



Research article

Minimum effective volume of bupivacaine in spinal anesthesia for elective cesarean section. Does it differ with height? A non-randomized parallel study



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ABSTRACT

Background: Spinal anesthesia is the preferred anesthetic technique for elective Cesarean deliveries. Hypotension is the most common side-effect and has both maternal and neonatal consequences. This study aims to determine the minimum effective volume of hyperbaric bupivacaine 0.5% with fentanyl in 90% of parturients (MEV90) with different height groups undergoing cesarean section.

Patients and Methods: Parturients scheduled for elective cesarean section under spinal anesthesia were divided into 3 groups according to their height (ht), group 1 including those with height between 150 and 159 cm, group 2 with ht between 160 and 169 cm and group 3 patients with ht between 170 and 179 cm. The starting volumes were 2.5, 2.6 and 2.7 ml respectively. We identified 3 responses to the injected volume and the volume given to each parturient depends on the response of the previous one. Every patient was assessed for hemodynamics, degree of sensory and motor blocks.

Results: Demographically, all the groups were comparable. The study was completed after recruiting 201 patients. The MEV90 for group 1 was approximately 2.62 ml (95% CI, 2.59–2.65 ml), 2.76 ml for group 2 (95% CI, 2.73–2.77 ml) and 2.80 for group 3 (95% CI, 2.76–2.81 ml). None of the babies had an Apgar score below 7 at 1 and 5 min after birth in the 3 groups.

Conclusion: The volumes of hyperbaric 0.5% bupivacaine with fentanyl which produced effective spinal block in 90% of parturients undergoing cesarean deliveries were 2.62, 2.76 and 2.8 ml in the 3 different height groups respectively.

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1. Introduction

Spinal anesthesia (SA) is popular for Cesarean section (CS) because of the ease, effectiveness, and rapidity. It is the preferred anesthetic technique for elective Cesarean deliveries. However, it is associated with some undesirable side effects like severe hypotension, respiratory distress, nausea, vomiting and delayed motor block recovery. These are common especially with higher doses of 0.5% hyperbaric bupivacaine. Hypotension is the most common side-effect and has both maternal and neonatal consequences [1].

The use of a lower dose aims to decrease maternal side-effects, reduce the time to discharge from the post- anesthesia care unit, and improve maternal satisfaction.

Low dose is associated with fewer adverse effects but lower anesthetic efficacy, such a strategy could compromise the adequacy of anesthesia, and require supplementary analgesia, with possible neonatal consequences and may require conversion to general anesthesia [2].

Effective surgical anesthesia is the primary objective of the spinal technique, it must be accomplished while minimizing maternal and neonatal side-effects. The volume of local anesthetic injected affects the extent and the level of the block. Over the past few years there was a substantial interest in determining the Minimum Effective Anesthetic Volume (MEAV) necessary to accomplish surgical anesthesia.

Also, clinical trials have confirmed that patient height is an important factor in determining the final block level [3,4].

The aim of this prospective study was to determine the minimum effective volume of hyperbaric bupivacaine 0.5% with fen-

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tanyl in 90% of parturients (MEV90) with different height groups undergoing cesarean section.

2. Patients and methods

This prospective, double-blind study was performed between January and October 2013, in Ain Shams University Hospital. After obtaining the local ethical committee approval and a written informed consent from all participating patients, we allocated parturients scheduled for elective cesarean section under spinal anesthesia to one of 3 groups according to their height (ht), group 1 including those with height between 150 and 159 cm, group 2 with ht between 160 and 169 cm and group 3 patients with ht between 170 and 179 cm. This is a non-randomized study in which the participants were allocated to the study groups according to their height. All the included parturients were ASA I or II having a singleton beyond 36 weeks' pregnancy.

We excluded all those with ht below 150 or above 179 cm, those with body mass index (BMI) above 30, with essential or pregnancy-induced hypertension, any neurological diseases, and those receiving any medications affecting the cardiovascular system. We also excluded those with polyhydramnios, multiple gestation, having fetus with congenital anomalies and those with any contraindication to spinal anesthesia.

Inside the induction room, a 16 G venous cannula was inserted under local anesthesia and according to our department protocols; 500 ml of hydroxyethyl starch (Voluven[®]) solution was given over 10 min to every female as a preload. All of them were premedicated with 1 mg of granisetron intravenously. In the operating theatre, standard monitors were applied in the form of 5 leads ECG, non-invasive blood pressure and pulse oximetry for SpO₂; baseline readings were recorded. All the procedures were done while the patient was in the sitting position. After sterilization of the back, the L3-4 intervertebral space was identified and local skin infiltration with lidocaine was done, failure to perform the procedure through this intervertebral space was a cause of patient exclusion from the study. Spinal anesthesia was performed using a 25-G Quincke spinal needle and after aspiration of 0.5 ml of CSF, the predetermined volume of local anesthetic was injected over 10 s. In all parturients, the volume injected is 0.5 ml (25 µg) fentanyl added to a certain volume of hyperbaric 0.5% bupivacaine (Marcaine Spinal Heavy; Astra Zeneca, Lund, Sweden) which is determined according to the response of the previous patient as will be discussed later. Then, the patient was immediately turned to supine position with a 15° left lateral tilt and a pillow below the patient's head and neck making an angle about 30° with the bed. Intraoperative fluids were given according to standard protocols.

Every patient was assessed for blood pressure, heart rate and SpO₂ every 2 min for 20 min. Any drop in the systolic blood pressure of more than 20% below the baseline or systolic blood pressure below 100 mmHg, provided that the patient is asymptomatic, was treated with 250 ml of hydroxyethyl starch (Voluven[®]) given under pressure and if there is no response within 5 min, increments of 6 mg of ephedrine were given intravenously. However, if the drop in blood pressure is associated with nausea, vomiting, sense of dizziness or dyspnea, ephedrine 6 mg is given along with the fluid bolus. Any ephedrine given was recorded. Also, any drop in the heart rate below 50/min was treated with atropine 1 mg intravenously. Oxygen mask at 8 l/min was given through face mask if SpO₂ drops below 95% or if there is a sense of respiratory distress.

Also, the upper level of sensory block, determined by the loss of cold sensation in the mid-clavicular line, was assessed bilaterally every 2 min together with the time needed to reach the T4 dermatome bilaterally. Failure to reach this level 10 min after the

spinal injection necessitates the assessor to make a 10° head down tilt. Surgical incision was allowed only when the sensory block reaches the T4 level. Any sense of discomfort or pain during surgery was managed with increments of 25 µg of fentanyl intravenously up to 100 µg together with increments of 1 mg of midazolam up to 3 mg. In case of failure of these maneuvers, general anesthesia was given.

The degree of motor block using the Bromage scale (see Table 1) every 2 min and the time needed to reach grade 3 were assessed.

According to the observed blood pressure, heart rate, onset of sensory and motor blocks, the response to the volume injected was classified as either positive, negative or exaggerated. The criteria for each response are shown in Table 2.

Assessment was done by another anesthesiologist who was, along with the patient, blinded to the volume given.

After delivery of the baby, oxytocin infusion started, and the baby was assessed by Apgar score at 1 and 5 min post-delivery by the attending neonatologist.

In the recovery period, the patients were assessed hemodynamically and then followed up in their wards for the regain of sensory and motor functions.

2.1. Statistical analysis

The main goal of this study is to estimate the MEV90 of bupivacaine 0.5% and fentanyl given for spinal anesthesia for different height groups of parturients undergoing cesarean section. Volume assignment was carried out using a biased coin design (BCD) up-and-down sequential method (UDM) [6], where the volume given to each parturient depends on the response of the previous one. The starting volumes in groups 1, 2 and 3 were 2.5, 2.6 and 2.7 ml respectively. These starting volumes were based on our routine clinical practice. Subsequent volumes given were based on the response of the previous patient. In case of negative response, the next subject received a higher volume (defined as the previous volume with an increment of 0.06 mL). These fractions of the milliliter were prepared by an insulin syringe.

Table 1
Description of the Bromage score [5].

Grade	Criteria	Degree of block
I	Free movement of legs and feet	Nil (0%)
II	Just able to flex knees with free movement of feet	Partial (33%)
III	Unable to flex knees, but with free movement of feet	Almost complete (66%)
IV	Unable to move legs or feet	Complete (100%)

Table 2
Criteria for each response.

Negative response:
1. Failure to reach T4 sensory level or Bromage grade III or both within 10 min
2. The need to 10° head down tilt
3. The need to fentanyl supplementation
4. Conversion to general anesthesia
Positive response:
1. T4 sensory block and Bromage grade III within 10 min
2. No need to change table position
3. No hypotension or hypotension corrected with fluids only
4. No medications were needed (atropine, ephedrine, fentanyl)
Exaggerated response:
1. Sense of nausea or vomiting
2. Ephedrine was needed to correct hypotension
3. Atropine given to treat bradycardia
4. Need for O ₂ or sense of respiratory distress

If the previous patient had a positive response, the next patient was randomized to a lower volume (defined as the previous volume with a decrement of 0.06 mL), with a probability of 11%, or the same volume, with a probability of 89% [6]. Also, if the response is exaggerated, the next patient will receive a lower volume as described above.

The MEV90 was calculated using isotonic regression with 95% bias-corrected confidence interval (CI) derived by 3000 boots trapping. To estimate the minimum sample size required, we followed the methods of Durham et al. [7] who applied different scenarios of dose distribution, sample size, and number of positive responses. They found that stabilization of the tested parameters was obtained after a minimum of 40 subjects applied [7,8]. So, the minimum sample size would be the smallest multiple of 9 above 40 which is 45 because the probability of receiving a lower volume after a successful response in the previous parturient is 0.11. According to this, we continued recruiting patients until 45 positive responses were obtained in each group, at which point the study will stop.

Statistical analysis was performed using the R statistical software package (R Foundation for Statistical Computing, Vienna, Austria [ISBN 3-900051-07-0; <http://www.R-project.org>]) and Microsoft® Excel 2016 (Microsoft, Seattle, WA, USA). Continuous variables are presented as mean standard deviation (SD) or median (range), while categorical variables are presented as frequency.

3. Results

Throughout the study, 9 eligible parturients were excluded,3 from each group, due to failure to perform the spinal anesthesia through the L3-4 interspace.

Table 3
Descriptive analysis of data related to the 3 groups.

	Group 1 (150– 159 cm)	Group 2 (160– 169 cm)	Group 3 (170– 179 cm)
Total number ^b	64	71	66
Age (years) ^a	28.92 ± 3.63	28.05 ± 3.01	27.82 ± 2.46
BMI ^a	24.05 ± 1.91	25.73 ± 1.35	27.26 ± 0.98
Frequency of Responses ^b (positive/ negative/exaggerated)	45/18/1	45/24/2	45/21/0

^a Data presented as mean ± SD.

^b Data are presented as count.

The 45 positive responses in each group were obtained after recruiting 64 parturients in group 1, 71 in group 2 and 66 parturients in group 3. Thus, the whole study was concluded with 201 parturients. Demographic data are shown in Table 3. All patients with positive responses had uneventful surgery. The number of patients with negative responses who needed general anesthesia was 3 in group 1, 2 in group 2 and 3 in group 3. Only 3 patients showed exaggerated response; one in group 1, two patients in group 2 and none in group 3, none of these with exaggerated responses needed any intervention apart from the ephedrine and the oxygen mask. The response of each parturient in each group is represented by Figs. 1–3. Number of each response in each group is shown in Fig. 4.

The MEV90 for group 1 was approximately 2.62 ml (95% CI, 2.59–2.65 ml), 2.76 ml for group 2 (95% CI, 2.74–2.77 ml) and 2.80 for group 3 (95% CI, 2.76–2.81 ml). The MEV90 and their confidence intervals for each group are illustrated in Figs. 1–3 respectively. Table 4 represents the statistical analysis of the volumes given in each group, the MEV90 and their confidence intervals.

None of the babies had an Apgar score below 7 at 1 and 5 min after birth in the 3 groups.

4. Discussion

This study resulted in 3 different MEV90 for the 3 different groups 2.62, 2.76 and 2.8 ml for groups 1, 2 and 3 respectively. Also, as expected, the MEV90 increases as the height of the parturient increases. We didn't have any limitations for the study since we strictly tried to control the other factors which may affect the intrathecal spread of the medication given, for example we excluded parturients in whom it was difficult to perform the spinal anesthesia through the predetermined intervertebral space.

Both regional anesthesia and general anesthesia are acceptable for cesarean section [9], however, the use of general anesthesia has fallen dramatically in the past few decades and is now used in less than 5% of cesarean deliveries in the United States and United Kingdom [10].

Pregnancy results in epidural venous engorgement due to increased intra-abdominal pressure and causes consequent thecal compression. This results in increased intrathecal spread of local anesthetics and the subsequent decrease in the intrathecal dose requirement [11].

Different strategies have been attempted to prevent spinal-induced hypotension, including the use of low-dose bupivacaine

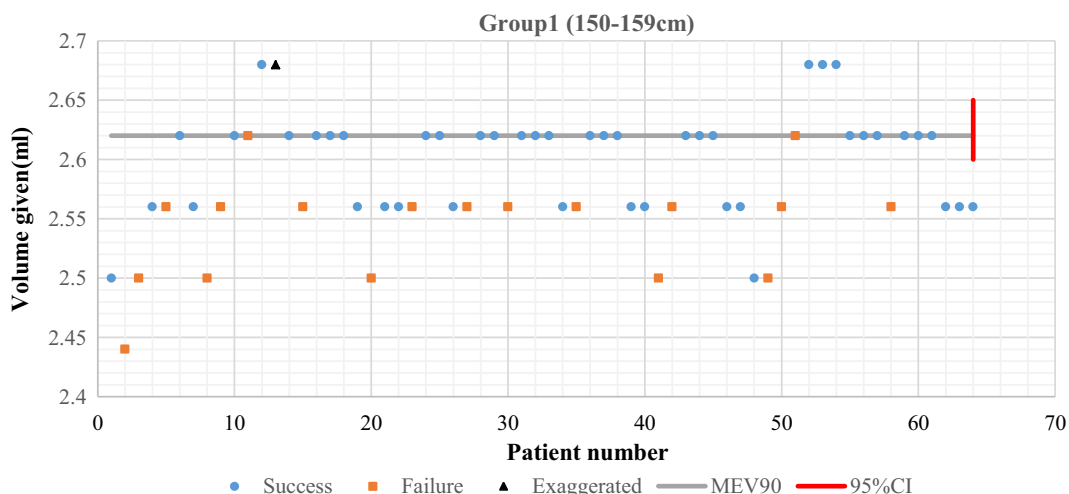


Figure 1. Patients' responses in group 1 to different volumes given.

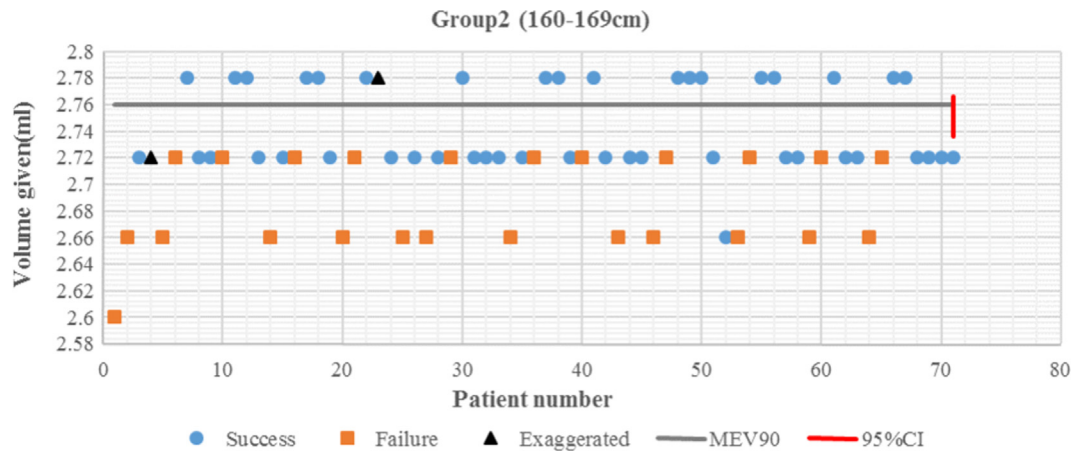


Figure 2. Patients' responses in group 2 to different volumes given.

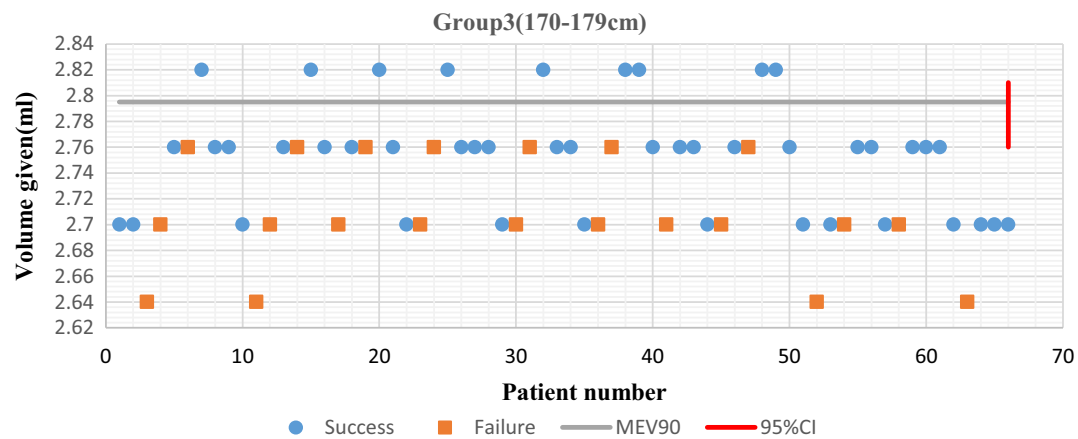


Figure 3. Patients' responses in group 3 to different volumes given.

[12]. We conducted a systematic search for randomized controlled trials comparing the efficacy of spinal bupivacaine in low dose ($LD \leq 8$ mg) with conventional dose ($CD > 8$ mg) for elective Cesarean delivery.

The use of a lower dose aims to decrease maternal side-effects (hypotension, intraoperative nausea/vomiting), reduce the time to discharge from the post-anesthesia care unit, and improve maternal satisfaction.

We are convinced that using an ED90 rather than ED50 as the minimum effective dose is more clinically relevant because it will result in an inadequate block in 5% as opposed to 50% of patients. However, published research regarding the requirement of local anesthetics frequently evaluates the minimum effective dose as the ED50 [13,14].

Anesthesia textbooks recommend bupivacaine in a dose that ranges between 12 and 15 mg. However, the use of this dose range has been associated with an incidence of maternal arterial hypotension of 69% to >80%, resulting in maternal and neonatal morbidity [15].

Moreover, the race may have an effect on the suitable dose for spinal anesthesia. Asian women are usually shorter in height than European women. Nagata et al. [11] have reported that a smaller dose (8 mg) of bupivacaine 0.5% produced an adequate surgical condition for cesarean section in Japanese women, whose frames are generally smaller than that of Caucasian women.

Subedi et al. [16] concluded that the bupivacaine dose was significantly reduced when adjusted for the body weight and height

of patients for cesarean section. This adjusted-dose use suitably restricted spinal block level for cesarean section with the advantage of less hypotension and with a similar neonatal outcome as compared with the fixed dose use.

Lower anesthetic doses cannot be recommended unless an epidural catheter is in place, combined spinal epidural (CSE), to rescue the block if anesthesia is inadequate or becomes inadequate during surgery. Low-dose CSE anesthesia may not be the optimal technique for all patients and institutions [17]. The dilemma of ensuring better anesthesia while avoiding the higher incidence and severity of hypotension is not yet resolved but we have a better understanding of dose schemes.

Venkata et al. [18], concluded that the addition of 25 μ g of fentanyl to 7.5 mg of hyperbaric bupivacaine in spinal anesthesia for elective cesarean section shows faster onset of sensory block with better hemodynamic stability and significantly prolongs postoperative analgesia.

In comparison to our study, Xiao et al. [19] demonstrated that the ED₅₀ and ED₉₅ of intrathecal ropivacaine for cesarean delivery were 8.28 mg and 12.24 mg when co-administered with intrathecal 5 μ g sufentanil.

Also Tyagi et al., found that in normotensive or severely pre-eclamptic patients for an elective cesarean delivery, the ED50 of intrathecal hyperbaric bupivacaine along with 20 μ g of fentanyl is 4.7 mg [20].

Danelli et al. [3] demonstrated that a dose as low as 0.06 mg/cm height represents the dose of intrathecal bupivacaine providing

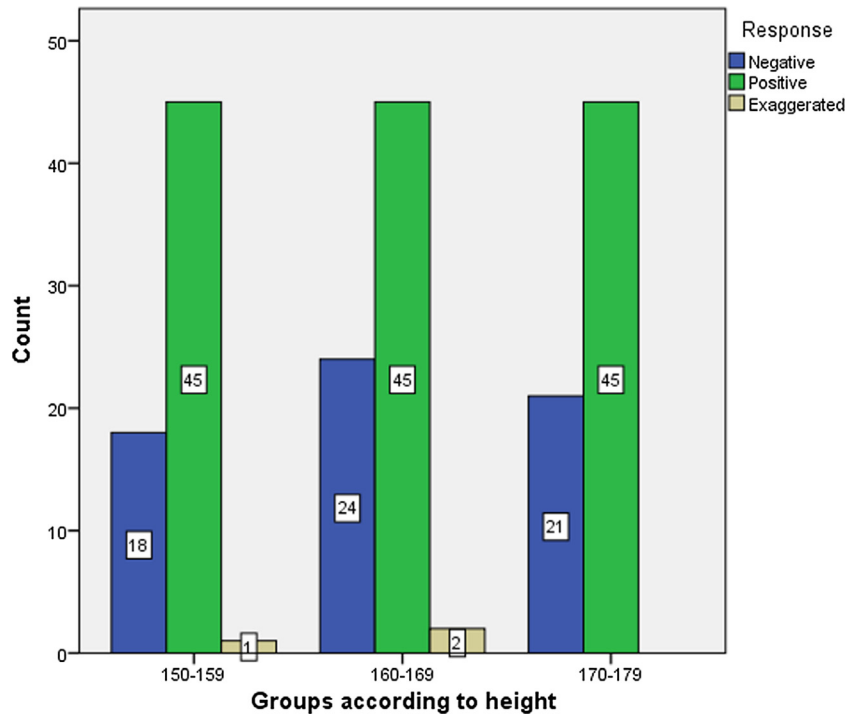


Figure 4. Number of different responses in each group.

Table 4

Analysis of the volumes given and the MEV90 for each group.

	Group 1 (150– 159 cm)	Group 2 (160– 169 cm)	Group 3 (170– 179 cm)
Volume given (ml) ± SD ^a	2.59 ± 0.05	2.72 ± 0.04	2.74 ± 0.05
Median (range) ^a	2.59 (2.44– 2.68)	2.72 (2.60– 2.78)	2.76 (2.64– 2.82)
MEV90 (ml) ± SE ^b	2.62 ± 0.02	2.76 ± 0.01	2.80 ± 0.03
95% Confidence ^b Interval (CI) of MEV90	2.59, 2.65	2.74, 2.77	2.76, 2.81

Confidence intervals are presented as upper, lower bounds.

^a Mean, median and range of volumes given.

^b MEV90 and their CI calculated after 3000 boot replications.

effective spinal block in 95% of women undergoing elective cesarean section and ED50 of hyperbaric bupivacaine (0.5%) to be 0.036 mg/cm height.

This is a dose-finding study, in which we used the biased coin design (BCD) to estimate the MEV90. The BCD was commonly used by many researchers to estimate the MEV50 and 90 of local anesthetics in regional anesthesia [21–24]. Also, the BCD was used for non-anesthetic drugs as by George et al. who adopted this technique to determine the ED90 of phenylephrine in the management of spinal anesthesia-induced hypotension in parturients undergoing cesarean section delivery [25].

The UDM methods are commonly used in drug toxicity studies. In anesthesia, this was the method used to find the minimum alveolar concentrations (MAC) of the commonly used inhalational anesthetics. This is the concentration of inhalational anesthetic agent required to prevent movement on surgical incision in 50% of patients (ED50) [26].

The ED90 for inhalational anesthetics can be derived from the ED50 because the concentration-response curve is steep, this is not the case with other anesthetics as the local anesthetics. The use of isotonic regression and confidence intervals derived by bootstrapping may be of help to calculate the MEV90 as explained by Pace and Stylianou [27,28].

5. Conclusion

The volumes of hyperbaric 0.5% bupivacaine with fentanyl which produced effective spinal block in 90% of parturients undergoing cesarean deliveries are 2.62, 2.76 and 2.8 ml in the 3 different height groups respectively.

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