Dose Requirement of Intrathecal Bupivacaine for Cesarean Delivery Is Similar in Obese and Normal Weight Women

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INTRODUCTION

The number of obese parturients seen in the practice of obstetric anesthesia is steadily increasing. Many of these women deliver by cesarean delivery under spinal anesthesia. The effect of weight and body mass index (BMI) on the spread of intrathecally administered local anesthetics is controversial. There are a limited number of studies that have correlated the weight or BMI with the spread of intrathecal local anesthetics. The majority of them investigated non-pregnant patients, and demonstrated conflicting results [1-3].

In the obstetrical population, no correlation between the level of sensory block and the BMI has been found in term women undergoing cesarean delivery when fixed doses of hyperbaric bupivacaine were given [4,5]. To our knowledge, there is no dose-response study of intrathecal hyperbaric bupivacaine comparing obese and normal-weight patients.

The purpose of this study was to establish the effective dose 95% (ED95) of 0.75% hyperbaric bupivacaine co-administered with fentanyl and morphine for spinal anesthesia for elective cesarean delivery in obese and non-obese women. We hypothesized that obese and normal weight women would require the same dose of bupivacaine.

METHODS

After obtaining Mount Sinai Hospital Research Ethics Board approval, eligible patients were approached for recruitment when the primary investigator was present. Written informed consent was obtained from all patients enrolled. The inclusion criteria included term pregnant patients undergoing elective cesarean delivery with a pre-pregnancy BMI < 25 $kg.m^{-2}$ or ≥ 30 $kg.m^{-2}$. The exclusion criteria were patients with a pre-pregnancy BMI ≥ 25 and < 30 $kg.m^{-2}$, multiple pregnancies or an inability to communicate effectively in English. The study was carried out in a single blinded fashion, as per an up-down sequential allocation method modified by the Narayana rule [6]. Both normal weight and obese patients were allocated sequentially into one single group according to the order of recruitment.

All patients were administered a combined spinal epidural anesthesia (CSE). Monitoring in the operating room included electrocardiogram, non-invasive blood pressure and pulse oximetry. A preload of 10 $mL.kg^{-1}$ of lactated Ringer's solution limited to a maximum of 1 liter was administered immediately prior to the placement of the CSE. The L_{3-4} interspace was used for the needle insertion, and the identification of such interspace was based on a longitudinal paramedian lumbar ultrasound scan [7].

With the patients in the sitting position, a needle through needle CSE technique was performed via a midline approach, with a 17-gauge Tuohy needle and a 27-gauge Whitacre needle. The loss of resistance to air technique was used to identify the epidural space. Subsequently, the Whitacre needle was inserted through the epidural needle until a clear backflow of cerebrospinal fluid (CSF) was observed. At this point the study solution was injected intrathecally at a uniform speed over 30 seconds. The spinal needle was then removed, and a 19-gauge epidural catheter was inserted into the epidural space. The catheter was aspirated to rule out any unintentional intravascular or intrathecal placement, but was not flushed at this moment. Upon completion of the CSE, the patient was quickly positioned supine with a wedge under the right hip to minimize aorto-caval compression. The patient was positioned supine within two minutes of the intrathecal administration.

The study solution consisted of a variable dose of hyperbaric 0.75% bupivacaine, plus a fixed dose of 10 µg of fentanyl and 100 µg of morphine. The first patient of the study received a pre-determined dose of 9 mg of bupivacaine. The subsequent patients received doses that were determined by the doses and outcomes of the previous patients, according to an up-down sequential allocation method modified by the Narayana rule [6]. The dose could be equal to, higher or lower than that received by the previous patients.

In order to allocate the bupivacaine dose, the proportion of satisfactory outcomes among all patients who received a certain dose ($P(d)$) was calculated. If $P(d) < 0.95$, and at least one of the previous 14 patients who received the same dose had an unsatisfactory outcome, the next patient would receive a pre-determined increment of 0.75 mg of bupivacaine. Conversely, if $P(d) \geq 0.95$, and all of the previous patients who received the same dose had satisfactory outcomes, the next patient would receive a pre-determined decrement of 0.75 mg of bupivacaine. Otherwise, the dose remained the same.

The primary outcome was patient satisfaction with the surgical anesthesia. An outcome was deemed satisfactory when the sensory block reached at least T6 within 15 minutes of the intrathecal injection, and the patient did not require supplemental anesthesia during the intraoperative period. Conversely, when either condition was not fulfilled, an unsatisfactory outcome was established.

The sensory block was assessed by pinprick bilaterally on the midclavicular line every five minutes for 15 minutes after the injection of anesthetic solution. Patients were questioned about their pain using a verbal rating scale from 0 to 10 at skin incision, uterine incision, delivery of infant, uterine exteriorization, uterine repair and skin closure. They were also encouraged to inform the investigator about the occurrence of pain at any other intraoperative moment.

In the event that supplemental anesthesia was required, aliquots of 5 mL of plain 2% lidocaine were administered via the epidural catheter. The patient, not the investigator, was the ultimate decision maker about receiving supplemental anesthesia. Intravenous fentanyl or ketamine was given, in boluses of 50 µg and 10 mg respectively, when the epidural lidocaine failed to provide pain relief.

The systolic blood pressure was targeted at 100% of the baseline value obtained on admission to the labor and delivery floor. Phenylephrine in aliquots of 100 µg was administered intravenously to prevent and treat hypotension. Alternatively, ephedrine in aliquots of 5 mg was given if the heart rate was below 50 bpm. The total dose of phenylephrine and ephedrine given was recorded. Occurrence of hypotension defined as a drop of over 20% of the baseline blood pressure value despite the use of prophylactic vasopressors, as well as the occurrence of nausea and vomiting were recorded

Immediately after delivery of the infant, an initial intravenous bolus of 0.5 IU of oxytocin was given, followed by a continuous infusion at the rate of 40 mIU per minute. Cefazolin 1g was given intravenously to all patients. Intravenous ketorolac 30 mg upon cord clamping, and acetaminophen 1.3 g per rectum upon completion of surgery were given for postoperative pain control.

The patient's age, height, and pre-pregnancy and current BMIs were reported as mean ± SD. The ED95 was determined by a logistic model with non-log-transformed doses, fit using Firth penalized maximum likelihood approach. The confidence intervals were based on the profile likelihood approach. A likelihood ratio test with 2 d.f. was used to test for a difference in the model parameters between the two subgroups (obese versus normal-weight).

RESULTS

Forty patients were successfully enrolled into the study from October 2006 to December 2007. The patients' age, height, and pre-pregnancy and current BMIs are shown in Table I. The pre-pregnancy BMIs varied from 16.9 to 52.5 $kg.m^{-2}$.

The dose of intrathecal bupivacaine given varied between 9 and 12 mg. The estimated ED95 for all 40 patients combined was 12.92 mg (95% CI: 11.49 to 34.77) (Figure 1). When nor-

Table I - Patient Characteristics

	Subgroup	
	Normal weight (n=24)	Obese (n=16)
Age (year)	35.21 ± 2.84	35.13 ± 3.14
Height (cm)	163.29 ± 6.86	163.19 ± 6.44
Pre-pregnancy BMI ($kg.m^{-2}$)	21.25 ± 2.03	38.58 ± 7.03
BMI at delivery ($kg.m^{-2}$)	27.22 ± 3.20	42.77 ± 6.54

Values expressed as Mean ± SD

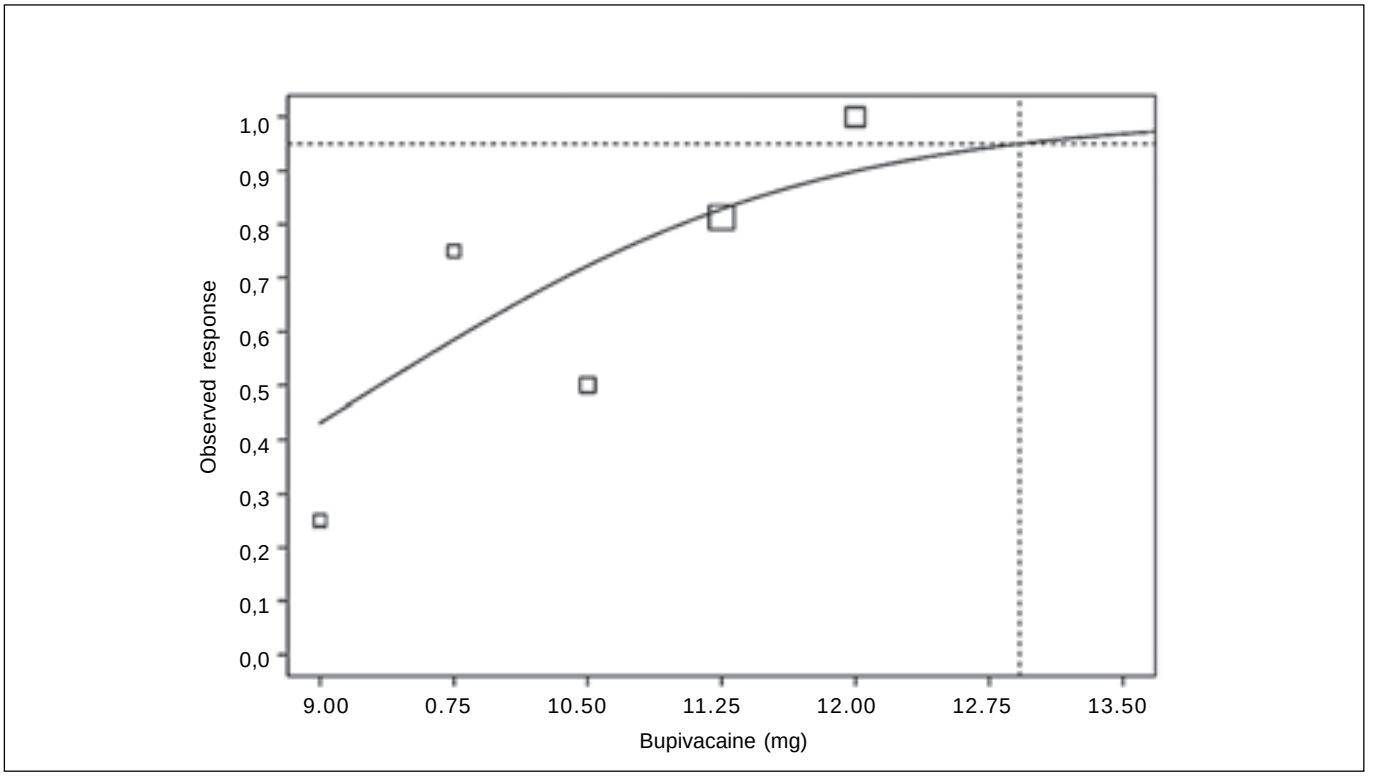

Figure 1 - Predicted dose-response curve for all 40 patients combined using logistic model. ED95 = 12.92 (95% CI: 11.49 to 34.77)

Table II - Patient Outcome According to the Bupivacaine Dose

	9.00 mg		9.75 mg		10.50 mg		11.25 mg		12.00 mg	
	NW n=3	OB n=1	NW n=4	OB n=0	NW n=4	OB n=2	NW n=8	OB n=8	NW n=5	OB n=5
Outcome										
Satisfactory	0	1	3	0	2	1	6	7	5	5
Unsatisfactory	3	0	1	0	2	1	2	1	0	0
SBL										
Minimum at 15 min	T_6	T_4	T_6	NA	T_8	T_7	T_6	T_6	T_6	T_6
Maximum at 15min	T_3	T_4	T_2	NA	T_4	T_5	T_2	T_3	T_4	T_3

NW: normal weight; OB: obese; SBL: sensory block level

mal weight and obese patients were analyzed separately, the estimated ED95 for both subgroups were similar: 12.78 mg (95%CI: 10.75 to + infinity) for the normal weight and 11.86 mg (95%CI: 11.31 to 15.61) for the obese subgroup. The estimated difference in the ED95 between the two subgroups (obese - normal weight) was -0.92 mg (95% CI of - infinity to + 3.23 mg). The *p*-value for the test that the true difference is zero is 0.58. No excessive spread of bupivacaine was noted in this series, and the highest sensory block level achieved was T_2.

Ten patients had unsatisfactory outcomes. Two patients had sensory block levels below T_6 at 15 minutes after the intrathecal injection of LA, and eight patients required epidural supplementation with lidocaine despite an adequate sensory block to pinprick. None of the patients who received a dose of bupivacaine of 11.25 mg or higher had sensory blocks below T6 at 15 minutes (Table II). Two patients had hypotension and four had nausea before delivery, and six patients had nausea and one had vomiting after delivery. The total dose of phenylephrine required ranged from 0.1 to 3 mg. No patient received IV fentanyl or ketamine.

DISCUSSION

The frequency of obese parturients requiring cesarean delivery has increased, and some modification of the anesthetic plan for this group of high-risk patients may be necessary for their safe management. The selection of the optimal dose of local anesthetics for spinal anesthesia for cesarean delivery is of paramount importance. Both excessive and insufficient sensory and motor blockades from spinal anesthesia may result in emergency management of a potentially difficult airway. An excessive motor blockade can produce serious respiratory insufficiency and failure. An insufficient sensory blockade may cause discomfort mandating conversion to general anesthesia. An excessive autonomic blockade can further compromise obese parturients, who usually exhibit some degree of cardiovascular and respiratory morbidity.

Whether obese parturients should receive a reduced dose of local anesthetics to avoid potentially excessive blocks while maintaining satisfactory analgesia is still controversial. Obese patients have increased intra-abdominal pressure and epidural fat, both contributing to the diversion of CSF away from the lumbosacral area, thus reducing its volume in this area.[8] The CSF volume in the lumbosacral area has proven to be one of the most important determinants of intrathecal local anesthetic spread [9,10], with a smaller volume causing more extensive drug spread. Greene [11] and Hocking and Wildsmith [12] did extensive reviews on the factors involved in the intrathecal spread of LA, and concluded that weight did not directly influence the drug spread. Instead, they suggested that the vertebral canal is in slightly head-down position when obese patients are positioned supine, which favours the cephalad spread of LA. In addition, the level of the puncture is usually higher than intended in obese patients because fat pads render the determination of the spinal level by palpation rather inaccurate.

Very few studies have investigated the correlation of obesity with the spread of intrathecal local anesthetics. Although results have been controversial, the majority favour the lack of a correlation between BMI and drug spread. In non-pregnant patients, no correlation was found by Pitkanen in patients receiving 15 mg of isobaric or hyperbaric 0.5% bupivacaine for lower extremity orthopedic procedures [1]. In contrast, significant correlation was found by McCulloch et al. [2] in patients receiving 20 mg of isobaric 0.5% bupivacaine for urologic procedures and by Taivainen et al. [3] in patients receiving 15 mg of isobaric 0.5% bupivacaine for lower extremity orthopedic surgery. The studies that favored a higher level of sensory blocks in obese patients used isobaric local anesthetics, and their conclusions were criticized because of the erratic variability in spread seen with plain solutions [13]. Only Norris [4,5] has studied the influence of BMI on the spread of intrathecal bupivacaine in parturients, however his study designs were not classical dose-response studies. He administered doses of 12 mg or 15 mg of hyperbaric bupivacaine to the parturients for cesarean

delivery, and did not identify any correlation between the drug spread and the weight or BMI of the patients.

The results of our study showed that there is no difference in the dose requirement of 0.75% hyperbaric bupivacaine between obese and normal weight patients undergoing elective cesarean delivery. Although this is in agreement with previous studies by Norris, our study has a completely different design. Instead of administering a fixed dose of local anesthetic, we used a modified up-down sequential allocation method to perform a dose-response study. As stated above, a dose-response study comparing normal weight and obese patients has not yet been published. The estimated ED95 for all 40 patients combined was 12.92 mg (95% CI: 11.49 to 34.77), which is only slightly higher than the ED95 of 11.2 mg obtained by Ginosar et al. under similar circumstances but using a different design of dose-response study and a normal weight population [14].

The up-down sequential allocation, modified by the Narayana rule used in the present study, clusters the doses around the ED95 unlike the classical up-down studies that cluster the doses around the ED50 [15]. We enrolled all patients, normal weight and obese, into only one group, both as a result of our working hypothesis that these patients require similar doses of local anesthetic, and as a result of the up-down sequential allocation method. The patients were only separated into two groups for analysis of the results. The major advantage of this method is that very few patients are needed before a dose close to ED95 is determined. On the other hand, the major limitation of the method is that it lacks precision in determining the exact ED95, since the ED95 sits on the flat part of the sigmoid dose-response curve being subject to a wide confidence interval. Despite this limitation, this study design is extremely interesting and ethical, as it does not subject patients unnecessarily to doses that are ineffective, as it is usually the case with classical dose-response studies. In addition, even if we could not determine the ED95 precisely, it is safe to say that it is at least equal to the lower limit of the 95% confidence interval, which in our case was 11.49 mg. This is already a very clinically useful information.

In this study, we tried to control several factors known to influence the intrathecal spread of local anesthetic. The level of the puncture was determined by lumbar ultrasound as opposed to the inaccurate palpation method [7]. This is especially important in this patient population, where the palpation method is highly inaccurate by as much as 1-4 segments. The duration of the injection of the study solution, and the time allowed between the end of the intrathecal injection and the positioning of the patient supine were strictly standardized.

Aside from the aforementioned disadvantages intrinsic to the up-down allocation methodology chosen, this study has a few other recognizable limitations. First, the study was single blinded. This potential bias was minimized because the assessment of the level of sensory block was objective, and the decision to receive additional analgesia was made by the patient. Second, we selected patients based on their pre-pregnancy BMI. It is not known whether the pre-pregnancy weight or the current weight better reflects the patient's degree of obesity. However, Ekelof et al. [16] demonstrated that the weight gain during pregnancy does not correlate with the cephalad spread of isobaric bupivacaine in women undergoing cesarean delivery. Third, since we recruited the patients into one group in sequence, only two obese patients received bupivacaine doses under 11.25 mg. However, this fact did not have a statistical impact on the calculation of the ED95 for the obese subgroup. Fourth, the CSE technique is well known to cause a higher sensory block of the intrathecal component, simply as a consequence of the epidural catheter insertion [17]. Therefore, the ED95 may be slightly higher when a single-shot spinal technique is used. Fifth, some might argue that there were not enough morbidly obese patients in our study. However, as a rule when we manage morbidly obese patients we do not consider single shot spinals for safety and practical reasons.

In conclusion, our study demonstrates that obese and normal-weight parturients need similar doses of 0.75% hyperbaric bupivacaine for elective cesarean delivery when it is co-administered with fentanyl and morphine. If a single shot spinal technique is planned, it is recommended that at least 11.49 mg of bupivacaine be administered. No excessively extensive blocks were observed in this series when up to 12 mg of hyperbaric bupivacaine was given intrathecally. The safety of these and higher doses should however be tested in a larger population of obese patients.

Clinical Trial Registration Number: NCT00403663.

Acknowledgements

The authors acknowledge Kristi Downey and Leda Weiss (Research Assistants) for organizing the database and recruiting patients for this study.

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RESUMEN

Lee Y, Balki M, Parkes R, Carvalho JCA – Las dosis de bupivacaína intratecal necesarias para cesáreas en mujeres obesas son similares a las usadas en mujeres con peso normal.

JUSTIFICATIVA Y OBJETIVOS: *Los efectos del IMC en la dispersión intratecal de bupivacaína son controvertidos. El presente estudio evaluó la ED95 de bupivacaína intratecal en cesáreas de elección en mujeres obesas y con peso normal.*

MÉTODO: *Evaluamos embarazadas con peso normal (IMC < 25 kg.m^{-2}) y obesas (IMC > 30 kg.m^{-2}), con feto único a término, sometidas a cesáreas de elección. Ese fue un estudio mono ciego y de ubicación secuencial, usando el método up-down (modificado por la regla de Narayana). Todas las pacientes recibieron bloqueo combinado raquiepidural con administración intratecal de dosis variables de bupivacaína hiperbárica a 0.75% más 10 µg de fentanil y 100 µg de morfina. La primera paciente recibió 9 mg de bupivacaína. La anestesia se suplementó cuando fue necesario, a través de un catéter epidural. El éxito de la anestesia, definido como bloqueo sensitivo hasta por lo menos T_6, sin necesidad de anestesia suplementaria, fue el objetivo primario. La ED95 para un resultado satisfactorio fue determinada por un modelo logístico sin transformación logarítmica de las dosis.*

RESULTADOS: *Veinte y cuarto embarazadas con peso normal y dieciséis embarazadas obesas participaron en este estudio. La ED95 estimada para todas las pacientes fue de 12,92 mg (IC 95%: 11,49 a 34,77). La ED95 estimada para las embarazadas con peso normal y las embarazadas obesas fue similar, 12,78 mg (IC 95%: 10,75 a + infinito) y 11,86 mg (CI 95%: 11,31 a 15,61), respectivamente.*

CONCLUSIONES: *Si la anestesia raquídea con inyección única es utilizada en cesáreas, las pacientes con peso normal y obesas deben recibir dosis parecidas de bupivacaína hiperbárica. A pesar de que no fuimos capaces de determinar con exactitud la ED95 en nuestro estudio, sí que podemos afirmar que es de por lo menos 11,49 mg.*