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Association between hyperbaric bupivacaine dose and maternal hypotension: Retrospective database study of 8,226 women undergoing cesarean delivery under spinal anesthesia

--Manuscript Draft--

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Abstract:	Background: Low dose (≤8 mg) hyperbaric bupivacaine for spinal anesthesia during cesarean delivery results in reduced efficacy, yet as a secondary outcome was associated with reduced frequency of spinal-induced hypotension. Our primary aim was to investigate the relationship between hyperbaric bupivacaine dose and the occurrence of spinal-induced hypotension for cesarean delivery. Methods: Retrospective study of cesarean delivery under spinal or combined-spinal anesthesia with hyperbaric bupivacaine in one academic institution (two centers – tertiary and district) from 2012 to 2018. Data were retrieved from the anesthesia information management systems (Metavision, iMDsoft, Tel Aviv, Israel) and the hospital information system, including potential confounding factors, maternal age and weight, hypertensive disease of pregnancy, single/multiple gestation, gestational age, vasopressor administration, planned/urgent surgery, position during anesthesia placement (sitting/lateral), anesthesiologist seniority. Spinal-induced hypotension was defined as systolic blood pressure that either dropped >20% from baseline or <100 mmHg. The primary outcome of interest was the incidence of spinal-induced hypotension according to hyperbaric bupivacaine dose. Logistic regression was used to characterize the association between the dose of hyberbaric bupivacaine and spinal-induced hypotension after adjusting for confounding factors. Results: A total of 8,226 women were identified. The hyperbaric bupivacaine dose administered was <9mg for 2395 (29.1%), 9-9.5mg for 1031 (12.5%), 10mg for 4155 (50.5%) and >10mg for 645 (7.8%). We used a cut-off (<10mg versus ≥10mg) to

	assess for the primary outcome, using multivariable logistic regression. The incidence of at least one spinal-induced hypotension episode was higher in patients who received ≥10 mg hyperbaric bupivacaine, 75.8% versus 62.9% for doses below 10 mg, P < 0.0001; however even women with lower doses had hypotension. Hyperbaric bupivacaine dose <10mg was associated with a lower incidence of spinal hypotension, adjusted Odds ratio (OR) 0.774, 95% CI 0.669 to 0.897, P = 0.0006, adjusted for confounding factors. Umbilical cord pH was available for 2,684 (32.6%) cases. There were significantly more neonates with pH<7.2, among women who received hyperbaric bupivacaine ≥10mg (10.1%) versus women who received <10 mg, (6.8%) P = 0.0032, however in the adjusted model, h yperbaric bupivacaine dose <10mg was not associated with pH<7.2, OR 0.955 (95% CI 0.631 to 1.446, P = 0.829). Conclusion: Our major finding was that hypotension occurred at all doses of hyperbaric bupivacaine, yet occurrence of spinal hypotension was significantly associated with doses ≥ 10 mg after adjustment for potential confounders.
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Author Comments:	

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Anesthesia & Analgesia

Obstetric Anesthesia Section Editor

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Dear Dr Pittet and Dr Mhyre

Thank you for considering our revised manuscript, "Association between hyperbaric bupivacaine dose and maternal hypotension: Retrospective database study of 8,226 women undergoing cesarean delivery under spinal anesthesia" for possible publication in your journal *Anesthesia & Analgesia*.

None of the authors have any financial and personal relationships with other people or organizations that could inappropriately influence (bias) their work. I have no conflicts of interest to declare.

An abstract of this manuscript was presented at the Society for Obstetric Anesthesia and Perinatology, Phoenix Arizona, 2019.

The manuscript has been read by and approved by all authors. The authors received no writing assistance in the construction and writing of the manuscript. I am the guarantor and archivist of the manuscript.

Yours sincerely

Carolyn Weiniger MB ChB

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Page and line numbers refer to word document. All changes in tables and manuscript made in red font to assist identification.

The manuscript comments were removed and **comments** in response are presented here.

Comment: Word count was amended and updated.

Please rephrase this sentence to make it clear that using a dose >10mg increases/decreases the risk of pH<7.2.

Comment: P5, L7, this paragraph was amended: There were significantly more neonates with pH<7.2, among women who received hyperbaric bupivacaine ≥10mg (10.1%) versus women who received <10 mg, (6.8%) *P* = 0.0032, however in the adjusted model, hyperbaric bupivacaine dose <10mg was not associated with pH<7.2, OR 0.955 (95% CI 0.631 to 1.446, *P* = 0.829).

Check whether any cases of CSE anesthesia that required epidural supplementation were included/excluded from the study.

Comment: Women with CSE were not excluded even if a top-up was administered. There were 92 women who had a CSE and received an epidural top. These details were added to P17, L3, Figure legend (Figure 1), P9 L13.

The arrows for the flow diagram in figure 1 appear to be missing.

Comment: Fig 1 was edited and arrows added and updated with the general anesthesia cases removed after the previous revision (we had neglected to update this figure).

Comment: Switched “occurred” for your suggested “complicated”, P16, L3.

P11L17-19 Were these categories based on clinically meaningful cut points or some other justification.

Comment: These 4 categories were based on quartiles, added to the manuscript, P11, L17-19.

Starting P11, L19. based on visual inspection of —Clarify how these cut points were defined the data (Figure 2) versus the ROC

Comment: This was clarified.

P13 L13. The hods state that multivariable adjustment was used to produce the ROC met curve, but that would have required construction of the model with the bupivacaine cut point already defined.

eld the cutpoint It would seem that a simple visual inspection of the data (figure 2) would yi between 9.5 and 10m

Comment: This was clarified.

P14 - Clarify the directionality of association here. As currently stated, the value <1 suggests that higher bupivacaine doses trend towards a 4.5% reduction in the incidence of neonatal acidosis (as defined by pH<7.2) after adjustment. Is this the correct direction of association

Comment: The OR was indeed < 1, but was highly not significant (P-value: 0.829, 95% CI:[0.631;1.446]). Therefore, higher dose of bupivacaine does not increase or decrease the risk for pH<7.2 in the adjusted model.

P15 analysis. In my -Verify that unpredictable spread was demonstrated in the arzola meta practice, lower doses are more likely to result in unpredictable spread, and higher doses patient positioning with the cephalad level matching that nadir of reliably spread based on the thoracic curvature, but density of the cephalad block varying in direct relation to the dose. In the Arzola abstract, high doses did reduce the need for intravenous supplementation

Comment: Arzola framed the discussion as low doses versus high doses. Our discussion was amended to reflect this:

A lower dose is associated with less profound and less frequent hypotension, yet may have unpredictable spread, and requires more analgesia to enhance the block experienced.

P15. Maybe bvariables that influence dose –reak this into two separate sentences selectionband variables that influence the resultant block height, cephalad density, and duration

Comment. Amended, see also responses below.

P15- CSF volume influences resultant block height, but shouldn't influence dose selection

same as above, this would influence resultant block height

Comment: This was edited.

Table feedback

Table 1. Verify that all values are presented with a comparable degree of precision. Low dose bup maternal age median [IQR] is presumably 33.0 [28.0 to 37.0].

Comment. Amended

Presumably the 95% CI for the difference refers to the difference in means? Present this before the *P*-value so the item aligns with the mean(SD) for continuous variables.

Comment. Amended

Table 4. Verify the calculation for the 95% CI of the difference between groups for pH<7.2, since the difference spans 1 but the *p*-value is <<0.05.

Comment: The CI is: [-5.6% to -1.16%]. As noted in the table column, we are presenting the difference of the % not the ratio, therefore the value of interest is “0” not “1”.

Association between hyperbaric bupivacaine dose and maternal hypotension: Retrospective database study of 8,226 women undergoing cesarean delivery under spinal anesthesia

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Conflicts of Interest: None

Abbreviated Title: Dose of hyperbaric bupivacaine and spinal hypotension

Author contribution:

Carolyn F Weiniger. This author helped with the study idea, analyzed the data and drafted, wrote and approved the manuscript.

Michael Heesen. This author helped with the study design, analyzed the data and drafted, wrote and approved the manuscript.

David Knigin. This author helped with the study design, assessed the data, revised and approved the manuscript

Frederic Deutsch. This author helped with the study design, analyzed the data, revised and approved the manuscript

Nicole Hilber. This author helped with the study design, assessed the data, revised and approved the manuscript

Alexander Avidan. This author helped with the study design, assessed and analyzed the data, revised and approved the manuscript

Word Count:

Abstract: 385

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Abstract

Background: Low dose (≤8 mg) hyperbaric bupivacaine for spinal anesthesia during cesarean delivery results in reduced efficacy, yet as a secondary outcome was associated with reduced frequency of spinal-induced hypotension. Our primary aim was to investigate the relationship between hyperbaric bupivacaine dose and the occurrence of spinal-induced hypotension for cesarean delivery.

Methods: Retrospective study of cesarean delivery under spinal or combined-spinal anesthesia with hyperbaric bupivacaine in one academic institution (two centers – tertiary and district) from 2012 to 2018. Data were retrieved from the anesthesia information management systems (Metavision, iMDsoft, Tel Aviv, Israel) and the hospital information system, including potential confounding factors, maternal age and weight, hypertensive disease of pregnancy, single/multiple gestation, gestational age, vasopressor administration, planned/urgent surgery, position during anesthesia placement (sitting/lateral), anesthesiologist seniority. Spinal-induced hypotension was defined as systolic blood pressure that either dropped >20% from baseline or <100 mmHg. The primary outcome of interest was the incidence of spinal-induced hypotension according to hyperbaric bupivacaine dose. Logistic regression was used to characterize the association between the dose of hyberbaric bupivacaine and spinal-induced hypotension after adjusting for confounding factors.

Results: A total of 8,226 women were identified. The hyperbaric bupivacaine dose administered was <9mg for 2395 (29.1%), 9-9.5mg for 1031 (12.5%), 10mg for 4155 (50.5%) and >10mg for 645 (7.8%). We used a cut-off (<10mg versus ≥10mg) to assess for the primary outcome, using

multivariable logistic regression. The incidence of at least one spinal-induced hypotension episode was higher in patients who received ≥10 mg hyperbaric bupivacaine, 75.8% versus 62.9% for doses below 10 mg, *P* < 0.0001; however even women with lower doses had hypotension. Hyperbaric bupivacaine dose <10mg was associated with a lower incidence of spinal hypotension, adjusted Odds ratio (OR) 0.774, 95% CI 0.669 to 0.897, *P* = 0.0006, adjusted for confounding factors.

Umbilical cord pH was available for 2,684 (32.6%) cases. There were significantly more neonates with pH<7.2, among women who received hyperbaric bupivacaine ≥10mg (10.1%) versus women who received <10 mg, (6.8%) *P* = 0.0032, however in the adjusted model, hyperbaric bupivacaine dose <10mg was not associated with pH<7.2, OR 0.955 (95% CI 0.631 to 1.446, *P* = 0.829).

Conclusion: Our major finding was that hypotension occurred at all doses of hyperbaric bupivacaine, yet occurrence of spinal hypotension was significantly associated with doses ≥ 10 mg after adjustment for potential confounders.

Glossary of Terms

AIMS = anesthesia information management system

AUC = area under the curve

CI = confidence interval

CSE = combined-spinal-epidural

ED = effective dose

IRB = Institutional Review Board

OR = Odds Ratio

ROC = receiver operator curve

Key Points Summary:

Question: Is there a relationship between the dose of hyperbaric bupivacaine and spinal-induced hypotension during cesarean delivery?

Findings: Women who received <10 mg hyperbaric bupivacaine also experienced hypotension, and hyperbaric bupivacaine dose <10mg was associated with a lower incidence of spinal hypotension, adjusted OR 0.774, 95% CI 0.669 to 0.897, *P* = 0.0006.

Meaning: The choice of spinal anesthesia hyperbaric bupivacaine dose was associated with the incidence of spinal-induced hypotension, however since use of lower doses was also associated with hypotension, prophylactic vasopressors should be considered regardless of dose administered.

Introduction

Cesarean delivery is mostly performed under spinal anesthesia. The reported cesarean delivery effective dose (ED) 95 of hyperbaric bupivacaine for spinal anesthesia has been inconsistently reported as 11.2 mg, [1] and 12.6 mg. [2] Hypotension is commonly seen after spinal anesthesia for cesarean delivery, with quoted rates up to 70%, [3] depending on the definition of hypotension. The accepted definition for spinal-induced hypotension in this circumstance is decreased systolic blood pressure >20% from baseline or systolic blood pressure <100 mm Hg. Studies that investigated spinal-induced hypotension in healthy women were summarized by Arzola et al, [4] and Roofthooft et al, [5] including hyperbaric bupivacaine doses from 2.5 mg, [6] 3.75 mg, [7] 6.5 mg, [8] 6.6mg, [9] 7-9 mg, [10] 7-10mg, [11] 10 mg, [12,13] up to 13 mg. [14]

A meta-analysis of 12 studies, including 1004 women, reported inadequate analgesia in clinical practice with the use of ≤8 mg hyperbaric bupivacaine for spinal anesthesia among women undergoing cesarean delivery.[4] A planned secondary study outcome was the occurrence of hypotension, and administration of ≤8 mg hyperbaric bupivacaine was associated with less frequent spinal-induced hypotension. There was considerable heterogeneity for the outcome of hypotension across these studies, including a recording of mean blood pressure, systolic blood pressure, or predetermined decrease from baseline blood pressure. Finally, although it is important to avoid spinal-induced hypotension to optimize neonatal outcomes, studies usually do not report umbilical artery pH, a marker of neonatal stress. [15]

The relationship between dose of hyperbaric bupivacaine and frequency of spinal-induced hypotension has not been investigated in a large cohort over a range of doses, as the

primary study outcome. To fill this gap, we assembled a two-center retrospective cohort, and collected a range of clinical and demographic variables to investigate the relationship between hyperbaric bupivacaine dose and the incidence of spinal-induced hypotension, with adjustment for potential confounding variables. In addition, we investigated the relationship between hyperbaric bupivacaine dose, vasopressor use and umbilical artery pH.

Methods

Ethical approval: The study was approved by the Institutional Review Board (IRB) of the Hadassah Medical Organization, Jerusalem, Israel and the requirement for written informed consent was waived by the IRB (0316-11-HMO, 30th November 2011, Chairperson Prof. Tova Chajek-Shaul).

Setting: This retrospective study was performed in a tertiary medical center with two labor and delivery units: Hadassah Medical Center, Ein-Kerem and Hadassah Medical Center, Mount Scopus, Jerusalem. The data collection period was from 01/2012 to 12/2018. There were approximately 11, 000 deliveries per year with a cesarean delivery rate 20%.

Inclusion criteria: Cesarean delivery, single-shot spinal or combined-spinal-epidural (CSE) anesthesia using hyperbaric bupivacaine, blood pressure measurements recorded in the electronic medical record.

Exclusion criteria: General and epidural anesthesia for cesarean delivery. Women who received CSE and had epidural top-up were not excluded.

Neuraxial anesthesia: In both institutions, spinal anesthesia was performed after a preload of 1L Ringer's Lactate solution. Spinal anesthesia was usually performed in the sitting position, but occasionally performed in the lateral position. After preparation of the back using Chlorhexidine 0.5%, and local anesthesia injection of 2-3 mL of 1% Lignocaine, a pencil point needle, usually 27 Gauge at the tip and 22 Gauge at the proximal shaft (Temena Group, Felsberg-Gensungen, Germany) was used to locate the intrathecal space. The spinal mixture included fentanyl 20-25

μg, intrathecal morphine 100 μg and hyperbaric bupivacaine. The dose was discretionary, but the recommended departmental dose was 10 mg (0.5%, 2 mL). After intrathecal injection, women were placed in the left lateral tilt position (bed tilted 15-20 degrees), and when a T8 sensory level was achieved, the surgeon started cleansing to place the urinary catheter. Prior to skin incision the surgeon usually requested that the operating table be levelled. When CSE was performed, clinicians used an 18G Touhy needle (B. Braun Melsunge AG, Melsunge, Germany) and a 25 G, 123 mm pencil-point spinal needle, (Temena Group, Felsberg-Gensungen, Germany).

Prophylactic vasopressors were not used for spinal-induced hypotension during the study period. The anesthesiologists aimed to maintain the systolic blood pressure above 100 mm Hg and to treat if the blood pressure dropped below 20% of baseline systolic blood pressure. Phenylephrine was the drug of choice, administered in doses of 50-200 μg boluses. Ephedrine bolus, 5-10 mg, was recommended if the maternal heart rate was below 70 beats per minute.

Data and sources: The following data were retrieved from the anesthesia information management system (AIMS) (Metavision, iMDsoft, Tel Aviv, Israel) and the hospital computerized information system: maternal age, maternal weight, gestation (single/multiple), hypertensive disease of pregnancy, gestational age at delivery, time of anesthesia start, neuraxial technique (spinal or combined-spinal epidural), position during neuraxial anesthesia placement (sitting/lateral), administration of vasopressor boluses (phenylephrine/ephedrine), and time of delivery. Emergency surgery was noted for women undergoing unscheduled cesarean who presented not in labor, and intrapartum cesarean deliveries. Umbilical cord pH

was retrieved for planned cesarean delivery, where available. The period of interest was from anesthesia start until neonatal delivery, also marked in the AIMS.

Study Outcome Measures:

The primary predictor variable was the dose of hyperbaric bupivacaine administered.

The primary study outcome was the occurrence of spinal-induced hypotension, which was recorded if the systolic blood pressure decreased either >20% below baseline or <100 mmHg.

There were two secondary study outcomes: vasopressor use and umbilical artery pH (where available).

Statistical Methods

The data were tabulated into Microsoft Excel 2013 (Microsoft Corporation, Redmond, WA). Continuous variables were summarized by a mean and standard deviation (after inspection for normality in the histogram and Q-Q plots) and compared between the doses of hyperbaric bupivacaine using t-test. Categorical data presented as counts and percentages and compared with the chi-square test or the Fisher's exact test. The Spearman Rank Correlation was performed to assess the relationship between hyperbaric bupivacaine dose and vasopressor treatment dose (phenylephrine, ephedrine). Hyperbaric bupivacaine dose was further categorized based on quartiles as a four-level variable (<9mg 9-9.5mg, 10mg, and >10mg) described using counts and percentages, and subsequently collapsed into a dichotomous variable for further analysis (<10mg versus ≥10mg). This threshold was assessed through the receiver operator (ROC) curve of bupivacaine dose extracted from a univariate logistic

regression model. For each point on the curve, the Euclidean distance to the (0, 1) point was calculated, and the bupivacaine dose with the smallest distance was selected as the optimal cutoff. For two doses (9.5 and 10) we received the minimal distance, and the cutoff of 10 mg was selected since this dose was also the median dose. [16]

We performed a univariable analysis to identify potential confounding factors ($P < 0.05$) for the dependent variable, spinal-induced hypotension. Logistic regression (multivariable) was used to characterize the association between spinal-induced hypotension and hyperbaric bupivacaine dose, adjusted for confounding factors listed in the multivariable logistic regression table.

Logistic regression (multivariable) was used to characterize the association between umbilical cord pH <7.2 (planned cesarean deliveries only, as other factors likely strongly influence pH after non-planned cesarean delivery) and hyperbaric bupivacaine dose after controlling for potential confounding factors. [17] We present odds ratios (OR) and 95% confidence intervals (CI) for the regression analyses.

An a priori sample size calculation was not performed, and the sample size is based on all available cesarean deliveries with spinal/combined-spinal anesthesia during the observation period.

Statistical analyses were performed using SAS® version 9.4 (SAS Institute, Cary NC, USA) software. $P < 0.05$ was defined as significant for the primary outcome and $P < 0.01$ for secondary outcomes. Missing data were not imputed.

Results

A total of 8, 226 women were identified in the AIMS. The study profile of the included cases is presented in Figure 1 and their characteristics are summarized in Table 1. The hyperbaric bupivacaine dose administered was <9mg for 2395 (29.1%), 9-9.5mg for 1031 (12.5%), 10mg for 4155 (50.5%) and >10mg for 645 (7.8%) (Table 2 and Figure 2). There were 2432 (29.6%) women who experienced no episodes of hypotension. The incidence of at least one hypotensive episode was higher for women who received ≥10mg hyperbaric bupivacaine that those who received less (75.8% versus 62.9%, $P < 0.0001$). Phenylephrine was administered to 3,039 (36.9%) women and ephedrine to 2,153 (26.1%) women (Table 2). Both vasopressors were administered to 844 (10.3%). The correlation coefficient for the association between the dose of hyperbaric bupivacaine and phenylephrine was 0.4450, $P < 0.0001$; and for the dose of hyperbaric bupivacaine and ephedrine was 0.0125, $P = 0.254$.

The minimal distance on the ROC curve of the hyperbaric bupivacaine dose (in a univariate logistic regression model) to the (0,1) point was obtained for 9.5 and 10.0 mg. Since the median hyperbaric bupivacaine dose was 10mg, this confirmed the threshold to assess for occurrence of hypotension in the multivariable regression model. Women who received lower hyperbaric bupivacaine doses had hypotension. The area under the receiver operator curve was 0.5757, Supplementary Figure 1, for discrimination between women who experienced hypotension and those who did not.

Table 3 presents the odds ratio of spinal-induced hypotension according to hyperbaric bupivacaine dose, and the OR adjusted for confounding factors listed in the Table. Hyperbaric

bupivacaine dose <10mg was associated with a lower incidence of spinal hypotension, adjusted OR 0.774, 95% CI 0.669 to 0.897, *P* = 0.0006.

Umbilical artery pH was available for 2,684 (32.6%) cases. Although high bupivacaine dose was associated umbilical pH < 7.2 in the bivariable analysis (Table 4), the association was not significant after adjustment for gestational age, hypertensive disease maternal weight and age, attending versus resident anesthesiologist, position placing spinal anesthesia (sitting vs. lateral), spinal vs. combined-spinal anesthesia, and tertiary vs/ district center, with adjusted OR 0.955, 95% CI 0.631 to 1.446, *P* = 0.829.

Discussion

In this retrospective study of cesarean deliveries under spinal anesthesia we report that hyperbaric bupivacaine dose <10 mg was associated with a lower incidence of spinal-induced hypotension, adjusted OR 0.774, 95% CI 0.669 to 0.897, *P* = 0.0006. Nevertheless, the majority of patients experience at least one hypotensive episode, regardless of bupivacaine dose (76% if ≥10mg hyperbaric bupivacaine versus 63% if <10mg). This study enabled an opportunity to examine the relationship between hyperbaric bupivacaine dose and spinal-induced hypotension in a clinical environment where a range of doses was selected according to anesthesiologists' preference, without use of vasopressor prophylaxis.

There are no universally recommended doses of hyperbaric bupivacaine for cesarean delivery.[4] The minimal efficacious dose may be associated with a higher block failure rate, yet less hypotension.[2,4,8,10] Onishi et al. reported the ED50 as 6 mg (95% CI, 4.5 to 7.5) while the ED95 was considerably higher (12.6 mg (95% CI, 7.9 to 17.2)). Ginosar et al. reported the ED95 as 11 mg; thus, the adequate cesarean delivery anesthesia dose range appears to be wide.[1,2] A lower dose is associated with less profound and less frequent hypotension, yet may have unpredictable spread, and requires more analgesia to enhance the block experienced. [4] Dose selection may be dependent on factors such as patient population, [9] body mass index, [2,20] anticipated surgical duration, and the desired sensory level for anesthesia. [21] Resultant block height and duration can be affected by variability in cerebro-spinal fluid volume, [18] patient position during spinal anesthesia placement, [1] and use of vasopressors that may limit spread of local anesthesia through vessel constriction. [19]

Given that lower doses of bupivacaine may be associated with less hypotension, it is plausible to anticipate that women receiving lower doses would require less vasopressor treatment. In our study, hypotension occurred in the majority of spinal anesthetics, even when lower doses were administered. Finding that lower doses were associated with spinal-induced hypotension, albeit less commonly, demonstrated that even with low doses (<10mg) of bupivacaine, vasopressor prophylaxis should be used.

Data for neonatal pH is usually available in smaller prospective studies yet often lacking in retrospective database studies. One strength of our study was neonatal pH data for >2,700 cesarean deliveries, that corroborated prior findings. The adjusted model showed that bupivacaine dose was not associated with neonatal pH <7.2 in the clinical context where vasopressor boluses were used to rapidly treat maternal hypotension. In an Israeli population of >900 women undergoing cesarean delivery, [15] hypotension appeared well-tolerated when looking only at Apgar scores (1% of neonates had an Apgar <7 at 1-min), but this study did not assess umbilical artery pH as was possible in the current study.

There are a number of limitations to this study. First, we lack comprehensive data on concurrent disease and there is a risk of residual confounding due to unobserved factors. For example, although we retrieved data for hypertensive disease of pregnancy, we were unable to identify women with preeclampsia, particularly those with severe features. We also lacked contemporary definition of emergency surgery, [22] thus the urgency of surgery, a factor associated with spinal hypotension occurrence could not be evaluated in a reproducible manner. Second, the generalizability of the data is unclear and depends on the applicability of

our clinical practice to other settings; for example, other centers may not achieve adequate anesthesia using hyperbaric bupivacaine doses used in our population. We excluded all cases of non-spinal anesthesia, including conversion to general anesthesia. In our cohort adequate analgesia was provided with hyperbaric bupivacaine doses below 10 mg, and among women who received a CSE, 92 received an epidural top-up (spinal hyperbaric bupivacaine dose was mean (SD) 9.2 (1.4) mg, median (IQR) 10 (8-10) mg). Importantly, use of the lower doses did not obviate occurrence of spinal-induced hypotension. Thirdly, the baseline blood pressure measurement was determined as the first available in the AIMS system, and not performed using three separate measurements, and the recommended blood pressure measurement interval was between 1 and 2.5 minutes. These reflect clinical practice and not that used in the artificial setting of a randomized controlled trial. A meta-analysis suggested that patient positioning during spinal performance was associated with spread of the resulting blockade, with more cephalad block in lateral versus sitting position.[23] We did not have a record of the sensory spread of the block. In addition, we lacked information on injection speed, barbotage, and time in the placement position after injection of spinal anesthesia.[24] Our practice is usually to immediately place the patient in the supine position following intrathecal injection. The dose of fentanyl may impact dose of bupivacaine required and intraoperative hypotension – and in all cases the fentanyl dose was 25 µg or below, however we did not control for this in our study. [25] Finally we did not use anti-hypotensive prophylaxis – rather treatment. Although use of prophylaxis would be ideal, and has since become more widespread practice, the lack of use in our center provided a unique opportunity to study the association with hyperbaric bupivacaine dose.

In conclusion, use of lower hyperbaric bupivacaine dose reduced but did not eliminate spinal-induced hypotension, in a clinical setting where hypotension was treated rather than prevented with prophylactic vasopressors. This confirms that even women who receive lower doses of hyperbaric bupivacaine for spinal anesthesia for cesarean delivery require vasopressor prophylaxis. The dose of required vasopressor prophylaxis should be investigated in future studies according to hyperbaric bupivacaine doses administered among different populations with varying patient characteristics.

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Figure Legends

Figure 1. Identification of the study cohort. Includes all women with spinal/combined-spinal-epidural (CSE) with blood pressure record available in the electronic medical record. Women with CSE who received epidural top-up administration (N=92) were not excluded.

Figure 2. The incidence of at least one spinal-induced hypotension episode plotted against the intrathecal bupivacaine dose (mg).

Supplementary Figure 1. Receiver operator characteristics (ROC) curve for the hyperbaric bupivacaine dose (as a continuous variable) for discrimination between women who experienced hypotension and those who did not.

Table

	All cohort N=8226*	Low dose bupivacaine <10 mg N=3425	High dose bupivacaine ≥10 mg N=4801	P value 95% confidence interval for difference of means
Maternal age years (mean(SD); median [IQR]) §	33.1 (6.0); 33.0 [29.0 to 37.0]	32.7 (6.1); 33 [28.0 to 37.0]	33.4 (5.8); 33.0 [30.0 to 37.0]	<0.0001 (-0.99 to -0.47)
Maternal weight kg (mean(SD); median [IQR]) §	79.3 (15.3); 77.0 [70.0 to 88.0]	77.7 (14.2); 75.0 [68.0 to 85.0]	80.5 (16.0); 78.0 [70.0 to 90.0]	<0.0001 (-3.42 to -2.11)
Gestation age weeks (mean(SD); median [IQR] (N)) §	37.5 (2.1); 38.2 [37.0 to 38.4] (N=7075)	37.3 (2.3); 38.0 [37.0 to 38.3] (N=3101)	37.7 (1.8); 38.0 [37.0 to 38.6] (N=3974)	<0.0001 (-0.51 to -0.32)
Center n% ∫ Tertiary District	4231 (51.4%) 3995 (48.6%)	343 (10.0%) 3082 (90.0%)	3888 (81.0%) 913 (19.0%)	<0.0001
Anesthesia mode n% ∫ Spinal Combined spinal-epidural	7680 (93.4%) 546 (6.6%)	3306 (96.5%) 119 (3.5%)	4374 (91.1%) 427 (8.9%)	<0.0001

Position Sitting Lateral	 7112 (87.2%) 1046 (12.8%) N=8158	 2837 (83.1%) 577 (16.9%) N=3414	 4275 (90.1%) 469 (9.9%) N=4744	 <0.0001
Planned cesarean delivery n% ∫	5736 (69.7%)	2210 (64.5%)	3526 (73.4%)	<0.0001
Seniority of anesthesiologists n% ∫ Resident Attending Resident + Attending	 2547 (31.0%) 3672 (44.6%) 2020 (24.4%)	 1416 (41.3%) 1778 (51.9%) 236 (6.8%)	 1131 (23.6%) 1894 (39.5%) 1784 (36.9%)	 <0.0001
Hypertensive Disease n% ∫ (N)	182 (2.6%) (N=7083)	97 (3.1%) (N=3103)	85 (2.1%) (N=3980)	0.009
Multiple gestation Single gestation n% (N) ∫	862 (12.2%) 6222 (87.8%) (N=7084)	423 (13.6%) 2681 (86.4%) (N=3104)	439 (11.0%) 3541 (89.0%) (N=3980)	0.0009

Table 1: Characteristics of center, anesthesia, maternal details for study cohort and according to low (<10mg) and high (10 mg or above) hyperbaric bupivacaine for spinal anesthesia

Key: * N noted where different; CI = confidence interval; the centers differed for seniority of anesthesiologists as one is mainly staffed by attending anesthesiologists; SD = standard deviation; IQR = interquartile range; ∫ = Chi-square test; § = Student's t-test

Table 2: Anesthesia details according to dose of hyperbaric bupivacaine used, <10 mg versus 10 mg or above

	All cohort N=8226	Low dose bupivacaine <10 mg N=3425	High dose bupivacaine ≥10 mg N=4801	P value (95% confidence interval for difference)
Bupivacaine dose mg mean(SD); median [IQR] §	9.19 (1.47); 10.0 [8.0 to 10.0]	7.76 (1.09); 8.0 [7.0 to 9.0]	10.21 (0.62); 10.0 [10.0 to 10.0]	
Hypotension occurred n% ∫	5794 (70.4%)	2153 (62.9%)	3641 (75.8%)	<0.0001 (10.96% to 15.0%)
Phenylephrine dose mcg mean(SD); median [IQR] §	141.0 (265.5); 0.0 [0.0 to 200.0]	24.5 (104.4); 0.0 [0.0 to 0.0]	224.1 (310.5); 100.0 [0.0 to 400.0]	<0.0001 (-209.1 to -190.2)

Ephedrine dose mg mean(SD); median [IQR] §	4.0 (10.7); 0.0 [0.0 to 5.0]	3.8 (7.9); 0.0 [0.0 to 5.0]	4.2 (12.3); 0.0 [0.0 to 5.0]	0.1235 (-0.78 to 0.09)
Anesthesia to incision time mins mean(SD); median [IQR] (N) §	18.7 (9.9); 17 [13 to 23] (N=8200)	15.2 (7.8); 5 [11 to 18] (N=3417)	21.3 (10.4) 20 [15 to 25] (N=4783)	<0.0001 (-6.47 to -5.68)
Anesthesia to delivery time mins mean(SD); median [IQR] §	25.7 (11.2); 24.0 [19.0 to 31.0]	21.3 (8.7); 21.0 [16.0 to 25.0]	28.9 (11.7); 28.0 [22.0 to 34.0]	<0.0001 (-8.01 to -7.13)
Anesthesia to surgery end time mins mean(SD); median [IQR] §	49.1 (54.2); 48.0 [38.0 to 60.0] (N=8200)	40.8 (43.8); 40.0 [33.0 to 48.0] (N=3417)	55.0 (59.9); 55.0 [44.0 to 67.0] (N=4783)	<0.0001 (-16.43 to -11.94)

Key: SD = standard deviation; IQR = interquartile range; ∫ = Chi-square test; § = Student's t-test

Table 3. Multivariable logistic regression model of hyberbaric bupivacaine dose effect on spinal-induced hypotension adjusted for confounders

	Odds Ratio	95% Confidence Intervals	P-value
Hyperbaric bupivacaine dose <10 vs ≥ 10 mg	0.774	0.669 to 0.897	0.0006
Maternal age, years (continuous)	1.022	1.013 to 1.031	<0.0001
Planned surgery vs emergency	1.336	1.187 to 1.503	<0.0001
Resident vs. Resident and Attending	0.851	0.723 to 1.003	0.286
Attending vs. Resident and Attending	0.827	0.707 to 1.003	0.057
Maternal weight, kg (continuous)	1.015	1.011 to 1.019	<0.0001
Gestational age, weeks (continuous)	1.027	0.999 to 1.055	0.0565

Tertiary vs district center	1.413	1.208 to 1.652	<0.0001
Multiple vs singleton gestation	1.147	0.967 to 1.361	0.115
Spinal vs not combined-spinal anesthesia	0.902	0.722 to 1.126	0.362
Hypertensive disease	0.755	0.532 to 1.070	0.114
Anesthesia performed in sitting vs lateral position	1.064	0.913 to 1.241	0.427

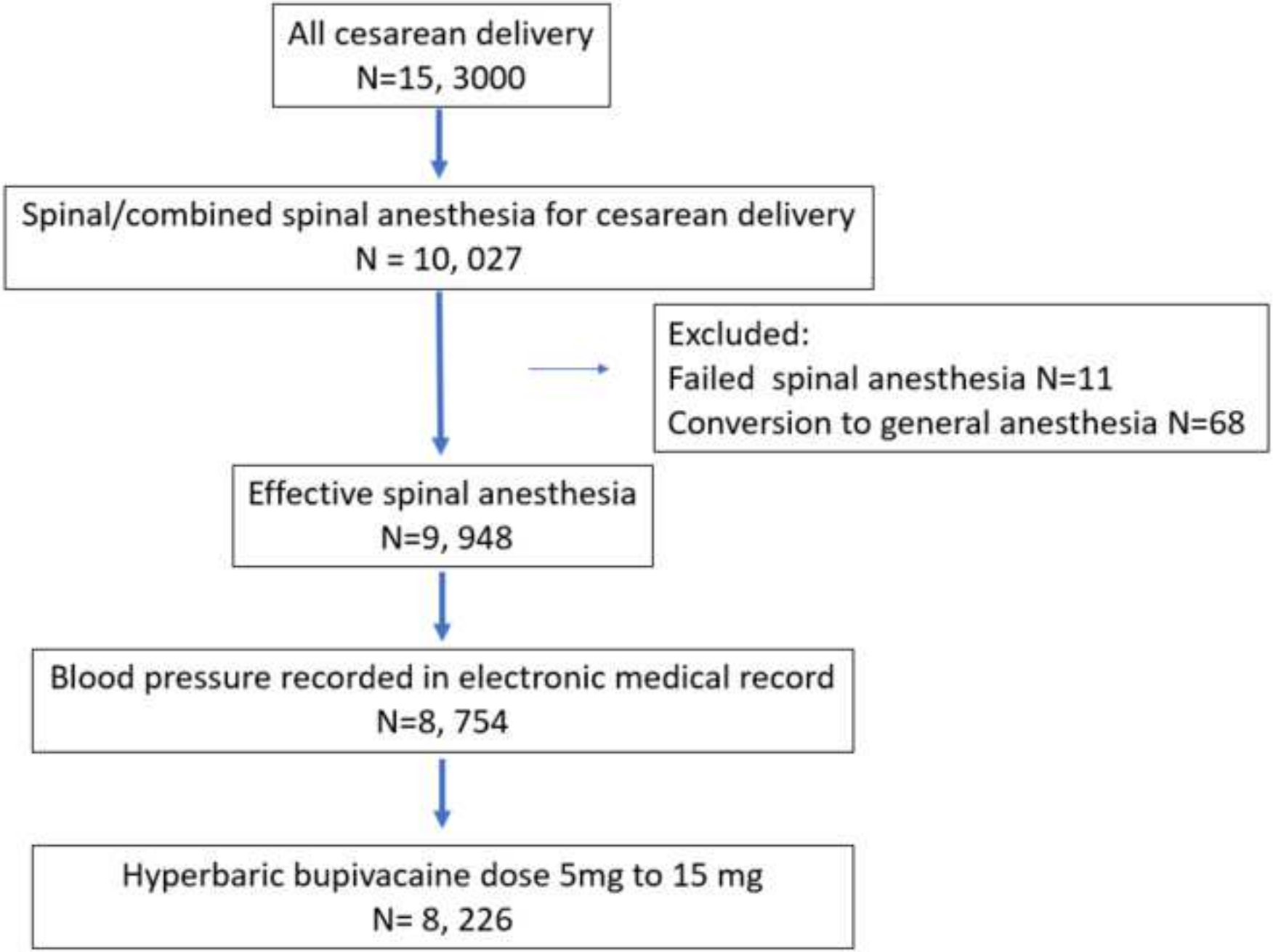
Table 4: Neonatal outcomes

	N=2684	Low dose bupivacaine <10 mg N=1103	High dose bupivacaine ≥10 mg N=1581	P value (95% confidence interval for the difference)
Umbilical artery pH mean(SD); median [IQR] §	7.30 (0.07) 7.31 [7.27 to 7.34]	7.31 (0.07); 7.32 [7.28 to 7.36]	7.28 (0.07); 7.30 [7.26 to 7.33]	<0.0001 (0.022 to 0.033)
pH < 7.2 n% ∫	234 (8.72%)	75 (6.80%)	159 (10.06%)	0.0032 (-5.36% to -1.16%)
pH < 7.0 n% ¥	12 (0.45%)	2 (0.18%)	10 (0.63%)	0.1386 (-0.92% to 0.01%)

Key: ∫ = Chi-square test; § = Student's t-test; ¥ = Fisher's exact test; IQR = interquartile range

Neonatal data are for planned cesarean delivery only

Flowchart



Figure

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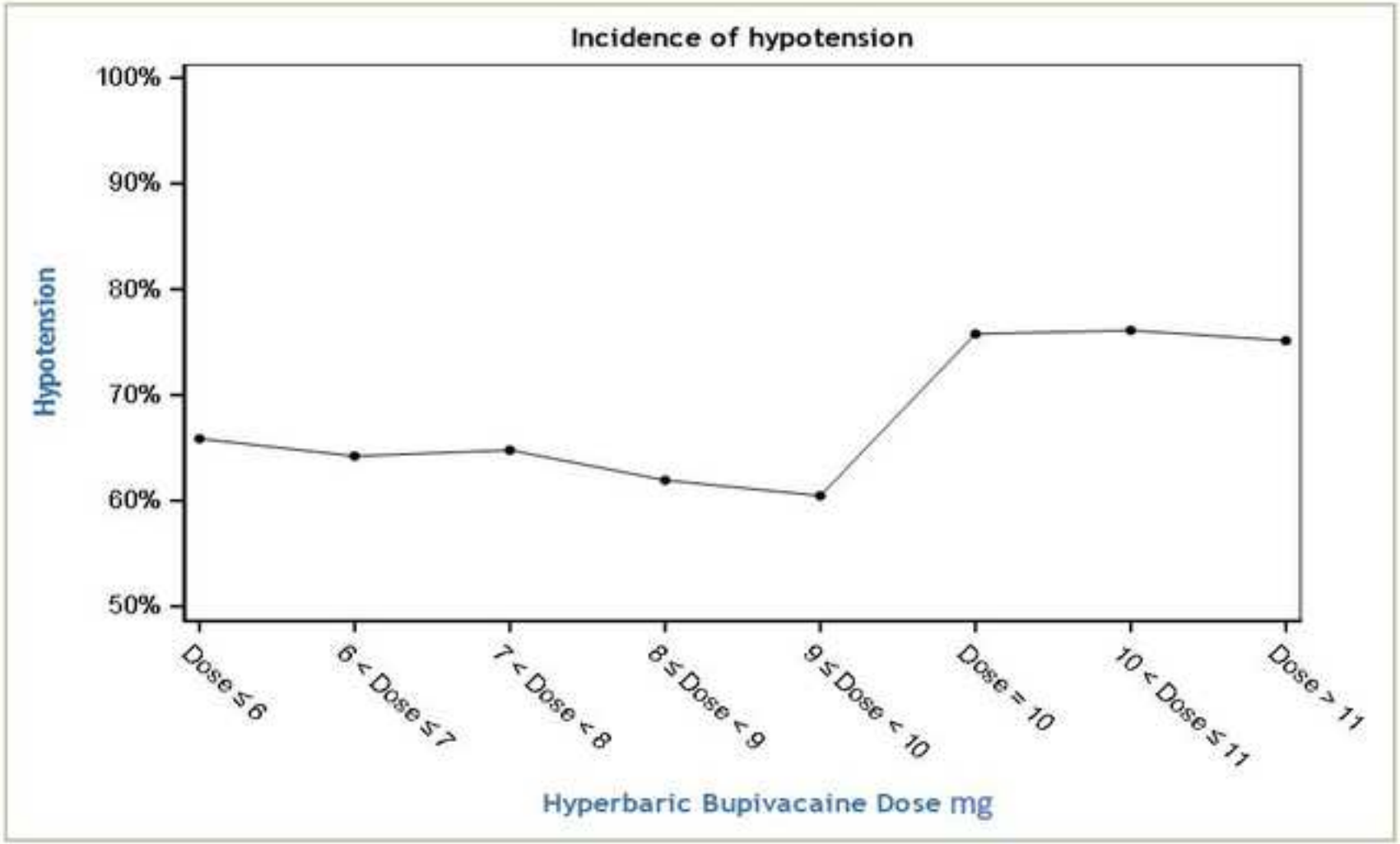

Supplemental Data File (.doc, .tif, .pdf, etc., Published Online Only)