ORIGINAL ARTICLE

Epidural anesthesia for cesarean section with 0.125% versus 0.25% bupivacaine: An Ecuadorian prospective cohort

Anestesia epidural en cesárea con bupivacaina al 0125% vs 0.25%: una cohorte prospectiva en pacientes ecuatorianas

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Abstract

Background: *In a cesarean section, epidural analgesia with 0.125% bupivacaine and 1.5% lidocaine or 0.25% bupivacaine with 1.0% lidocaine concentrations can be used. A higher concentration of bupivacaine reaches better analgesia but with a higher rate of drug-related adverse events.* **Aim:** *The aim of the study was to assess analgesia and safety of 0.125% bupivacaine and 1.5% lidocaine or 0.25% bupivacaine with 1.0% lidocaine during cesarean.* **Materials and methods:** *Prospective cohort stratified following both bupivacaine concentrations.* **Results:** *One hundred women with full-term pregnancies were selected (fifty per cohort). At 20 and 30 min after epidural administration, there was a higher proportion of motor blockade cases from the 0.125% bupivacaine and 1.5% lidocaine cohort ($p = 0.0229$ and $p = 0.0006$, respectively). There was no significant difference among sensitive blockage. A 0.25% bupivacaine and 1.0% lidocaine concentration showed a tendency to hypotension ($p < 0.001$) and bradycardia ($p = 0.4100$). From 0.125% bupivacaine and 1.5% lidocaine cohort, 25 cases (50%) presented at least one adverse event; in contrast with 44/50 (88%) from 0.25% bupivacaine and 1.0% lidocaine cohort ($p < 0.001$).* **Conclusion:** *In epidural analgesia during cesarean, using 0.125% bupivacaine and 1.5% lidocaine presented similar analgesia than 0.25% bupivacaine and 1.0% lidocaine. However, a higher bupivacaine concentration is significantly related to more frequent drug-related adverse events (especially hypotension).*

Key words: *Bupivacaine. Cesarean section. Drug-related side effects and adverse Reactions. Hypotension.*

Resumen

Antecedentes: *En una cesárea se puede emplear analgesia epidural con bupivacaína 0.125% and lidocaína 1.5% ó bupivacaína 0.25% and lidocaína 1.0%. Una concentración mayor de bupivacaína alcanza mayor analgesia con más eventos adversos.* **Objetivo:** *evaluar la analgesia y seguridad de bupivacaína 0.125% and lidocaína 1.5% ó bupivacaína 0.25% and lidocaína 1.0%* **Materiales y métodos:** *Cohorte prospectivo estratificado según ambas concentraciones de bupivacaína.* **Resultados:** *Se recu-*

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peró cien gestantes a término (cincuenta por cohorte). A los 20 y 30 minutos tras la administración epidural hubo más casos con mayor bloqueo motor en quienes se empleó bupivacaína 0.125% and lidocaína 1.5% (p = 0.0229 y p = 0.0006, respectivamente). No hubo diferencia significativa respecto al bloqueo sensitivo. Bupivacaína 0.25% and lidocaína 1.5% mostró una tencencia a la hipotensión (p < 0.001) y a la bradicardia (p = 0.4100). De la cohorte de bupivacaína 0.125% and lidocaína 1.5%, 25 casos (50%) presentaron cuando menos un evento adverso, en contraste con 44/50 (88%) de la cohorte de bupivacaína 0.25% and lidocaína 1.0% (p < 0.001). **Conclusión:** *En la analgesia epidural durante cesárea, bupivacaína 0.125% and lidocaína 1.5% está asociado con un efecto analgésico similar a bupivacaína 0.25% and lidocaína 1.0%. Sin embargo, mayores concentraciones están significativamente relacionadas con mayor tasa de eventos adversos (especialmente hipotensión).*

Palabras claves: *Cesárea. Bupivacaína. Efectos colaterales y reacciones adversas relacionados con medicamentos. Hipotensión.*

Introduction

Pregnancy represents a challenge to the anesthesiologist, attending two patients simultaneously, each with different physiology than usual, but linked. In Ecuador, the cesarean section represented 9% of hospital admissions among childbearing women during 2012, in contrast with 15% of spontaneous vaginal delivery[1]. In the cesarean section, it is crucial to consider analgesia based on the following criteria: short latency time, adequate duration of the effect, motor and sensorial block, minimal risk of systemic toxicity, and ideal concentration. Bupivacaine is a sodium channel blocking local anesthetic, which induces a dose-depending effect on the sensorial and motor block. It has a high binding to maternal plasma proteins, with less analgesia transfer to the fetus[2].

In the cesarean section, epidural analgesia with bupivacaine without epinephrine is indicated. In this context, some studies describe opposite results when comparing different bupivacaine concentrations diluted in lidocaine, in terms of analgesic effect versus safety, commonly 0.125% or 0.25%[3,4]. The Hospital Gineco-Obstétrico Enrique C. Sotomayor (HES; Subsequently reopened as Alfredo Paulson Women's Hospital) is a non-profit institution, considered a referral maternity referral center from Guayaquil – Ecuador. Here, the decision about bupivacaine concentration for the previously described purpose bases on clinical individualization. This study aims to better define the analgesic effect and safety of epidural analgesia with 0.125% bupivacaine (without epinephrine) and 1.5% lidocaine or 0.25% bupivacaine (without epinephrine) and 1.0% lidocaine in an Ecuadorian population. We hypothesized that 0.125% bupivacaine and 1.5% lidocaine reach a similar or even better analgesic effect than 0.25% bupivacaine and 1.0% lidocaine but with lower drug-related adverse events.

Materials and Methods

Study design

The following is an independent, observational, analytical, longitudinal, and prospective cohort study carried out at the HES between October 2015 and January 2016. The study comprehended two pregnant patients' cohorts, based on bupivacaine concentration diluted in lidocaine: 0.125% bupivacaine without epinephrine and 1.5% lidocaine or 0.25% bupivacaine without epinephrine and 1.0% lidocaine. The present study was presented following the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement[5].

Population and sample

We selected pregnancy patients between 15 and 35 years old, in whom a cesarean section was indicated based on a justified clinician decision (e.g. possibility of vertically transmitted infections during childbirth, fetal dystocia, cephalopelvic disproportion, fetal distress), who underwent epidural blockade with 0.125% or 0.25% bupivacaine without epinephrine and 1.5% or 1.0% lidocaine, respectively. There were excluded patients with an American Society of Anesthesiologists (ASA) classification type III or IV, pre-eclampsia or eclampsia, suspected alteration in the spine's anatomy, or history of allergies or hypersensitivity to local anesthetics[6].

Procedure, monitoring, and retrieval of information

Based on anesthesiologist discretion, epidural analgesia was prepared using 0.125% bupivacaine (25 mg diluted in 300 mg of 2% lidocaine; 20 ml total volume dilution, with 1.5% lidocaine final concentration), or 0.25%

Table 1. Pharmacological concentrations of bupivacaine without epinephrine

	2% Lidocaine without epinephrine (1 mL = 20 mg)	0.5% Bupivacaine without epinephrine (1 mL = 5 mg)	Total volume dilution (mL)
0.125% bupivacaine + 1.5% lidocaine	15 mL = 300 mg	5 mL = 25 mg	20 mL
0.25% bupivacaine + 1.0% lidocaine	10 mL = 200 mg	10 mL = 50 mg	20 mL

mL: milliliter.

bupivacaine (50 mg diluted in 200 mg of 2% lidocaine; 20 ml total volume dilution, with 1% lidocaine final concentration); both without epinephrine (Table 1). Hereafter, 0.125% or 0.25% bupivacaine without epinephrine concentrations cohort studies will be denominated as "0.125% bupivacaine and 1.5% lidocaine cohort" or "0.25% bupivacaine and 1.0% lidocaine cohort," respectively.

Using an online-encrypted spreadsheet, the following data were prospectively recorded: demography, length of surgery, and analgesia (hours and minutes, hh: mm); motor and sensoria blockade assessed with modified Bromage scale (from grade 0 "Lack of movement" to grade 4 "Full muscle strength in relevant muscle groups")[7] and Pinprick technique (blockade level from T10 to T4)[8], respectively; vital signs during pre-, trans-, and post-operatory (mean arterial pressure [MAP], heart rate [HR], respiratory rate [RR], and oxygen saturation [SpO_2]); drug-related adverse events (e.g., nausea, vomiting, shaking chills, hypotension, bradycardia, rash, allergies, or hypersensitivity).

Statistical analysis

Technical considerations

The data analysis was performed by M.P-T and K.R-M. using the program R v3.6.3 (R Foundation for Statistical Computing; Vienna, Austria). A $p < 0.05$ was considered to be statistically significant.

Sample size calculation

The sample size was calculated using power diagnostic test function from the MKmisc (v1.6; Kohl M, 2019) package[9]. A similar number of patients per study group was considered (1:1 ratio, k value = 1). The size of each group was estimated using the formula for comparing the proportions between two samples[10], considering an α and β-error of 5% and 20%, respectively, a 95% confidence interval, and a proportion of adverse effects per each group, similar as described by Lopez-Espinoza et al. (54% and 74%, for a dose of 10 mg of bupivacaine 0.5% vs. 15 mg of bupivacaine 0.5% in urgent cesarean sections)[11].

Descriptive statistics

Continuous variables were described as mean (standard deviation), median, or mode (minimum-maximum range) as appropriate for their statistical distribution (Shapiro–Wilk test). The categorical variables were described in frequencies (percentage).

Inferential statistics

The association between the analyzed variables versus the cohort groups was determined through the corresponding hypothesis contrast test: Student's t-test or Mann–Whitney's U for continuous variables, Pearson's Chi-square or Fisher's exact test for categorical variables. A significant potential fluctuation among each vital sign along the pre-, trans-, and post-operatory was verified with the Friedman rank-sum test. A $p < 0.01$ was considered to be statistically significant.

Ethic aspects

The present study is based on direct findings from the thesis by N.D-P. and C.B-C., respectively, the author and advisor[12]. This study respected the stipulations of the Declaration of Helsinki (2008). There was obtained the approval of the HES Institutional Review Board and the Ethics and Research Committee of the Universidad Católica de Santiago de Guayaquil (UCSG). All patients included in the study signed informed consent.

Results

Baseline characteristics

A total of 50 pregnancy patients per study cohort was estimated, who were successfully recorded during the research period. The median age was 24 (15-37) years old with a full-term pregnancy (38.0-39 weeks), with a median surgery and analgesia

Table 2. Demography, surgery, and analgesia length per each cohort study

	General (n = 100)	0.125% bupivacaine and 1.5% lidocaine (n = 50)	0.25% bupivacaine and 1.0% lidocaine (n = 50)	p-value
Age (years), median (range)	24 (15-37)	25 (15-37)	23 (16-36)	0.396[a]
Surgery length (hh:mm), median (range)	0:47 (0:20-1:55)	00:52 (00:30-01:54)	00:45 (00:20-01:35)	0.025[a]
Analgesia length (hh:mm), median (range)	01:20 (0:50-2:30)	01:25 (00:54-02:30)	01:20 (00:50-02:05)	0.032[a]

a. Mann–Whitney U test.

length of 00:47 (00:20-01:55) and 01:20 (00:50-02:30), respectively (Table 2).

Motor and sensitive blockade

Both motor and sensitive blockade assessment showed a decreasing scoring from a high blockade at the beginning of the analgesia effect. At 20 min after epidural administration, 46/50 patients from the 0.125% bupivacaine and 1.5% lidocaine cohort presented a Bromage-grade 0-1 and 4/50 a grade 2, comparing with 36/50 and 14/50 from the 0.25% bupivacaine and 1.0% lidocaine cohort, respectively ($p = 0.0229$). At 30 min after epidural administration, 50/50 patients from the 0.125% bupivacaine cohort presented a Bromage-grade 1-2, compared with 36/50 from 0.25% bupivacaine cohort; the remaining 14/50 presented a Bromage-grade 3-4 ($p = 0.0006$) (Fig. 1A). In general, there was no significant difference in sensitive blockade assessment among both cohorts (Fig. 1B).

Vital signs

The median MAP presented significant fluctuations throughout the pre-, trans-, and post-operative in 0.125% bupivacaine and 1.5% lidocaine ($p < 0.001$) and 0.25% bupivacaine cohort ($p < 0.001$) (Fig. 2A). These fluctuations were more noticeable toward the end of the analgesic length, where 0.25% bupivacaine and 1.0% lidocaine cohort showed a tendency to hypotension ($p = 0.0002$) (Table 3 and Fig. 2A). HR fluctuated non-significantly during the pre-, trans-, and post-operative in 0.25% bupivacaine cohort ($p = 0.4100$), but 0.25% bupivacaine and 1.0% lidocaine cohort showed a significantly lower median of HR comparing with 0.125% bupivacaine and 1.5% lidocaine cohort, not corresponding median HR necessarily to bradycardia (Table 3 and Fig. 2B). The median RR and SpO_2 during the pre-, trans-, and post-operative were 15/min and 99%, respectively, without significant fluctuations or differences between both cohorts.

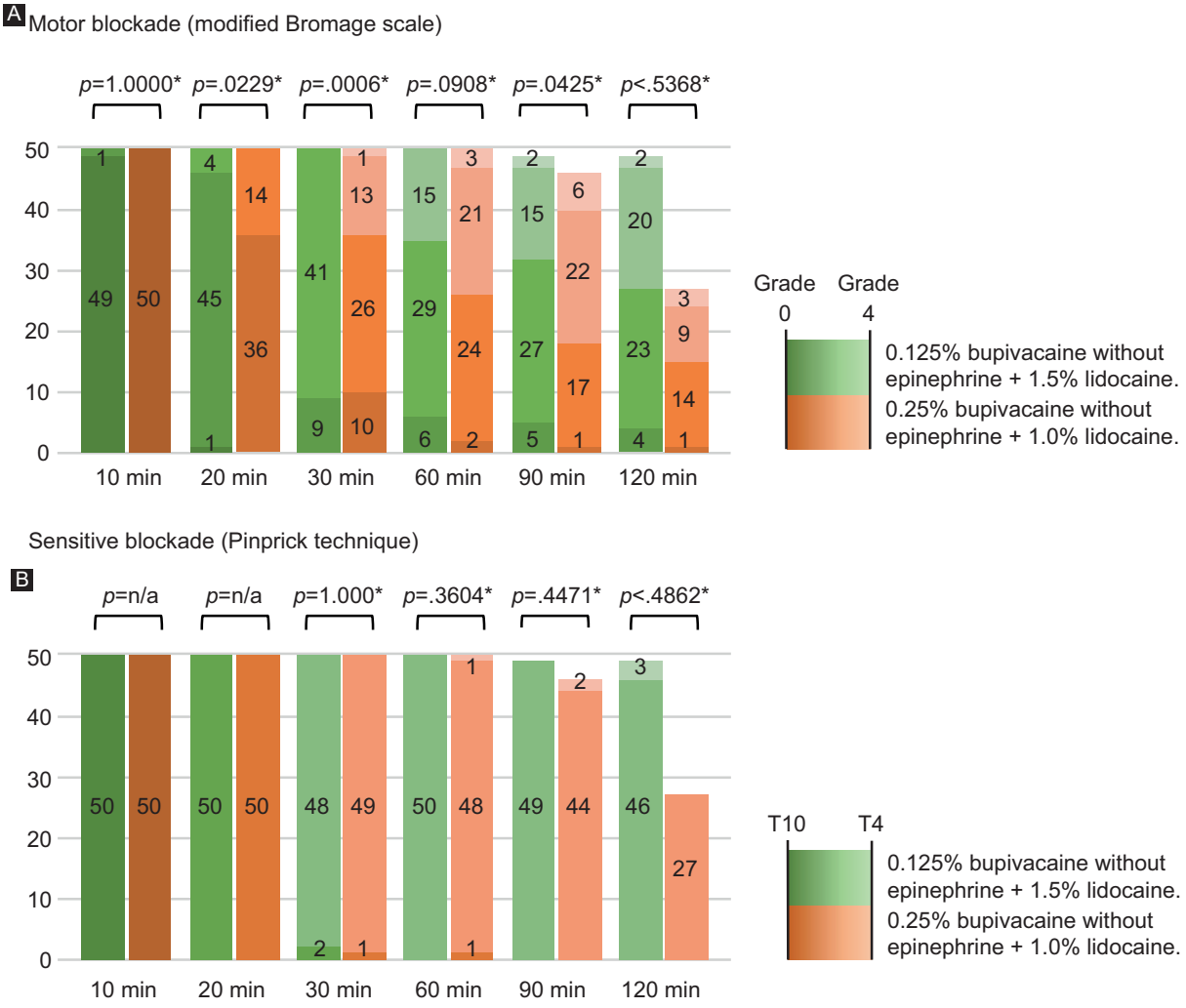
Adverse events

In general, shaking chills were the most common adverse effect (29%), followed by hypotension (20%), bradycardia (13%), nausea (12%), and vomiting (8%). It was found that 44/50 (88%) patients from the 0.25% bupivacaine and 1.0% lidocaine cohort presented at least one adverse event, in contrast with 25/50 (50%) from the 0.125% bupivacaine and 1.5% lidocaine cohort ($p < 0.001$) (Fig. 3).

Discussion

This research aimed to establish bupivacaine diluted in lidocaine therapeutic performance when comparing different concentrations (0.125% vs. 0.25%) in terms of analgesic effect and safety (a lower rate of adverse events) during a cesarean section. In our study, a 0.125% bupivacaine concentration was demonstrated to be as effective as a 0.25% dissolution in the context of sensitive blockade assessment but even better when analyzing motor blockade (Fig. 1A). Patients from the 0.25% bupivacaine and 1.0% lidocaine cohort showed a significant tendency to hypotension toward the end of the analgesic effect. Likewise, patients from the 0.25% bupivacaine and 1.0% lidocaine cohort presented certain fluctuations in HR (Fig. 2B). Both RR and SpO_2 were stable in both groups (Friedman rank-sum test non-significant p-value). In the studied population, a lower bupivacaine concentration reached a more stable hemodynamic parameter. Regarding the adverse events, it was noteworthy that the 0.125% bupivacaine and 1.5% lidocaine cohort presented a significantly lower rate (50% vs. 80%; $p < 0.001$). Of these, hypotension occurred only in 4/50 patients in 0.125% bupivacaine and 1.5% lidocaine cohort, but 16/50 from 0.25% bupivacaine and 1.0% lidocaine cohort ($p = 0.006$).

The usefulness of bupivacaine with lidocaine as analgesic agents in a cesarean section has been previously studied, mainly due to its side effects:



* Pearson's Chi-squared test with Yates' continuity correction.

Figure 1. *Motor and sensitive blockade along with pre-, trans-, and post-operative, per each cohort study (0.125% bupivacaine and 1.5% lidocaine, green-gradient bars; 0.25% bupivacaine and 1.0% lidocaine, red-gradient bars). Notice that toward minute 20, 30, and 90, a significant deeper motor blockade.* **A:** *was reached in the 0.25% bupivacaine and 1.0% lidocaine cohort. Meanwhile, sensitive blockade.* **B:** *was statistically non-different between both study cohorts. *Pearson's Chi-squared test with Yates' continuity correction.*

cardiotoxicity and neurotoxicity[13]. Compared with ropivacaine, a higher therapeutic benefit has been demonstrated, mainly due to reducing adverse effects during the post-operative. Rodríguez-Ramón et al., in a recent clinical trial in which 114 pregnancy patients were included, determined that the 0.25% bupivacaine concentration presented better therapeutic efficacy than the 0.125% bupivacaine, without statistical differences regarding the variation of vital signs or adverse effects[14]. However, there is no reference in this research about the use of lidocaine. Lidocaine provides faster onset on epidural analgesia when compared to bupivacaine alone[4]. Neither does it provide detail regarding the different potentially studied adverse effects. Finally, it concludes that the measurement of other variables of interest is warranted to enrich the results. On the other hand, authors such as Rivero-Delgado[15] and Tejada-Perdomo[16], who also carried out clinical trials in a similar number of patients, demonstrated that subarachnoid administration of low doses of 3.75% bupivacaine with fentanyl is practical in terms of reducing adverse effects, particularly the hypotension, as shown in this study.

A recent meta-analysis concluded that in general interventions, combination of bupivacaine with lidocaine may decrease post-operative pain and opioid

Figure 2. *Mean arterial pressure (MAP; mmHg) and heart rate (HR; per minute) fluctuations along with pre, trans and post-operative, per each cohort study: 0.125% bupivacaine and 1.5% lidocaine, green line; 0.25% bupivacaine and 1.0% lidocaine, red line). Notice that median MAP.* **A:** *held out to hypotension in the 0.25% bupivacaine and 1.0% lidocaine cohort, but HR.* **B:** *remained stable along the pre-, trans-, and post-operative. *Mann–Whitney U test. †Friedman rank-sum test.*

consumption. Lidocaine had a stronger effect on the reduction of opioid consumption compared to bupivacaine[17]. It could explain similar outcomes when comparing sensitive blockade between both cohorts. Our 0.25% bupivacaine and 1.0% lidocaine cohort presented also a better motor blockade but at the expense of significant hypotension toward the end of the cesarean section. Those results are in agreement with Wang et al. double-blind and randomized trial. In this study, hypotension was shown in 8/20 (40%) pregnant women who underwent cesarean section using a lower concentration of bupivacaine 5 mg with lidocaine 5 mL, in contrast with 15/20 (75%) using a more concentrated preparation of bupivacaine 10 mg diluted on normal saline 5 mL[18]. The quality of analgesia and incidence of maternal hypotension is related to block level, which depends on the dose of bupivacaine[19]. However, Wang et al. research did not show a significant difference among motor or sensitive blockade. Furthermore, they did not detail hemodynamic data about as HR[18].

This research has several strengths. First, it was carried out in a gynecological referral institution, where the use of bupivacaine with lidocaine is widely spread. In this cohort, no patient required additional sedation during post-operative due to insufficient blockade. Second, it had an ideal number of patients for inferential analyses. In the same way, the consecutive recovery of data provides adequate fidelity to the obtained information. One of the study limitations was

Table 3. Mean arterial pressure (mmHg) and heart rate (per minute) fluctuations along with pre-, trans-, and post-operative, per each cohort study

	0.125% bupivacaine and 1.5% lidocaine (n = 50)	0.25% bupivacaine and 1.0% lidocaine (n = 50)	p-value
Mean arterial pressure (MAP) (median [minimum-maximum])			
	87.7 (66.7-120)	87.3 (73.3-130)	0.9230[a]
Pre–blockade	82.3 (63.3-119)	84.0 (63.3-117)	0.7880[a]
Blockade	79.3 (56.7-116)	77.0 (56.0-109)	0.6715[a]
10 min	75.7 (56.7-114)	74.3 (53.3-101)	0.5553[a]
20 min	73.3 (52.0-107)	73.7 (42.3-101)	0.3867[a]
30 min	73.7 (54.7-127)	75.5 (46.7-100)	0.3009[a]
60 min	80.2 (60.7-105)	74.3 (52.0-93.3)	0.0684[a]
90 min	83.3 (56.7-107)	73.3 (59.3-92.7)	0.0496[a]
120 min	86.7 (65.7-112)	67.3 (60.7-93.3)	0.0002[a]
Heart rate (HR) [median (minimum-maximum)]			
	90.0 (70.0-130)	80.0 (50.0-117)	0.0103[a]
Pre–blockade	90.5 (72.0-120)	83.0 (52.0-114)	0.0336[a]
Blockade	90.0 (70.0-113)	86.0 (48.0-103)	0.0072[a]
10 min	90.0 (70.0-115)	83.0 (43.0-107)	0.0090[a]
20 min	91.0 (56.0-117)	82.0 (49.0-110)	0.0285[a]
30 min	90.0 (52.0-110)	86.0 (49.0-112)	0.0474[a]
60 min	89.5 (70.0-120)	86.0 (15.0-117)	0.0621[a]
90 min	90.0 (70.0-110)	90.0 (66.0-118)	0.5307[a]
120 min	90.0 (70.0-110)	89.0 (70.0-103)	0.1530[a]

a. Mann–Whitney U test.

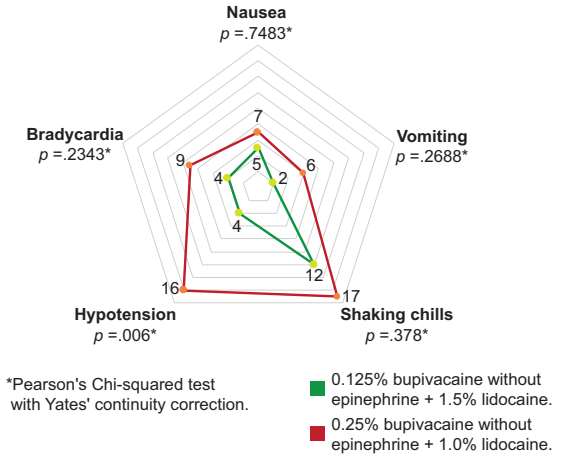


Figure 3. *Radar diagram representing the number of adverse effects associated with bupivacaine in the study population, according to each cohort study (0.125% bupivacaine and 1.5% lidocaine, green line; 0.25% bupivacaine and 1.0% lidocaine, red line). *Pearson's Chi-squared test with Yates' continuity correction.*

its observational and consequently non-randomized design, with lack of documentation about fluid administration, vasopressor requirements, post-operative bleeding, and assessment of patient satisfaction after cesarean section. This research was developed in a single healthcare center instead of a multicentric collaboration. These research results represent the only experience of a referral institution. Finally, our high rate of adverse events could be understood as secondary to the analgesic agents, surgical intervention, gestation per se, and its capability of exacerbating the side effects of administrated analgesic.

Conclusion

In the context of epidural analgesia during a cesarean section, using 0.125% bupivacaine without epinephrine and 1.5% lidocaine is associated with similar analgesic effects than 0.25% bupivacaine without epinephrine and 1.0% lidocaine. However, a higher bupivacaine concentration is significantly related to more frequent drug-related adverse events, especially hypotension toward the end of the cesarean section.

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Conflicts of interest

The authors declare no conflicts of interest.

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Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that no patient data appear in this article.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

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