulation disorders, anatomic abnormalities and technical difficulties.

During anesthesia, patients were monitored with cardioscope, pulse oximetry and noninvasive blood pressure (BP) monitor. Patients were hydrated with lactated Ringer's solution and/or 0.9% saline (NaCI), after venous puncture with 18G Teflon catheter. Patients were not premedicated.

Thoracic epidural anesthesia was induced with patients preferably in the left lateral position, in spaces T_2-T_3, T_3-T_4 or T_4-T_5, with 16G Tuohy needle followed by catheter insertion and fixation. Group M patients (morphine) received 12 mL of 0.75% ropivacaine associated to 2 mg preservative-free morphine, and Group K patients (ketamine) received 12 mL of 0.75% ropivacaine associated to 50 mg preservative-free (S+) ketamine. All patients received venous sedation with midazolam and/or fentanyl.

After puncture, patients returned to the supine position being observed epidural block sensory level as well as systemic BP and heart rate (HR) monitoring after epidural anesthesia. When clinical signs or hemodynamic responses were observed, which indicated inadequate anesthesia levels (hypertension, tachycardia, pain complaint) ropivacaine was administered in intermittent doses via catheter and when there were clinical signs indicating inadequate sedation levels, intravenous midazolam and/or fentanyl were administered in intermittent doses.

With regard to intraoperative sedation, continuous change in alertness which may reach unconsciousness, there may be consciousness depression levels which vary from mild to deep. In mild sedation, consciousness depression level is minimal and patient is able to contact with the environment, respond to commands, distinguish events and report facts. The numeric scale proposed by Filos et al.[26] was used to check consciousness level: 1 – awaken and nervous; 2 – awaken and relaxed; 3 – sleepy but easily awaked; 4 – sleepy and difficult to awake. Sedation references were scores three and four of this scale.

BP, HR and SpO_2 data were recorded after monitoring, epidural anesthesia induction and then every 15 minutes until surgery completion. After procedure, all patients were referred to the post-anesthetic care unit (PACU)

Systolic blood pressure (SBP) below 30% of pre-blockade levels or below 90 mmHg was corrected with intravenous mixed-action sympathomimetic amine (ephedrine); marked HR decrease below 50 beats.min^{-1}, causing low cardiac output, was treated with intravenous atropine.

With regard to postoperative analgesia, pain intensity was evaluated with the 10-cm visual analog scale (VAS), being "zero cm" corresponding to "no pain" and varying until "10 cm", corresponding to "worst imaginable pain", in the following moments: PACU discharge; 12h and 24h after surgery completion.

Intravenous dipirone and/or tramadol were administered to complement analgesia, when needed. Amount of analgesics needed during the 24 hours was recorded.

The following variables were compared between groups:

age, weight, height, physical status, presence of comorbidities and preoperative use of drugs. BP and HR values, anesthetic-surgical intercurrences and need for analgesic-sedative supplementation were recorded, in addition to intraoperative vasopressors consumption. The following parameters were compared between groups in the postoperative period: pain evaluation by VAS, total analgesic and antiemetic consumption, side-effects and possible complications.

Sample size was estimated based on a previous and similar study. Mean pain VAS after 24 postoperative hours was 2.25 ± 1.6 for the morphine subgroup[27]. Twelve patients from each group were enough to show pain VAS decrease with type I error of 0.05 and power of 80%. The number was increased to 26 patients for safety reasons. Parametric and non-parametric tests were used for statistical analysis of results. Chi-square, Fisher Exact and Mann-Whitney-Wilcoxon tests were used for non-parametric data and Student's *t* and ANOVA tests were used for remaining parametric data, considering statistically significant $p < 0.05$. Data were expressed in mean ± 2 standard deviation, or number of patients per event.

This study was approved by the Research Ethics Committee, Health Department of the Federal District, opinion 380599.

RESULTS

From 26 patients, 4 patients were excluded for refusing to participate in the study. Demographic and clinical data have not shown statistical difference between groups (Table 1).

Surgery duration has not differed between groups, as well as the incidence of tachycardia, bradycardia, hypotension, hypertension (Table 2) and total local anesthetic dose (Table 3). All patients needed additional sedation without concomitant pain complaint. Total midazolam dose was higher for KG ($p = 0.0005$). Total fentanyl dose was also higher for KG, however this difference was not statistically significant (Table 3).

Intraoperative hemodynamic stability was satisfactory; SBP and DBP did not vary between groups (Figure 1). However, KG had higher HR as compared to MG until 2h30 of surgery (Figure 2), without tachycardia.

MG had higher incidence of postoperative vomiting ($p = 0.034$) (Table 4) and higher dipirone ($p = 0.009$), tramadol ($p = 0.0268$) and metoclopramide ($p = 0.032$) consumption as compared to KG (Table 5).

KG had lower pain scores at PACU discharge ($p = 0.018$), 12 h ($p = 0.0001$) and 24 h ($p = 0.0094$) after surgery completion (Figure 3).

Table 1 – Patients' demographic and clinical data.

	Morphine Group (n = 9)	Ketamine Group (n = 13)	p value
Age (years)	47.22 ± 14.96	46.00 ± 12.64	0.8437
Weight (kg)	64.56 ± 13.08	66.69 ± 11.72	0.6995
Height (cm)	158.33 ± 5.59	159.69 ± 4.35	0.5499
Physical status (n)			
ASA I	5	8	0.2191
ASA II	4	4	
Associated morbidities (n)			
SH	7	5	0.414
Drugs used (n)			
Betablockers	1	0	0.307
ACEI	3	3	1.000
Diuretics	3	2	0.615

Values in mean ± SD and numbers.
SH = systemic hypertension; ACEI = angiotensin converting enzyme inhibitors; statistical significance $p < 0.05$.

Table 2 – Intraoperative data.

	Morphine Group (n = 9)	Ketamine group (n = 13)	p value
Surgery duration (min)	135.00 ± 37.75	166.92 ± 33.39	0.0580
Axillary complementation	0	0	-
Hypertension	1	1	-
Hypotension	1	2	0.537
Bradycardia	0	1	0.307
Tachycardia	0	0	-

Values in mean ± SD and numbers; there were no differences between groups.

Table 3 – Intraoperative drugs.

	Morphine Group (n = 9)	Ketamine Group (n = 13)	p value
Ropivacaine (mg)	12.92 ± 1.69	12.83 ± 1.98	0.9130
Midazolam (mg)	4.00 ± 1.80	8.77 ± 3.46	0.0005*
Fentanyl (µg)	27.78 ± 44.10	60.38 ± 56.88	0.1464
Ephedrine (n)	1	2	0.5900
Atropine (n)	0	1	0.3276

Values in mean ± SD or numbers.
There has been difference between groups in midazolam consumption *($p = 0.005$).

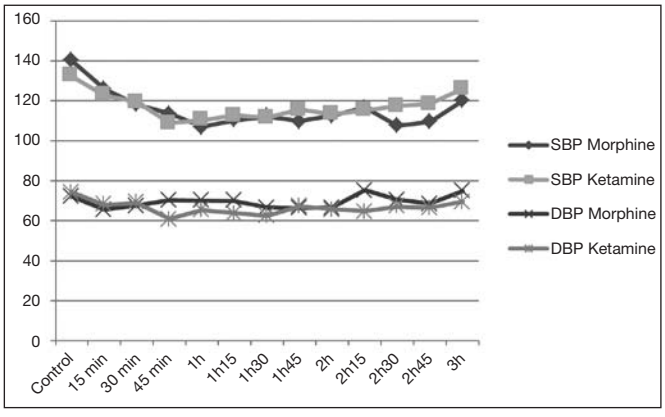

Figure 1 – Behavior of intraoperative blood pressures.
SBP = systolic blood pressure; DBP = diastolic blood pressure; there has been no statistical difference between groups in SBP and DBP.

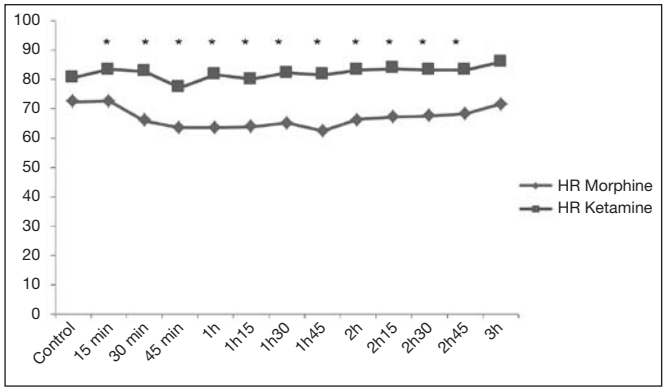

Figure 2 – Behavior of intraoperative heart rate.

There has been statistical difference *(p < 0,05) in times 15 min, 30 min, 45 min, 1h, 1h15, 1h30, 1h45, 2h, 2h15, 2h30 and 2h45.
HR = heart rate.

Table 4 – Postoperative adverse events.

	Morphine Group (n = 9)	Ketamine Group (n = 13)	p value
Nausea	2	3	0.6150
Vomiting	4	1	0.034*
Pruritis	0	0	-

Values in number of patients.
* There has been difference between groups in the incidence of vomiting.

Table 5 – Postoperative analgesic and antiemetic drugs.

	Morphine Group (n = 9)	Ketamine Group (n = 13)	p value
Dipirone (mg)	5.33 ± 2.24	1.69 ± 1.38	0.0009*
Tramadol (mg)	44.44 ± 52.70	7.69 ± 27.74	0.0268*
Metoclopramide (mg)	8.89 ± 3.33	3.08 ± 4.80	0.0032*

Results in mean ± SD.
There has been difference between groups in dipirone *(p = 0.0009), tramadol *(p = 0.0268) and metoclopramide *(0.0032) consumption.
No patient had postoperative pruritis.

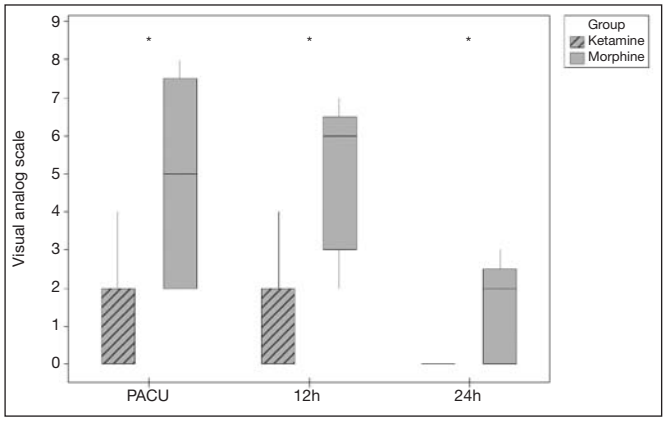

Figure 3 – Postoperative visual analog scale.

Ketamine group had lower VAS in moments PACU, 12 h and 24 h (p < 0.05, *significant) as compared to morphine group.
PACU = post-anesthetic care unit.

DISCUSSION

Our results confirm national and international literature data about perioperative analgesic effects of epidural ketamine[27,28]. This study was able to identify and analyze variables that may help professionals acting on acute pain control to better manage surgical patients.

Results have shown that S(+) ketamine has some advantages over morphine (phenanthrene derivative considered the "gold standard" to manage postoperative pain)[29], especially with regard to postoperative analgesia, analgesic consumption and incidence of vomiting.

There are few references addressing the epidural use of S(+) ketamine and it seems that analgesia induced by this drug is dose-dependent and also dose-ceiling. With regard to the adequate epidural dose, studies indicate a variation between 30 and 50 mg[30,31].

Notwithstanding significantly higher midazolam doses needed to maintain adequate sedation levels, this study emphasizes conductive technique advantages and efficiency, because the mixture of epidural local anesthetics and adjuvants promotes better attenuation of metabolic response to surgical trauma[1] and higher quality analgesia as compared to intravenous non steroid anti-inflammatory drugs and morphine for major surgeries[27,32].

Our results confirm similar observations reported by other studies[2,6,7], however it is the only study analyzing S(+) ketamine effects in upper epidural space where cardioaccelerator fibers emerge, without the interference of the association with general anesthesia.

Data indicate that S(+) ketamine associated to ropivacaine is safe when administered in the upper epidural space because it has maintained adequate HR and BP hemodynamic stability, although higher HR values were found. It is to be expected that ketamine induces HR and BP increase secondary to sympathetic stimulation and catecholamines reuptake inhibition, both centrally and peripherally[33].

The mechanism through which ketamine acts on the vascular system is complex. There are some evidences that ketamine attenuates baroreceptors function by changing NMDA receptors function in solitary tract nuclei[34]. This drug also promotes adrenergic bundles norepinephrine release, increasing its venous blood concentration. Epidural block sympatholysis and benzodiazepines may inhibit such effects[35], however our study has observed significant HR increase.

The clinical use of ketamine was, for many years, restricted to anesthetic induction in hypovolemic or asthmatic patients or in situations with little anesthetic support material. Currently, its use is being expanded to sedation, maintenace of total venous anesthetic techniques and postoperative pain control[10]. The discovery of the role of NMDA receptors on analgesia, on the wind-up phenomenon and on the possible activity during the development of acute tolerance to opioids when blocking NMDA receptors (inhibiting aspartate and glutamate action) provides new areas for the indication of ketamine[36].

Low intravenous doses may significantly decrease intraoperative opioid and halogenate consumption, with pro-nociceptive sys-

tem inhibition, central hypersensitivity block and consequent hyperalgesia[34]. Studies using ketamine in the neuraxis had always as limiting factor the toxicity of chemical preservatives, initially chlorobutanol, soon replaced by benzethonium chloride. However, with the development of preservative-free S(+) ketamine, its safe epidural utilization with low incidence of side-effects was made possible[12].

Our study has not evaluated clinical neurotoxicity and patients' observation was limited to 24 hours, which may be considered a limitation. There are still controversies about the use of ketamine in the neuraxis, even without preservatives, as it is the case of the isomer S(+) ketamine. A recent study with subarachnoid administration of this drug in dogs suggests that this route should be avoided[37].

Our study has shown that S(+) ketamine was superior to morphine in preventing postoperative pain, as well as in immediate analgesic consumption due to its high liposolubility. After 12 and 24 hours, pain scores were even lower, probably due to its preemptive action[38] and interaction with non-NMDA, nicotinic, muscarinic, monoaminergic and serotoninergic glutamate receptors, in addition to action on mu and kappa receptors at spinal level and mu at supraspinal level[39].

CONCLUSION

S(+) ketamine had adequate profile to be used in upper thoracic epidural anesthesia being hemodynamically safe and effective, with better performance to control postoperative pain as compared to morphine, generating less analgesic consumption as well as lower incidence of adverse effects.

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