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Spinal bupivacaine dose and recorded blood pressure during caesarean delivery without intrathecal opioids: a retrospective cohort study

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Abstract

Background

The association between spinal bupivacaine dose and recorded blood pressure within commonly used dose ranges remains uncertain, particularly without intrathecal opioids. We examined this association in historical clinical practice.

Methods

This single-centre retrospective study included 999 caesarean deliveries in 955 women given single-shot spinal anaesthesia without preceding epidural labour analgesia, 2016–2020. Hyperbaric bupivacaine doses were 9–16 mg, with 85.9% receiving 11–13 mg. The primary outcome was the lowest recorded systolic pressure between spinal injection and delivery. Doses ≥ 12 and < 12 mg, after exclusion of conversions to general anaesthesia, were compared using multivariable regression, propensity-score weighting and matching. Outcomes and covariates were chosen after preliminary results. A separate exploratory cohort of 207 records after epidural labour analgesia used fixed 0–25-minute measurements. Eight published definitions of hypotension were also applied.

Results

The adjusted mean difference in the primary outcome was − 0.19 mmHg (95% confidence interval [CI] − 2.43 to 2.05); the association per additional milligram was − 0.14 mmHg (− 1.02 to 0.74). Weighted and matched estimates were also near zero. Post-delivery intravenous fentanyl was given in 31.6% versus 24.7% of deliveries at < 12 versus ≥ 12 mg (adjusted odds ratio for ≥ 12 mg, 0.71; 95% CI 0.49 to 1.03). Hypotension (≤ 90 mmHg) occurred in 42.3% and 43.1% of lower- and higher-dose deliveries (adjusted odds ratio 1.19; 0.83 to 1.69). In the secondary cohort, the adjusted difference in the lowest recorded pressure was 1.55 mmHg (− 2.82 to 5.92). Across the eight definitions the measured incidence ranged from 20.9% to 88.8% and the direction of the association with baseline systolic pressure reversed, while the dose estimate remained compatible with the null under every definition.

Conclusions

Observed adjusted differences in recorded systolic pressure were small in this historical cohort. Hypotension incidence and its association with baseline pressure varied by definition, so outcome definitions need to be specified explicitly when studies are interpreted or compared. Non-random dose selection, intermittent measurements and incompletely recorded vasopressor treatment limit interpretation; these findings do not establish equivalent clinical safety, the optimal dose or the benefit of changing dose in contemporary practice.

Background

Selecting an intrathecal bupivacaine dose for caesarean delivery requires consideration of surgical anaesthesia and haemodynamic stability. Guidance emphasises sufficient local anaesthetic and opioid dosing,[1] while uncertainty about the appropriate bupivacaine dose continues to be discussed.[2] The American Society of Anesthesiologists cites an effective dose in 95% of patients (ED95) of approximately 12 mg of hyperbaric bupivacaine when combined with intrathecal opioids.[3] Such estimates do not directly establish the dose requirement without opioid adjuvants.

A meta-analysis of twelve randomised trials found that low-dose bupivacaine (≤ 8 mg) increased intraoperative analgesic supplementation (risk ratio 3.76, 95% confidence interval [CI] 2.38 to 5.92) while reducing hypotension (0.78, 0.65 to 0.93).[4] A separate systematic review reported inadequate neuraxial anaesthesia in 14.6% of elective caesarean deliveries in trials using doses at or above ED95 estimates.[5] These findings illustrate why haemodynamic outcomes alone cannot establish the overall suitability of a dose strategy.

Dose-ranging trials and subsequent reviews have examined the balance between haemodynamic effects and adequate anaesthesia,[6–8] but comparisons across studies are complicated by opioid adjuvants, neuraxial technique and vasopressor management. The association between modest dose differences and blood pressure within the dose range used in opioid-free single-shot spinal practice remains incompletely characterised.

Outcome definition also matters. A systematic search identified fifteen definitions of spinal-induced hypotension, which produced incidences from 7.4% to 74.1% when applied to one cohort.[9] A database study of 8226 women examined a lower dose distribution than ours, with a median of 10 mg in its higher-dose group.[10] Published dose-finding studies with opioids[6, 11] and evidence concerning hypobaric preparations[12] cannot be transferred directly to hyperbaric bupivacaine without intrathecal opioids.

We had two aims. The first was to estimate the association between bupivacaine dose and the lowest recorded systolic pressure before delivery in a historical cohort receiving spinal anaesthesia without intrathecal opioids, across the dose range actually used. The second was to explore how alternative definitions of hypotension affected its measured incidence and the adjusted associations with bupivacaine dose and with baseline systolic pressure within the same cohort. A clinically distinct cohort undergoing spinal anaesthesia after epidural labour analgesia was analysed separately. We report adjusted associations and their uncertainty; exploratory post hoc equivalence analyses are confined to the supplementary material.

Methods

Design, setting and reporting

This was a retrospective cohort study at Taipei Veterans General Hospital, a tertiary referral centre, reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement and approved by the institutional review board (IRB-TPEVGH no. 2020-10-010CC), which waived written informed consent for this analysis of existing records. Repeat deliveries by the same woman, within and across the two cohorts, were identified from the medical record number held in the source files; no individually identifiable information is reported.

Relationship to previous reports from this cohort

One analysis of these records has been published and a second accepted for publication. The first examined risk factors for ephedrine requirement and hypotension; bupivacaine dose was considered in stepwise selection but did not enter the final models.[13] The accepted report examined prior epidural labour analgesia, with conversion to general anaesthesia as its primary outcome and hypotension among its findings.[14] The present analysis reuses records from these reports to address the dose comparison. The overlap is disclosed because the additional contribution is the dose-specific analysis, rather than a new source population.

Participants

We analysed 999 caesarean deliveries under single-shot spinal anaesthesia without preceding epidural labour analgesia between April 2016 and March 2020, comprising 955 women, 44 of whom contributed two deliveries. The cohort is defined by the anaesthetic pathway rather than by urgency. The recorded indications include previous caesarean section, malpresentation, dysfunctional labour, prelabour rupture of membranes and non-reassuring fetal status; that field is not a validated classification of urgency, and these records should not be read as a wholly elective series. Of 1522 records screened for caesarean delivery in that period, 283 were excluded: 181 on blood-pressure criteria (baseline systolic pressure below 90 mmHg 2, pre-existing hypertension 36, pregnancy-induced hypertension 47, pre-eclampsia 96), 32 for surgical anaesthesia other than spinal (epidural top-up 6, general anaesthesia 26), 3 for vaginal delivery before transfer to the operating theatre and 67 for missing data. The flow of deliveries into the two cohorts is shown in Fig. 1. Of the remaining 1239 deliveries, 1025 were under spinal anaesthesia without labour epidural analgesia; 26 of these were converted to general anaesthesia, leaving the 999 analysed here. A separate secondary cohort comprised 207 delivery records of intrapartum caesarean delivery under spinal anaesthesia after epidural labour analgesia, assembled for the accepted report.[14] The same 1239 deliveries included 214 in which spinal anaesthesia followed labour epidural analgesia; 7 were converted to general anaesthesia, leaving 207. These 207 records came from 205 women and included no delivery that also appears in the primary cohort, although 25 women contributed to both cohorts on different dates. The cohorts were analysed separately because prior epidural treatment and obstetric circumstances differed. The secondary cohort was not treated as an independent validation sample for the primary endpoint.

Anaesthetic management

Spinal anaesthesia was performed at the L3–4 or L4–5 interspace with a 25- or 27-gauge pencil-point needle, using 0.5% hyperbaric bupivacaine. Intrathecal opioid was not part of departmental practice during the study period and is not a separately recorded variable in the analysis datasets; heavy bupivacaine alone was the departmental standard throughout, reflecting institutional practice rather than case-by-case choice. The attending anaesthetist chose the dose according to habitus. Crystalloid loading was routine, beginning before the block and continuing through and after it; the datasets record only the total volume given, which cannot separate preload from co-load. Prophylactic ephedrine was given at the anaesthetist's discretion rather than by protocol. Blood pressure and heart rate were measured non-invasively at least every five minutes; sensory level was assessed by pinprick. Duration of anaesthesia was taken from the recorded start and end of anaesthesia.

Relation of the recorded practice to current recommendations

The recorded practice was the departmental standard throughout the study period and differs in several respects from current recommendations for enhanced recovery after caesarean delivery.[15–17] Accrual ran from April 2016 to March 2020 and therefore overlaps the period in which those recommendations were issued rather than preceding all of them: the international consensus statement on vasopressor management became available online in November 2017, by which point 415 of the 999 deliveries had been accrued,[18] the Enhanced Recovery After Surgery Society recommendations for caesarean delivery appeared during 2018,[16] and the consensus statement of the Society for Obstetric Anesthesia and Perinatology was published after accrual had ended.[15] The following features of the recorded practice bear on interpretation: hypotension was treated with ephedrine at the anaesthetist's discretion rather than with a prophylactic phenylephrine or norepinephrine infusion; arterial pressure was measured at least every five minutes rather than at least every minute until delivery; crystalloid administration began before spinal injection according to departmental practice, although the recorded total volume does not distinguish preload from co-load; and no intrathecal opioid was given. The absence of intrathecal opioid was an institutional standard applied uniformly rather than a case-by-case choice, and it is not explained by the timing of any guideline; unplanned post-delivery intravenous fentanyl was recorded in a quarter to a third of deliveries, although with no opioid-containing comparison group that record cannot be attributed to the absence of intrathecal opioid. The absence of an opioid adjuvant does, however, mean that opioid-containing dose-finding estimates cannot be assumed to apply directly to these records.[3, 6, 11] The analyses that follow describe this recorded practice; they are not an estimate of what dose selection would achieve under contemporary enhanced-recovery care.

Exposure

The exposure was the dose of hyperbaric bupivacaine. The main comparison was ≥ 12 versus < 12 mg, retaining the threshold used in the original cohort report.[13] Although a similar dose is cited in opioid-

containing dose-finding evidence,[3] 12 mg was not established as an optimal threshold for this opioid-free regimen. Dose was also analysed per 1 mg increment and in four descriptive strata (≤ 10, 11–11.5, 12–12.5 and ≥ 13 mg; twelve deliveries used half-milligram doses). The < 12 mg group represents lower doses within this dataset and should not be equated with low-dose techniques defined as ≤ 8 mg in other literature.[4, 7]

Outcomes

The primary outcome was the lowest systolic arterial pressure recorded between intrathecal injection and delivery. When the anaesthetic charts were transcribed, the pre-delivery and post-delivery segments of each record were abstracted separately, and only pre-delivery pressures were carried into the analysis dataset; the window was therefore applied at abstraction rather than derived afterwards. That segmentation was manual, and the analysis dataset holds no separate time of delivery against which it could be re-audited. Secondary outcomes were hypotension in that interval, defined as a recorded systolic pressure ≤ 90 mmHg; ephedrine dose before delivery; any ephedrine administration before delivery; and unplanned intravenous fentanyl after delivery. This last outcome was recorded when intravenous fentanyl was given for pain between delivery of the fetus and the end of surgery; fentanyl was the first drug used for intraoperative pain in this department, and midazolam given only to let the mother rest was not recorded as supplementation. Intravenous fentanyl was documented as a matter of departmental practice, but the completeness of this outcome was not formally validated and its absence should not be read as evidence that no pain occurred; the threshold for giving it rested with the attending anaesthetist, so it is a record of treatment rather than a validated measure of pain or block failure, and it does not capture sedation given without an analgesic. Six exploratory outcomes were examined in the secondary cohort. Four were derived from the systolic pressures recorded at spinal induction and at 5, 10, 15, 20 and 25 minutes: the lowest of the six values; their time-weighted mean over the 25 minutes by the trapezoidal rule; the area of that curve below the woman's own baseline; and whether the lowest value was ≤ 90 mmHg. The recorded ephedrine dose and whether any ephedrine was recorded were taken from the drug record, which carries no administration times, so their observation period cannot be verified as the same 0–25-minute interval. This fixed window can include post-delivery measurements and differs from the primary cohort's pre-delivery endpoint.

Statistical analysis

The analysis plan, outcomes, covariate set and equivalence margin were finalised after inspection of preliminary results from the same dataset. These are post hoc analyses of existing records. We focus on adjusted mean differences with 95% confidence intervals rather than interpreting a non-significant test as evidence of no association.

Exploratory equivalence analyses used two one-sided tests against a ± 5 mmHg margin[19] and against a ± 3 mmHg margin. The margin reflected the investigators' judgement after preliminary results were available; no independently validated minimal important difference exists for this endpoint, and a

previous dose comparison used a wider 15 mmHg margin,[20] which does not validate the present choice. Because no margin was pre-specified and none is validated, these tests are reported only in Additional file 1, Supplementary Tables S2 and S3, with the 90% confidence intervals and the boundary magnitude of each interval; they are not used to draw the main conclusions, and none of them establishes equivalence of clinical safety.

Multivariable models were adjusted, without data-driven selection, for body mass index, baseline systolic pressure, baseline heart rate, parity, largest fetal weight, height, gestational age, twin pregnancy, maternal age and duration of anaesthesia. Baseline systolic pressure and baseline heart rate were the first values recorded after the woman arrived in the operating room, before spinal injection; that baseline also provided the exclusion criterion of a systolic pressure below 90 mmHg and the denominator of the proportional-fall definitions of hypotension. Duration of anaesthesia is determined after the dose is given, so a sensitivity model omitting it was also fitted, as was a model with standard errors clustered on the mother, since 44 women contributed two deliveries. After the exclusions described above, which removed 67 records for missing data, the exposure, the primary outcome, every covariate and every secondary outcome were complete in the analysed records.

A propensity score was estimated from the nine covariates other than duration of anaesthesia. Stabilised inverse-probability-of-treatment weights were truncated at the 1st and 99th percentiles. Optimal 1:1 matching without replacement used a caliper of 0.2 standard deviations of the logit propensity score; optimal matching was used because greedy estimates depended on matching order. Weighted models used standard errors clustered on the mother, and matched-sample models used standard errors clustered by matched pair. Six women contributed a record to two different pairs, so pair clustering does not cover all within-woman correlation; clustering the matched models on the mother instead was examined as a sensitivity analysis (Additional file 1, Supplementary Table S3). Balance was assessed by standardised mean differences (SMDs), with |SMD| >0.10 indicating imbalance. Weighted and matched models were additionally adjusted for the same covariates to address residual measured differences; this does not remove unmeasured confounding and does not guarantee that residual bias has been eliminated. The two designs target different quantities: the stabilised weights estimate the association across the whole cohort, whereas 1:1 matching, in which every lower-dose delivery was matched, estimates it in the lower-dose group. These approaches address measured covariates but cannot eliminate unmeasured confounding.

The recorded time of the nadir, which is charted in five-minute units, was compared between dose groups with the same covariate set as a descriptive analysis. For the second aim, eight published definitions of hypotension were applied to the same deliveries, including the composite used in the previous database study,[10] and the same covariate set was used to estimate the adjusted association of dose and of baseline systolic pressure with each. Sensitivity analyses refitted the primary model within 11–13 mg, with crystalloid volume added, and restricted to deliveries whose nadir was recorded within 25 minutes. Departure from linearity in dose was assessed by adding a quadratic term and comparing it with the linear model by F test on one degree of freedom. A separate exploratory model

fitted the two cohorts together by ordinary least squares, with cohort, dose group, their interaction and the eight covariates recorded in both cohorts, with covariate effects held common across cohorts and standard errors clustered on the mother, since 25 women contributed to both cohorts. Because the pressure outcome is defined over different observation windows in the two cohorts, this model cannot separate a difference in the dose association from a difference in outcome definition; it was not used to estimate a common pooled dose association. The sample size was determined by the available cohort records, without an a priori calculation. Analyses used Python 3.11 with statsmodels 0.15, scipy 1.17 and pandas 3.0; optimal matching used the linear-sum-assignment routine of scipy.optimize. Two-sided α was 0.05; each one-sided equivalence test used α = 0.05. Secondary analyses were exploratory and were not adjusted for multiple comparisons.

Use of artificial intelligence tools

Claude (Anthropic) and ChatGPT (OpenAI) were used to draft and cross-check the analysis and plotting code, to draft and revise manuscript text, and to check the manuscript against the analysis output. No image was generated by an artificial-intelligence image model: Fig. 1 was drawn by code from the investigators' source selection diagram, and Figs. 2 to 4 were plotted by code from the statistical analysis output. Every reported estimate was regenerated from the source files and checked against the manuscript by the authors, who take full responsibility for the content.

Results

Cohorts

The primary cohort comprised 999 deliveries in 955 women; mean dose 12.3 mg (standard deviation [SD] 1.0), median 12 mg, range 9–16 mg, with 803 (80.4%) receiving ≥ 12 mg and 858 (85.9%) receiving 11–13 mg. The secondary cohort comprised 207 delivery records, with mean dose 12.1 mg (SD 1.0); 155 (74.9%) received ≥ 12 mg. The distribution of individual doses is given in Additional file 1, Supplementary Table S4.

Baseline characteristics are shown in Table 1. Height showed the largest imbalance, 4.0 cm greater in the higher-dose group (SMD + 0.81), with smaller imbalances in weight, body mass index and parity (|SMD| 0.11 to 0.16); all others were below 0.09. Weighting reduced it to + 0.15 and left duration of anaesthesia at − 0.15, both above the 0.10 threshold; matching (196 pairs) reduced height to + 0.01 and left every covariate below |SMD| 0.08 (Additional file 1, Supplementary Table S1). Estimated propensity scores ranged from 0.296 to 0.948 in the lower-dose group and from 0.264 to 0.994 in the higher-dose group; the lower-dose range lay inside the higher-dose range, although support was less comparable at the extremes. After truncation the largest stabilised weight was 2.49 and the effective sample size was 910 of 999. Both models were also fitted with covariate adjustment.

Table 1
Baseline characteristics by spinal bupivacaine dose group, in each cohort.

Characteristic	< 12 mg	≥ 12 mg	SMD
Spinal anaesthesia cohort (999 deliveries in 955 women)			
n	196	803	
Age, y	34.8 (5.0)	34.7 (4.5)	−0.02
Height, cm	157.0 (4.5)	161.0 (5.2)	+ 0.81
Weight, kg	67.9 (10.5)	69.6 (10.8)	+ 0.16
Body mass index, kg m^{-2}	27.5 (3.9)	26.9 (3.9)	−0.16
ASA physical status ≥ III, n (%)	12 (6.1)	49 (6.1)	−0.00
Gestational age, weeks	37.7 (2.6)	37.5 (2.8)	−0.07
Multiparous, n (%)	111 (56.6)	409 (50.9)	−0.11
Twin pregnancy, n (%)	23 (11.7)	88 (11.0)	−0.02
Largest fetal weight, g	2969 (630)	2916 (651)	−0.08
Baseline systolic pressure, mmHg	128.0 (13.7)	127.8 (15.6)	−0.01
Baseline heart rate, beats min^{-1}	84.0 (14.0)	83.4 (14.1)	−0.04
Duration of anaesthesia, min	112.7 (21.8)	111.4 (20.7)	−0.06
Bupivacaine dose, mg	10.8 (0.4)	12.7 (0.8)	—
Spinal anaesthesia after epidural labour analgesia (207 delivery records)			
n	52	155	
Age, y	34.4 (4.5)	33.7 (4.4)	−0.16
Height, cm	155.6 (5.3)	159.3 (5.1)	+ 0.72
Weight, kg	68.5 (12.7)	69.2 (11.2)	+ 0.06
Body mass index, kg m^{-2}	28.3 (5.0)	27.3 (4.4)	−0.21
ASA physical status ≥ III, n (%)	1 (1.9)	0 (0)	−0.20
Gestational age, weeks	39.3 (1.1)	39.3 (1.3)	+ 0.02

Values are mean (SD) or n (%). SMD, standardised mean difference (≥ 12 mg minus < 12 mg); |SMD| > 0.10 indicates imbalance; no SMD is given for bupivacaine dose, which defines the groups. ASA, American Society of Anesthesiologists. In the primary cohort, largest fetal weight is the weight of the heavier fetus in twin pregnancies. Duration of anaesthesia and twin-pregnancy status were not available as complete covariates in the epidural-labour-analgesia dataset.

Characteristic	< 12 mg	≥ 12 mg	SMD
Spinal anaesthesia cohort (999 deliveries in 955 women)			
Multiparous, n (%)	2 (3.8)	20 (12.9)	+ 0.33
Fetal weight, g	3219 (436)	3254 (467)	+ 0.08
Baseline systolic pressure, mmHg	125.1 (16.3)	120.5 (12.8)	−0.31
Baseline heart rate, beats min^{-1}	77.4 (12.3)	77.0 (13.0)	−0.03
Bupivacaine dose, mg	10.7 (0.5)	12.6 (0.7)	—

Values are mean (SD) or n (%). SMD, standardised mean difference (≥ 12 mg minus < 12 mg); |SMD| > 0.10 indicates imbalance; no SMD is given for bupivacaine dose, which defines the groups. ASA, American Society of Anesthesiologists. In the primary cohort, largest fetal weight is the weight of the heavier fetus in twin pregnancies. Duration of anaesthesia and twin-pregnancy status were not available as complete covariates in the epidural-labour-analgesia dataset.

Primary outcome

Baseline systolic pressures were 128.0 and 127.8 mmHg in the lower- and higher-dose groups, respectively. The mean falls to the recorded nadir were 32.9 and 32.0 mmHg; the mean of the individual falls expressed as a proportion of that woman's own baseline was 25.3% and 24.5%. The adjusted difference in the primary outcome (≥ 12 minus < 12 mg) was − 0.19 mmHg (95% CI − 2.43 to 2.05); clustering by mother gave a 95% CI of − 2.53 to 2.16. Each additional milligram was associated with − 0.14 mmHg (− 1.02 to 0.74). Estimates were − 0.05 mmHg (− 2.87 to 2.77) after weighting, − 0.58 (− 3.22 to 2.07) after weighting with covariate adjustment, − 0.87 (− 3.87 to 2.14) after matching, and − 0.45 (− 3.16 to 2.27) after matching with covariate adjustment (Fig. 2).

Timing of the nadir, dose range and sensitivity analyses

The recorded nadir occurred a median of 15 minutes after the block (interquartile range [IQR] 10–20, maximum 45). Recorded in five-minute units, its adjusted between-group difference was 0.7 minutes (95% CI − 0.5 to 1.8); this does not establish comparable observation windows or exclude differences in measurement frequency or in the timing of treatment. Restriction to 858 deliveries at 11–13 mg gave an adjusted pressure difference of − 0.98 mmHg (− 3.39 to 1.43); omission of anaesthesia duration gave − 0.14 mmHg (− 2.38 to 2.11). Crystalloid volume was almost identical in the two groups (2123 and 2116 mL), and adding it to the model moved the estimate by less than 0.001 mmHg, so it is unchanged at the two decimal places reported here (− 0.19 mmHg, − 2.43 to 2.05). Restriction to the 930 deliveries whose nadir was recorded within 25 minutes gave − 0.42 mmHg (− 2.73 to 1.90); that restriction selects deliveries by the timing of the observed outcome rather than reconstructing a common 25-minute window, and is descriptive. A quadratic dose term gave no evidence of departure from linearity (P = 0.22), although this test cannot establish a linear dose–response relationship, and few deliveries lie at either end of the dose range. Detailed intervals and exploratory tests are retained in Additional file 1, Supplementary Table S3.

Vasopressor use and post-delivery fentanyl

The adjusted difference in pre-delivery ephedrine dose was − 0.97 mg (95% CI − 3.07 to 1.13) for ≥ 12 versus < 12 mg (Table 2). Ephedrine was given before delivery in 68.4% and 64.3% of lower- and higher-dose deliveries (adjusted odds ratio 0.91, 0.63 to 1.31). However, treatment timing was unavailable, so these summaries cannot establish comparable treatment exposure throughout the blood-pressure observation window.

Table 2

Primary and secondary outcomes by spinal bupivacaine dose group, spinal anaesthesia cohort (n = 999).

Outcome	< 12 mg (n = 196)	≥ 12 mg (n = 803)	Multivariable regression	IPTW	Propensity-score matching
Haemodynamic outcomes					
Lowest systolic pressure before delivery, mmHg	95.1 (15.8)	95.8 (15.2)	−0.19 (− 2.43 to 2.05)	−0.05 (− 2.87 to 2.77)	−0.87 (− 3.87 to 2.14)
per 1 mg increment	—	—	−0.14 (− 1.02 to 0.74)	—	—
Hypotension (systolic pressure ≤ 90 mmHg), n (%)	83 (42.3)	346 (43.1)	1.19 (0.83 to 1.69)	1.14 (0.80 to 1.63)	1.18 (0.78 to 1.79)
Vasopressor use					
Ephedrine dose before delivery, mg	13.9 (14.0)	12.3 (13.5)	−0.97 (− 3.07 to 1.13)	−1.08 (− 3.35 to 1.18)	−0.95 (− 3.68 to 1.78)
per 1 mg increment	—	—	−0.26 (− 1.08 to 0.56)	—	—
Any ephedrine before delivery, n (%)	134 (68.4)	516 (64.3)	0.91 (0.63 to 1.31)	0.84 (0.58 to 1.23)	1.02 (0.65 to 1.61)
Post-delivery analgesic requirement					
Post-delivery intravenous fentanyl, n (%)	62 (31.6)	198 (24.7)	0.71 (0.49 to 1.03)	0.61 (0.41 to 0.89)	0.70 (0.44 to 1.11)

Descriptive columns are mean (SD) or n (%). Effect columns are adjusted mean differences (continuous outcomes) or adjusted odds ratios (binary outcomes) for a dose ≥ 12 mg versus < 12 mg, each with its 95% confidence interval. Multivariable models were adjusted for body mass index, baseline systolic pressure, baseline heart rate, parity, largest fetal weight, height, gestational age, twin pregnancy, maternal age and duration of anaesthesia. Inverse-probability-of-treatment weights (IPTW) were stabilised and truncated at the 1st and 99th percentiles, and weighted models used standard errors clustered on the mother; the propensity score was estimated from the nine covariates excluding anaesthesia duration. Matching was optimal 1:1 without replacement (196 matched pairs, caliper 0.2 SD of the logit propensity score). Exploratory post hoc equivalence analyses, using a margin selected after preliminary results, are reported in Additional file 1, Supplementary Table S3. Weighted models used standard errors clustered on the mother and matched-sample models standard errors clustered on the matched pair. The lowest systolic pressure and the ephedrine dose cover the interval between intrathecal injection and delivery. Any ephedrine administration counts every delivery in which ephedrine was given before delivery; it is described as a care characteristic and cannot establish co-intervention balance. Post-delivery intravenous fentanyl counts every delivery in which intravenous fentanyl was given for pain between delivery of the fetus and the end of surgery; it is not a measure of block failure at induction.

Post-delivery intravenous fentanyl was given in 31.6% versus 24.7% of lower- and higher-dose deliveries. The adjusted odds ratio for ≥ 12 versus < 12 mg was 0.71 (95% CI 0.49 to 1.03), compared with 0.61 (0.41 to 0.89) after weighting and 0.70 (0.44 to 1.11) after matching. The unadjusted proportions were 33.3% at ≤ 10 mg and 24.1% at ≥ 13 mg (Fig. 3). The association met a conventional significance threshold only after weighting and remains exploratory. Stratum estimates are descriptive; only 33 deliveries received ≤ 10 mg.

Effect of the definition of hypotension

Applying eight published definitions to the same 999 deliveries moved the reported incidence from 20.9% to 88.8% (Fig. 4). The adjusted odds ratio for a dose ≥ 12 mg included the null under every one, from 0.93 (95% CI 0.62 to 1.39) to 1.38 (0.96 to 1.99); precision varied across definitions, and the widest interval, for a fall exceeding 10% from baseline, was 1.30 (0.75 to 2.24) — compatible with a 25% reduction and with a 124% increase in the odds. The definitions applied and the estimates under each are listed in Additional file 1, Supplementary Table S5; the composite used in the previous database study[10] is the row defined as a systolic pressure ≤ 90 mmHg or below 80% of baseline, for which the adjusted odds ratio was 1.38 (0.96 to 1.99). The association with baseline systolic pressure reversed direction: lower odds under absolute thresholds (0.61 per 10 mmHg, 0.55 to 0.67), higher odds under proportional-fall definitions (1.91, 1.60 to 2.29), and null under the composite of a fall exceeding 20% or a pressure below 100 mmHg (1.00, 0.90 to 1.10).

Secondary cohort

In the 207 records after epidural labour analgesia, the adjusted difference in the lowest recorded systolic pressure was 1.55 mmHg (95% CI − 2.82 to 5.92), and the difference in the time-weighted mean over 25 minutes was 1.53 mmHg (− 2.21 to 5.27). The adjusted difference in the recorded ephedrine dose was − 3.68 mg (− 7.02 to − 0.35) and the adjusted odds ratio for receiving any ephedrine was 0.47 (0.22 to 0.96); both intervals exclude the null, and both are exploratory analyses of 207 records (Additional file 1, Supplementary Table S2). The cohort-by-dose interaction was imprecise (2.53 mmHg, − 2.23 to 7.29; P = 0.30), so similarity between cohorts cannot be established.

Discussion

In this historical cohort receiving spinal anaesthesia without intrathecal opioids, adjusted differences in the lowest recorded pre-delivery systolic pressure were small across the observed dose range. Estimates were near zero after regression adjustment, weighting and matching, although these analyses share the same measurement and confounding limitations. Post-delivery intravenous fentanyl was more frequent in the lower-dose group descriptively, but adjusted estimates varied in precision. The results describe associations under the recorded care conditions and do not estimate the benefit or harm of changing an individual patient's dose.

The previous database study reported more hypotension with doses ≥ 10 mg (adjusted odds ratio for < 10 mg, 0.77; 95% CI 0.67 to 0.90).[10] Its group means were 7.8 versus 10.2 mg, compared with 10.8

versus 12.7 mg here. Differences in dose distributions, intrathecal opioid use and vasopressor management limit direct comparison. Applying that study's composite definition to our records gave an adjusted odds ratio of 1.38 (0.96 to 1.99): the point estimate lies in the same direction as that report, but the interval includes the null, so these records neither reproduce nor exclude its finding. This does not establish a dose threshold or demonstrate flattening of a causal dose–response curve.

Applying eight published definitions to the same 999 primary-cohort records produced hypotension incidences from 20.9% to 88.8%, consistent with previous evidence that the definition drives the measured incidence within a single cohort.[9] We additionally examined the adjusted associations under each definition. The association with baseline systolic pressure changed direction between absolute-threshold and proportional-fall definitions, whereas the dose estimate remained compatible with the null under all eight. Because a proportional-fall outcome incorporates the baseline on both sides of the relationship, much of that pattern is expected by construction rather than being an empirical finding.[21] These observations argue for stating the outcome definition explicitly, and for caution when incidences or covariate associations are compared across studies that used different definitions. They do not show that binary outcomes are invalid, nor that continuous outcomes are generally preferable: the two answer different questions, and a recorded nadir depends in its own way on monitoring frequency and on treatment.

The historical regimen used hyperbaric bupivacaine without intrathecal fentanyl or morphine. Dose requirements derived with opioid adjuvants cannot be assumed to apply directly. Sensory block level was assessed clinically but is not held in the analysis dataset, so no comparison of block extent between the dose groups was possible; recommendations on sensory testing would in any case complicate comparison between pinprick-based records and assessment of a block to light touch.[1, 22] We did not measure validated block adequacy, pain intensity or patient-reported recovery. The post-delivery fentanyl outcome records treatment given at the attending anaesthetist's discretion between delivery and the end of surgery; it does not capture sedation given without an analgesic, does not measure pain intensity and cannot establish an optimal dose.

The secondary cohort provides additional exploratory observations in a different clinical setting. Prior epidural treatment, the intrapartum setting and the fixed 25-minute pressure window prevent it from validating the primary pre-delivery endpoint. The imprecise interaction estimate cannot exclude a clinically relevant difference between cohorts. In that cohort the higher-dose group received less ephedrine and was less likely to receive any, with intervals excluding the null; with 207 records, no adjustment for multiple comparisons, a different clinical setting and no comparable finding in the primary cohort, we treat these as observations to be tested elsewhere rather than as evidence that a higher dose reduces vasopressor requirement. A recent repeat-spinal study used ropivacaine and a different failure definition,[23] so its findings do not quantify the consequence of reducing bupivacaine in these records.

The recorded practice overlaps, rather than precedes, the period in which the current enhanced-recovery framework was issued, as set out in the Methods. That framework recommends a prophylactic vasopressor infusion and blood-pressure measurement every minute after spinal injection,[18] whereas these records reflect ephedrine given at the anaesthetist's discretion and measurement at least every five minutes; the absence of intrathecal opioid is a separate matter and is not explained by the timing of any guideline. Opioid adjuvants and vasopressor strategies alter the clinical context in which a dose is chosen, but these data cannot quantify those differences, establish the direction of their net effect on the observed dose-pressure association, or rank the contributions of alternative management strategies. A study intended to guide current dose selection would need standardised haemodynamic management, sufficiently frequent measurement, and assessment of pain, block adequacy and recovery.

Limitations

Non-random dose selection and the baseline height imbalance indicate confounding by indication; measured-covariate adjustment cannot exclude clinician-level or other unmeasured confounding. The matched analysis also depends on the chosen pairs. Vasopressor timing was unavailable, so similar mean pressures may reflect different treatment trajectories. The narrow dose distribution limits inference about low-dose techniques; the small subgroup at ≤ 10 mg is insufficient for a reliable separate comparison. Pressure was measured at least every five minutes and the time of the nadir is charted in five-minute units, so brief episodes between readings are not captured and the timing of the nadir is known only to that resolution, with an uncertain direction of bias in group differences. The primary pressure outcome and the post-delivery fentanyl outcome concern different periods of the operation. Largest fetal weight was measured at birth, and anaesthesia duration is a post-exposure variable, although omission of duration gave a similar estimate. Because the analysis plan was finalised after preliminary results and multiple exploratory analyses were performed, these findings are not confirmatory. Deliveries converted to general anaesthesia were excluded from both cohorts. Individual data for the 26 conversions in the primary cohort are not held in the analysis dataset, so they cannot be assigned to a dose group; the secondary workbook does retain doses for its seven conversions (11, 11, 12, 12, 14, 14 and 15 mg), but those records carry no haemodynamic data and were not analysed. Because conversion may be related to dose and to block adequacy, this exclusion may introduce selection bias; the estimates describe recorded blood pressure among deliveries not converted to general anaesthesia and cannot weigh the overall benefits and harms of a dose strategy. Finally, this was a single-centre study of reused historical records; the analysis used an inclusive ≤ 90 mmHg threshold, whereas the original report described < 90 mmHg;[13] 106 records had a recorded nadir of exactly 90 mmHg, so the stricter threshold would give an incidence of 32.3% rather than 42.9%. Both analysis datasets had undergone manual verification by the investigators, and the corrected versions were used throughout; three transcription errors identified in the secondary cohort were corrected before the analyses reported here. Residual transcription or measurement error cannot be excluded, and the primary dataset retains no separate time of delivery, so the pre-delivery abstraction window cannot be reconstructed from it. Within-woman correlation in the interaction analysis was addressed with standard

errors clustered on the mother; the different outcome windows still prevent that analysis from distinguishing a difference in the dose association from a difference in outcome definition.

Conclusions

For the dose contrast actually studied in this historical cohort — means of 10.8 and 12.7 mg — bupivacaine dose was associated with small adjusted differences in recorded pre-delivery systolic pressure, and regression adjustment, propensity-score weighting and matching gave estimates of similar size and direction, although they target different quantities. The per-milligram estimate is too imprecise to constrain the association across the full 9–16 mg range. Applying eight published definitions of hypotension to the same records moved the measured incidence from 20.9% to 88.8% and changed the direction of the association with baseline pressure, while leaving the dose estimate compatible with the null; outcome definitions therefore need to be stated explicitly when such estimates are interpreted or compared. These observational findings do not establish equivalent clinical safety, the optimal dose, or the effect of changing dose in contemporary practice, and the uncertain association with post-delivery intravenous supplementation requires confirmation with validated analgesia outcomes under standardised care.

Abbreviations

ASA
American Society of Anesthesiologists
CI
confidence interval
ED95
effective dose in 95% of patients
IPTW
inverse-probability-of-treatment weighting
IRB
institutional review board
IQR
interquartile range
SD
standard deviation
SMD
standardised mean difference
STROBE
Strengthening the Reporting of Observational Studies in Epidemiology.

Declarations

Ethics approval and consent to participate

The study was conducted in accordance with the Declaration of Helsinki. The Institutional Review Board of Taipei Veterans General Hospital approved it (IRB-TPEVGH no. 2020-10-010CC) and waived written informed consent for this analysis of existing records. No individually identifiable information is reported.

Clinical trial number

Clinical trial number: not applicable.

Consent for publication

Not applicable. No identifiable individual patient information is reported.

Competing interests

The authors declare that they have no competing interests.

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Author Contribution

YHW: Formal analysis; Writing – review and editing. MYT: Supervision; Writing – review and editing. YSL: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Software; Visualization; Writing – original draft; Writing – review and editing. YHW, Yu-Hsien Wang; MYT, Mei-Yung Tsou; YSL, Yi-Shiuan Li. All authors read and approved the final manuscript.

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Not applicable.

Availability of data and materials

The datasets generated and analysed during the current study are not publicly available because they contain information that could compromise the privacy of the women concerned, but are available from

the corresponding author on reasonable request and with the permission of Taipei Veterans General Hospital.

References

1. Plaat F, Stanford SER, Lucas DN, Andrade J, Careless J, Russell R, et al. Prevention and management of intra-operative pain during caesarean section under neuraxial anaesthesia: a technical and interpersonal approach. Anaesthesia. 2022;77:588–97. 10.1111/anae.15717.
2. Waddell E, Bhatia K. Intrathecal bupivacaine dose in spinal anaesthesia for prevention of pain during caesarean delivery - the white elephant in the guidelines - in response to Shedding more light on the management of intraoperative pain during cesarean delivery: a review of the American Society of Anesthesiologists statements. Int J Obstet Anesth. 2025;64:104741. 10.1016/j.ijoa.2025.104741.
3. American Society of Anesthesiologists Committee on Obstetric Anesthesia. Statement on pain during cesarean delivery. 2023. https://www.asahq.org/standards-and-practice-parameters/statement-on-pain-during-cesarean-delivery. Accessed 12 Sep 2026.
4. Arzola C, Wieczorek PM. Efficacy of low-dose bupivacaine in spinal anaesthesia for Caesarean delivery: systematic review and meta-analysis. Br J Anaesth. 2011;107:308–18. 10.1093/bja/aer200.
5. Patel R, Kua J, Sharawi N, Bauer ME, Blake L, Moonesinghe SR, et al. Inadequate neuraxial anaesthesia in patients undergoing elective caesarean section: a systematic review. Anaesthesia. 2022;77:598–604. 10.1111/anae.15657.
6. Ginosar Y, Mirikatani E, Drover DR, Cohen SE, Riley ET, editors. ED50 and ED95 of intrathecal hyperbaric bupivacaine coadministered with opioids for cesarean delivery. Anesthesiology. 2004;100:676 – 82. 10.1097/00000542-200403000-00031
7. Rucklidge MWM, Paech MJ. Limiting the dose of local anaesthetic for caesarean section under spinal anaesthesia - has the limbo bar been set too low? Anaesthesia. 2012;67:347–51. 10.1111/j.1365-2044.2012.07104.x.
8. Pınarbaşı A, Altıparmak B, Karaçay T. Low-dose spinal anesthesia in cesarean section: a narrative review. J Anesth. 2026;40:438–53. 10.1007/s00540-025-03632-5.
9. Klöhr S, Roth R, Hofmann T, Rossaint R, Heesen M. Definitions of hypotension after spinal anaesthesia for caesarean section: literature search and application to parturients. Acta Anaesthesiol Scand. 2010;54:909–21. 10.1111/j.1399-6576.2010.02239.x.
10. Weiniger CF, Heesen M, Knigin D, Deutsch F, Hilber N, Avidan A. Association between hyperbaric bupivacaine dose and maternal hypotension: retrospective database study of 8226 women undergoing cesarean delivery under spinal anesthesia. Anesth Analg. 2021;133:967–75. 10.1213/ANE.0000000000005518.
11. Onishi E, Murakami M, Hashimoto K, Kaneko M. Optimal intrathecal hyperbaric bupivacaine dose with opioids for cesarean delivery: a prospective double-blinded randomized trial. Int J Obstet Anesth. 2017;31:68–73. 10.1016/j.ijoa.2017.04.001.

12. Li M, Xie G, Chu L, Li Y. Efficacy of low-dose hypobaric anesthetics in spinal anesthesia for cesarean delivery: systematic review and meta-analysis. J Matern Fetal Neonatal Med. 2025;38:2519655. 10.1080/14767058.2025.2519655.
13. Li YS, Lin SP, Horng HC, Tsai SW, Chang WK. Risk factors of more severe hypotension after spinal anesthesia for cesarean section. J Chin Med Assoc. 2024;87:442–7. 10.1097/JCMA.0000000000001056.
14. Wu CC, Li YS, Lin SP, Chen YJ, Chang WK, Ting CK. November. Association between prior epidural labour analgesia and increased incidence of hypotension after spinal anaesthesia for caesarean section: a retrospective propensity score-matched cohort study. Anaesth Intensive Care. In press (accepted 19 2025).
15. Bollag L, Lim G, Sultan P, Habib AS, Landau R, Zakowski M, et al. Society for Obstetric Anesthesia and Perinatology: consensus statement and recommendations for enhanced recovery after cesarean. Anesth Analg. 2021;132:1362–77. 10.1213/ANE.0000000000005257.
16. Wilson RD, Caughey AB, Wood SL, Macones GA, Wrench IJ, Huang J, et al. Guidelines for antenatal and preoperative care in cesarean delivery: Enhanced Recovery After Surgery Society recommendations (part 1). Am J Obstet Gynecol. 2018;219:523e1. 10.1016/j.ajog.2018.09.015.
17. Caughey AB, Wood SL, Macones GA, Wrench IJ, Huang J, Norman M, et al. Guidelines for intraoperative care in cesarean delivery: Enhanced Recovery After Surgery Society Recommendations (Part 2). Am J Obstet Gynecol. 2018;219:533–44. 10.1016/j.ajog.2018.08.006.
18. Kinsella SM, Carvalho B, Dyer RA, Fernando R, McDonnell N, Mercier FJ, et al. International consensus statement on the management of hypotension with vasopressors during caesarean section under spinal anaesthesia. Anaesthesia. 2018;73:71–92. 10.1111/anae.14080.
19. Schuirmann DJ. A comparison of the two one-sided tests procedure and the power approach for assessing the equivalence of average bioavailability. J Pharmacokinet Biopharm. 1987;15:657–80. 10.1007/BF01068419.
20. Langesæter E, Rosseland LA, Stubhaug A. Continuous invasive blood pressure and cardiac output monitoring during cesarean delivery: a randomized, double-blind comparison of low-dose versus high-dose spinal anesthesia with intravenous phenylephrine or placebo infusion. Anesthesiology. 2008;109:856–63. 10.1097/ALN.0b013e31818a401f.
21. Oldham PD. A note on the analysis of repeated measurements of the same subjects. J Chronic Dis. 1962;15:969–77. 10.1016/0021-9681(62)90116-9.
22. Calpin P, ffrench-O'Carroll R. Using light touch to assess the level of spinal block during caesarean section: what dose of local anaesthetic should we be using? Anaesthesia. 2022;77:1062. 10.1111/anae.15747.
23. Wei Y, Liu K, Lu X, Wang J, Li J, Yao L. Repeat spinal anesthesia for intrapartum cesarean section after epidural labor analgesia: a retrospective cohort study of failure rate and the volume-risk relationship. BMC Anesthesiol. 2026;26:67. 10.1186/s12871-025-03593-y.

Figures

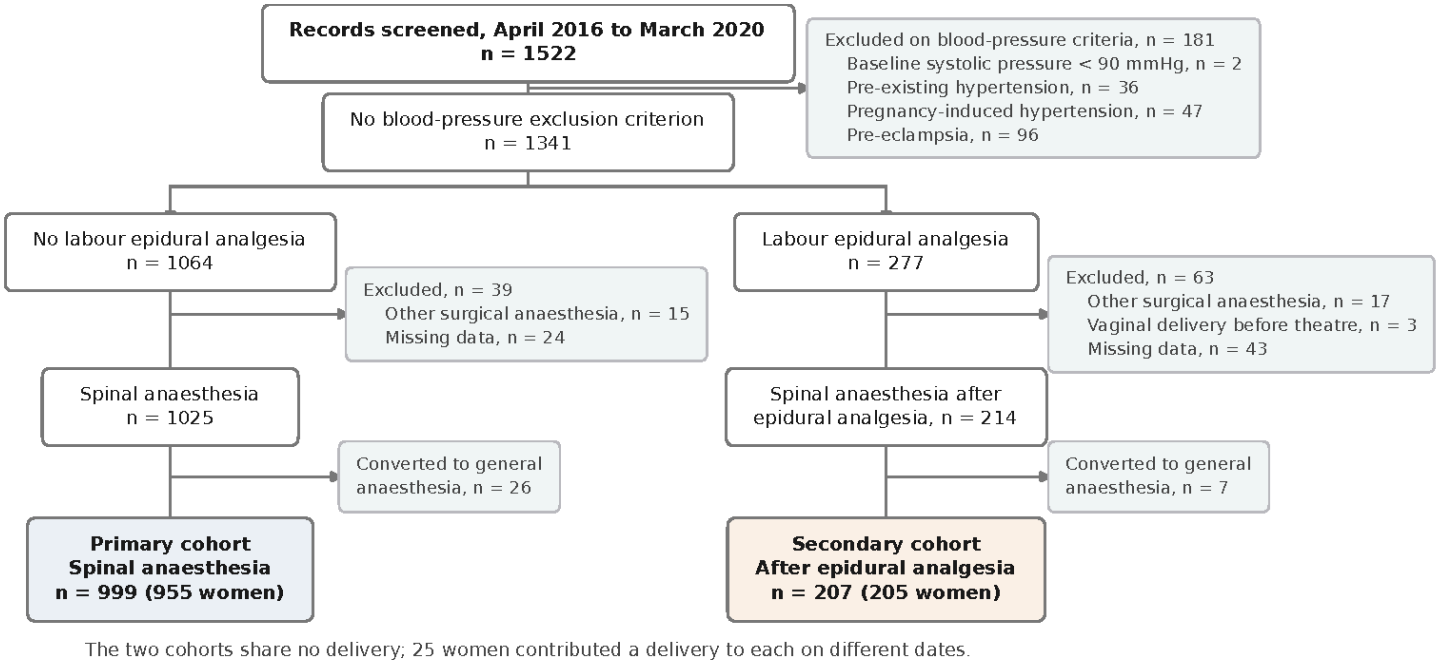


Figure 1

Flow of caesarean deliveries into the two analysed cohorts.

Counts are deliveries and are taken from the investigators' source selection diagram; the analysis datasets hold the 999 and 207 records at the foot of each branch. Exclusions on blood-pressure criteria were applied to the whole period; the remaining deliveries were then separated by whether labour epidural analgesia had been given, and within each branch deliveries under a surgical anaesthetic other than spinal, those delivered vaginally before transfer to theatre, and those with missing records were excluded before conversions to general anaesthesia were removed. Of the 17 deliveries excluded for other surgical anaesthesia in the epidural-analgesia branch, 6 received an epidural top-up and 11 general anaesthesia; the 15 excluded in the other branch all received general anaesthesia. The two cohorts contain no delivery in common; 25 women contributed one delivery to each on different dates.



Figure 2

Adjusted differences in the lowest recorded pre-delivery systolic pressure by analysis method.

Adjusted difference in the lowest systolic arterial pressure recorded between intrathecal injection and delivery (dose ≥ 12 mg minus dose < 12 mg) among 999 caesarean deliveries in 955 women, under single-shot spinal anaesthesia without preceding epidural labour analgesia and without intrathecal opioid. Multivariable regression was adjusted for body mass index, baseline systolic pressure, baseline heart rate, parity, largest fetal weight, height, gestational age, twin pregnancy, maternal age and duration of anaesthesia. The propensity score was estimated from the nine covariates excluding anaesthesia duration. Inverse-probability weights were stabilised and truncated at the 1st and 99th percentiles; matching was optimal 1:1 without replacement using a caliper of 0.2 standard deviations of the logit propensity score. The weighted and the matched models were each also fitted with adjustment for the ten covariates; weighting left height and duration of anaesthesia above a |standardised mean difference| of 0.10, and matching left none. Exploratory post hoc equivalence analyses are reported in Additional file 1, Supplementary Table S3; these results do not establish equivalent clinical safety.

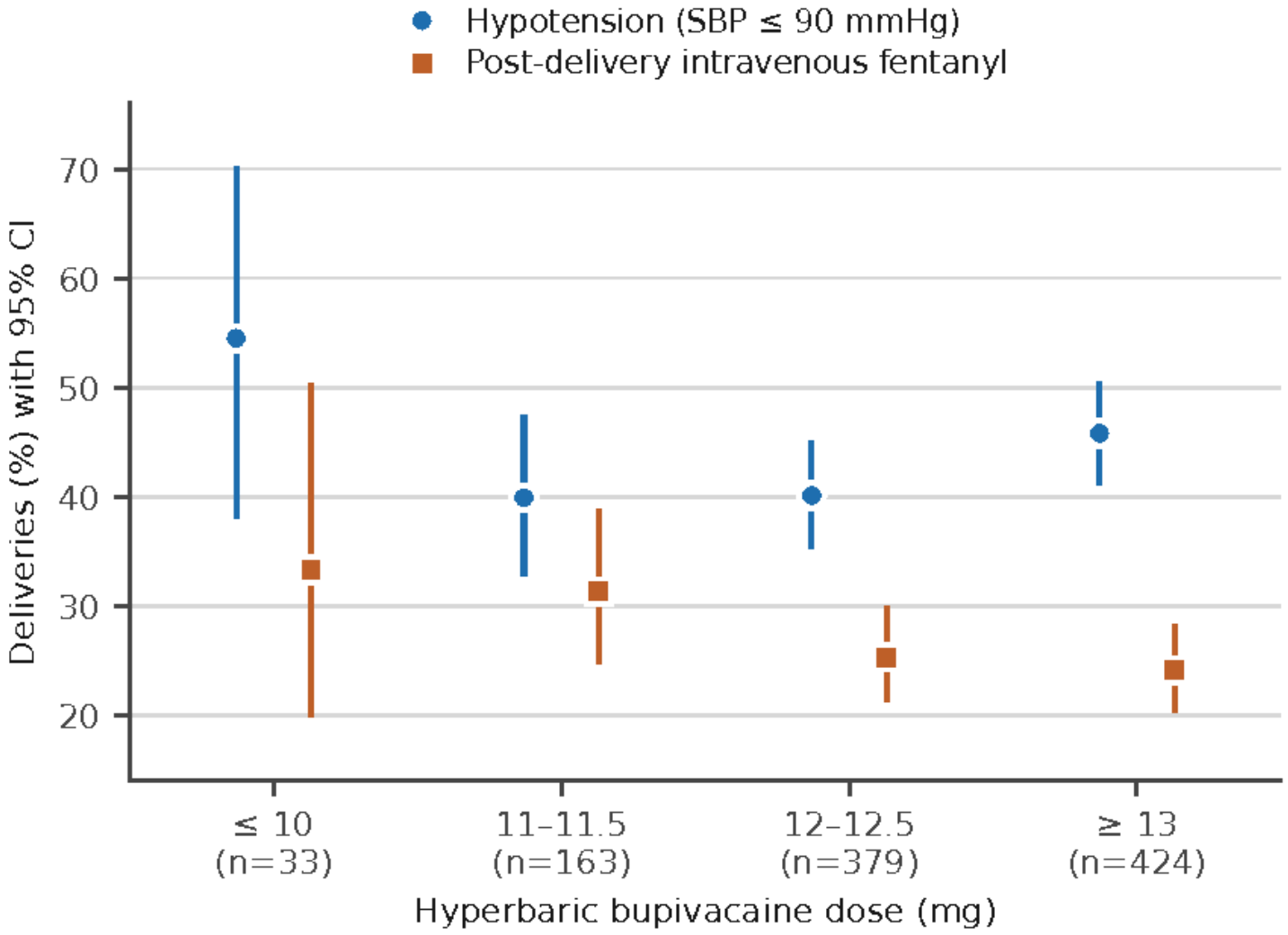


Figure 3

Hypotension and post-delivery intravenous fentanyl across bupivacaine dose strata.

Unadjusted proportions with Wilson 95% confidence intervals among 999 caesarean deliveries in 955 women, under single-shot spinal anaesthesia without preceding epidural labour analgesia and without intrathecal opioid. Dose strata are ≤ 10, 11–11.5, 12–12.5 and ≥ 13 mg; twelve deliveries used half-milligram doses. Hypotension is defined as a lowest systolic arterial pressure ≤ 90 mmHg before delivery; post-delivery intravenous fentanyl counts every delivery in which intravenous fentanyl was given for pain between delivery of the fetus and the end of surgery, which is not a measure of block failure at induction. Stratum-specific proportions are descriptive. Only 33 deliveries received ≤10 mg. These records do not establish pain intensity, block adequacy or the benefit of changing dose.

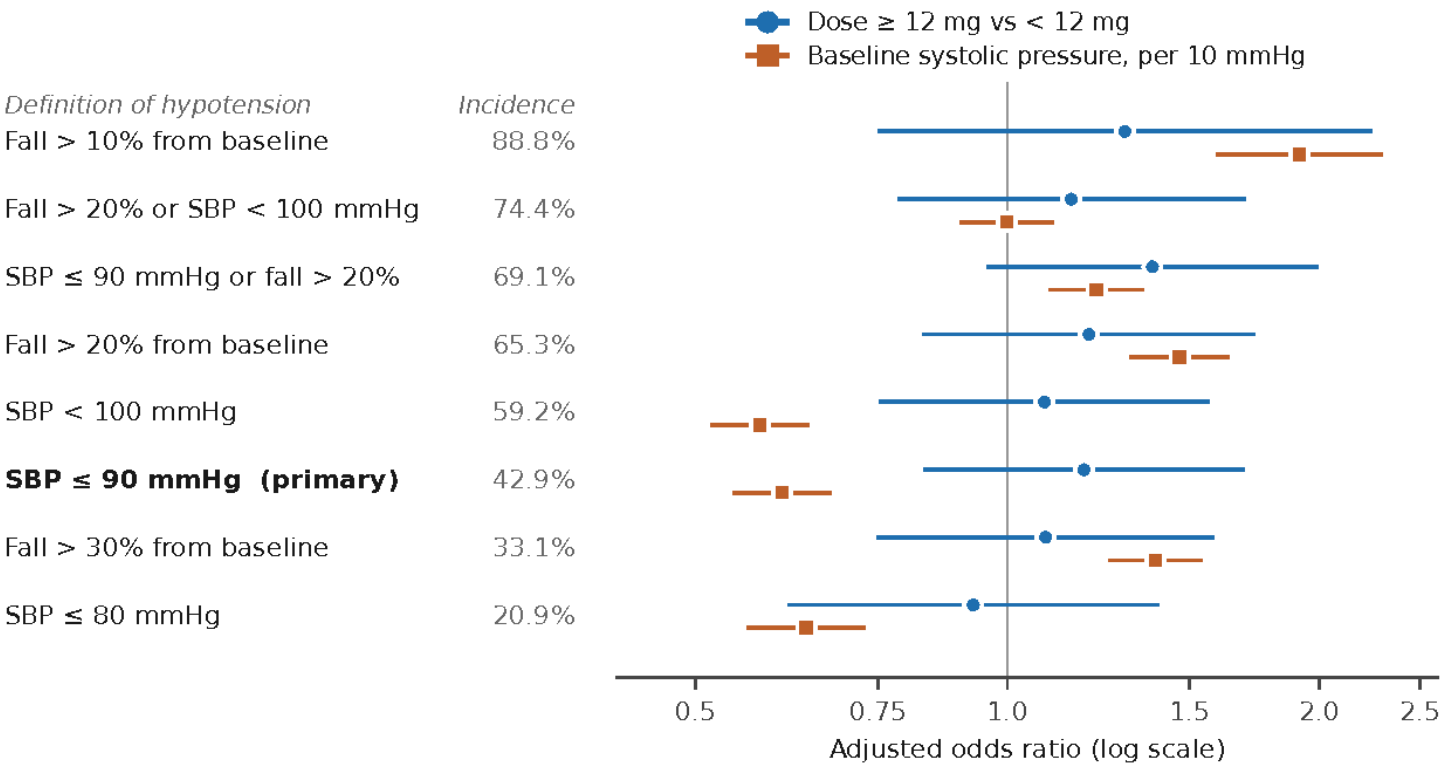


Figure 4

Associations under eight definitions of hypotension applied to the same delivery records.

Eight published definitions of spinal-induced hypotension applied to the same 999 deliveries. Adjusted odds ratios are shown for a bupivacaine dose ≥ 12 mg versus < 12 mg and for baseline systolic arterial pressure, expressed per 10 mmHg. Horizontal bars are 95% confidence intervals. Both models were adjusted for body mass index, baseline systolic pressure, baseline heart rate, parity, largest fetal weight, height, gestational age, twin pregnancy, maternal age and duration of anaesthesia. Definitions are ordered by the incidence they produce. The measured incidence ranged from 20.9% to 88.8%, and the direction of the association with baseline systolic pressure reversed between absolute-threshold and proportional-fall definitions, whereas the dose estimate remained compatible with the null under every definition.

Supplementary Files

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