

Minimum Local Analgesic Dose of Intrathecal Bupivacaine in Labor and the Effect of Intrathecal Fentanyl

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Background: Combining bupivacaine with fentanyl for intrathecal analgesia in labor is well recognized, but dosages commonly used are arbitrarily chosen and may be excessive. This study aimed to determine the median effective dose (ED₅₀) of intrathecal bupivacaine, defined as the minimum local analgesic dose (MLAD), and then use this to assess the effect of different doses of fentanyl.

Methods: In this double-blind, randomized, prospective study, 124 parturients receiving combined spinal epidural analgesia at 2–6-cm cervical dilatation were allocated to one of four groups to receive bupivacaine alone or with 5, 15, or 25 µg fentanyl, using the technique of up–down sequential allocation. Analgesic effectiveness was assessed using 100-mm visual analog pain scores, with less than or equal to 10 mm within 15 min defined as effective. MLAD was calculated using the formula of Dixon and Massey. Pruritus and duration of spinal analgesia were also recorded.

Results: Minimum local analgesic dose of intrathecal bupivacaine was 1.99 mg (95% confidence interval, 1.71, 2.27). There were similar significant reductions in MLAD ($P < 0.001$) for all bupivacaine–fentanyl groups compared with bupivacaine control. There was a dose-dependent increase in both pruritus and duration of spinal analgesia with increasing fentanyl ($P < 0.0001$).

Conclusion: Under the conditions of this study, the addition of intrathecal fentanyl 5 µg offers a similar significant bupivacaine dose-sparing effect as 15 and 25 µg. Analgesia in the first stage of labor can be achieved using lower doses of fentanyl, resulting in less pruritus but with a shortening of duration of action.

INTRATHECAL analgesia in labor has become an established technique, and various local anesthetics and opioids have been used, either alone or in combination. The use of intrathecal bupivacaine with fentanyl has been described for labor,^{1,2} but dosages have been arbitrarily chosen with little knowledge of their contribution to the

overall effectiveness of analgesia. A popular dosage combination of bupivacaine 2.5 mg with fentanyl 25 µg, for example, is associated with high success rates for the provision of analgesia,^{1,3} but recent studies suggest that effective analgesia can still be achieved with lower doses, albeit with a shortening of duration of action.^{4,5}

The aim of this study was to assess the ability of different dosages of intrathecal fentanyl to reduce the requirement for intrathecal bupivacaine in women in the first stage of labor. We wished to achieve this by applying a clinical model, previously designed to estimate the minimum local analgesic concentration of epidural local anesthetics.⁶ This model allows the median effective dose (ED₅₀) of intrathecal bupivacaine to be estimated, which we define as the minimum local analgesic dose (MLAD), and quantifies the bupivacaine dose-sparing effect of the addition of intrathecal fentanyl by determining its effect on the MLAD of bupivacaine. By estimating the MLAD for intrathecal bupivacaine in combination with various doses of fentanyl, it is then possible to compare these equipotent combinations in terms of side effects.

Materials and Methods

After obtaining approval from the hospital Ethics Committee (Hampstead, London, United Kingdom) and written informed consent, 124 parturients classified as American Society of Anesthesiologists physical status I and II who requested labor analgesia were enrolled. All women were at more than 37 weeks' gestation and between 2–6 cm of cervical dilatation. We excluded women who had received opioid or sedative medication within 6 h of requesting regional analgesia, but the use of transcutaneous electrical nerve stimulation and entonox (Cryoservice Ltd., Worcester, UK) was not regarded as an exclusion criterion.

After intravenous prehydration with 500 ml saline, 0.9% wt/vol, women underwent a combined spinal–epidural technique administered while they were in the flexed sitting position. The epidural space was identified using loss of resistance to saline at the L2–L3 or L3–L4 intervertebral space with a 16-gauge Tuohy needle (SIMS Portex, Hythe, Kent, United Kingdom). A 27-gauge, 119-mm Whitacre spinal needle (Becton Dickinson, Franklin Lakes, NJ) was then placed through the Tuohy needle until the dura mater was punctured and cerebrospinal fluid obtained. The dose of intrathecal drug un-

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dergoing evaluation for each patient was always administered in a constant volume of 2.5 ml. To confirm that all of the drug solution was administered intrathecally, cerebrospinal fluid was aspirated at the beginning and end of the spinal injection. The spinal needle was then withdrawn and an 18-gauge, closed-end, multiport epidural catheter (SIMS Portex) was inserted 3 to 4 cm into the epidural space for subsequent epidural labor analgesia after the regression of intrathecal analgesia.

Women were allocated to one of four groups ($n = 30$ per group) in a double-blind, randomized, prospective study design. The study design incorporated two phases. In the first phase of the study, women were randomized to receive either bupivacaine alone (Marcaine, Astra Pharmaceuticals Ltd., Kings Langley, United Kingdom) or bupivacaine in combination with 25 μg fentanyl (Janssen Pharmaceuticals, Piscataway, NJ). Similarly, in the second phase of the study, patients were randomized to receive bupivacaine in combination with either 5 or 15 μg fentanyl. The first patient to be studied in each group received 2.25 mg bupivacaine, a dose arbitrarily chosen. Thereafter, the dose of bupivacaine received by a particular subject was determined by the analgesic response of the previous subject within that group. This resulted in the administration of either a higher or a lower dose of bupivacaine according to up-down sequential allocation. The testing interval was set at 0.25 mg bupivacaine. To simplify the administration of the drugs, 10 ml of drug solution was freshly prepared in advance each day by an anesthesiologist not involved in patient assessment. Each solution was prepared using preservative-free saline and 0.25% wt/vol plain bupivacaine with or without fentanyl. The actual quantity of drug within each solution was calculated to provide the necessary dose, when 2.5 ml solution was withdrawn for the intrathecal injection, according to the ongoing up-down sequences of the study. The remaining 7.5 ml drug solution was then discarded. After the combined spinal-epidural anesthesia was administered, women were placed at a 45° head-up position with left uterine displacement, and routine maternal cardiovascular and fetal monitoring were performed. Time zero was defined as the end of the intrathecal injection.

The patient and the anesthesiologist conducting the assessment were blind to the dose used and the group allocation. Effectiveness of the study drug was assessed using a 100-mm visual analog pain score (VAPS), where 0 represented "no pain" and 100 represented "worst pain ever," at 5-min intervals for 15 min after intrathecal injection. An effective dose was defined as a VAPS of 10 mm or less within 15 min of injection and directed a decrement of 0.25 mg bupivacaine for the next patient randomized to that group. An ineffective dose was defined as a VAPS of more than 10 mm after 15 min of injection and directed an increase of 0.25 mg bupivacaine for the next patient randomized to that group.

Women with ineffective analgesia at this time were offered 15 ml bupivacaine, 0.1% wt/vol, with 2 $\mu\text{g}/\text{ml}$ fentanyl as an epidural rescue bolus.

For all women, age, weight, height, gestation, parity, cervical dilatation, and use of oxytocin and prostaglandin for induction were recorded. In addition to VAPS assessment, other data collected at 5-min intervals included sensory level, the degree of motor block and the incidence of pruritus, nausea, and vomiting. Sensory level was determined by a perceived temperature difference to ethyl chloride spray and to the sensation of pin prick. Motor block was assessed using a modified Bromage scale, where 1 = complete block, unable to move feet or knees; 2 = ability to move feet only; 3 = just able to move knees; 4 = detectable weakness of hip flexion; and 5 = full flexion of hips and knees while supine. The presence of pruritus was ascertained by direct questioning, and each woman who experienced it was made aware that treatment was available. To facilitate analysis, pruritus was scored using a scale where 0 = no pruritus, 1 = pruritus present, and 2 = pruritus present necessitating treatment. The onset of successful analgesia was assessed at each 5-min interval when the VAPS assessments were performed. The duration of effective spinal analgesia, defined as the time taken for the woman to first feel her contraction becoming uncomfortable, in accordance with guidelines suggested by Morgan and Kadim,⁷ was also recorded. At that time, the study was discontinued and a bolus dose of 15 ml bupivacaine, 0.1% was administered with 2 $\mu\text{g}/\text{ml}$ fentanyl for epidural analgesia.

Statistical Analysis

Patient and obstetric data were collected and are presented as mean (SD), median (interquartile range), and count, as appropriate, and were analyzed using analysis of variance, Kruskal-Wallis, and chi-square tests, respectively. The ED_{50} was estimated from the up-down sequences using the formula of Dixon and Massey,⁸ which enabled MLAD with 95% confidence intervals to be determined. The dose-response effects of fentanyl were evaluated using analysis of variance with the Bartlett test for homogeneity of variance. Additional analyses included the Dunn *post hoc* test for multiple comparisons, chi-square trend, and Cuzick trend. Analyses were performed using the following software: Excel 97 (Microsoft Corp., Redmond, WA), Number Crunching Statistical System 2000 (NCSS Inc., Kaysville, UT), and GraphPad Instat 3.01 (GraphPad Software Inc., San Diego, CA). Statistical significance was defined for an overall α error at the 0.05 level. All P values were two-sided.

Sample size estimations were based on an assumed SD of 0.5 mg as being one sixth the range of likely doses (0–3 mg). Power was given as 0.9 to detect a difference of 0.75 mg at $P < 0.05$. It was then estimated that a

Table 1. Demographic and Obstetric Data

	Bupivacaine–Control	Bupivacaine–5 μ g Fentanyl	Bupivacaine–15 μ g Fentanyl	Bupivacaine–25 μ g Fentanyl
Age (yr)	29.8 (5.64)	28.7 (6.22)	30.7 (5.60)	30.0 (5.72)
Height (cm)	161.1 (6.69)	160.2 (4.38)	159.7 (6.64)	160.1 (6.87)
Weight (kg)	74.7 (11.17)	72.9 (9.22)	77.3 (17.25)	72.9 (12.70)
Gestation (weeks)	40.0 (1.30)	39.3 (1.24)	39.6 (1.16)	39.9 (1.50)
Cervical dilatation (cm)	3.3 (0.96)	3.7 (1.12)	3.5 (1.11)	3.2 (1.03)
Nulliparous*	24	21	17	14
Oxytocin use	3	1	0	2
Prostaglandin use	9	4	9	10
Initial VAPS (mm)†	74 [61–87]	86 [72–100]‡	75 [61–89]	68 [56–80]‡

Results are expressed as mean (SD), median [interquartile range], and count, as appropriate.

* Chi-square, $P = 0.04$. † Kruskal-Wallis, $P = 0.022$. ‡ Dunn post test, $P < 0.05$.

VAPS = visual analog pain score.

minimum of 28 subjects would be necessary in each of the four groups.

Results

Of the 124 women enrolled, 4 were excluded. One woman had an accidental dural puncture, another two rapidly progressed to the second stage of labor, and a fourth woman reported atypical subcostal pain after combined spinal-epidural anesthesia, not related to labor pain, but which influenced her scoring for pain relief. On these occasions, the dose was repeated for the next woman randomized to that group. One hundred twenty women remained for further analysis.

Demographic and obstetric characteristics are shown in table 1. There was variability in the parity (chi-square, $P = 0.04$) distributions across groups, the smallest probability for the specific comparisons of groups being $P = 0.088$ (Bonferroni-corrected). Baseline VAPS differed ($P = 0.022$) in the 5- μ g bupivacaine-fentanyl group (median, 86 mm) compared with the 25- μ g bupivacaine-fentanyl group (median, 68 mm) at $P < 0.05$ (Dunn post test).

The sequences of effective and ineffective analgesia are shown in figure 1. Using the formula of Dixon and Massey,⁸ the MLAD for intrathecal bupivacaine in the first stage of labor was 1.99 mg (95% confidence interval, 1.71, 2.27). The effect of fentanyl (analysis of variance, $P < 0.0001$) was associated with a significant difference in variance in the groups using the Bartlett test ($P < 0.0001$). The data were subsequently analyzed using Kruskal-Wallis nonparametric one-way analysis ($P < 0.0001$), with Dunn post test for multiple comparisons. There was a significant reduction ($P < 0.001$) in MLAD for all bupivacaine-fentanyl groups compared with the bupivacaine control group, but MLAD did not differ significantly in the bupivacaine-fentanyl groups (table 2). A dose-dependent effect of fentanyl on MLAD was not shown.

Onset of analgesia was not affected by the addition of

fentanyl (table 3). Duration of spinal analgesia was significantly (Kruskal-Wallis, $P < 0.0001$) increased by the addition of fentanyl. In addition, a significant (Cuzick trend, $P < 0.0001$) dose-dependent effect of fentanyl to increasing the duration of analgesia was shown (table 3).

There were no significant differences in groups for the maximum level of sensory block achieved, the degree of motor block, and the incidence of nausea and vomiting (table 4). The incidence of pruritus was significantly (chi-square, $P < 0.0001$) increased by the addition of fentanyl, but no woman required treatment. In addition, the effect of fentanyl was also shown to be significantly (chi-square trend, $P < 0.0001$) dose-dependent (table 4).

Discussion

We have shown that for the women in this study, the MLAD of intrathecal bupivacaine in the first stage of labor is 1.99 mg, and the addition of 5, 15, or 25 μ g fentanyl resulted in a similar significant bupivacaine-sparing effect. There was also a dose-dependent increase in the incidence of pruritus and duration of action with fentanyl.

Methods

The method used in this study was similar to that used for estimating minimum local analgesic concentration of epidural local anesthetics.^{6,9,10} Compared with random allocation, the technique of up-down sequential allocation allows the ED₅₀ to be determined in a more efficient way. The effect of concentrating testing around the ED₅₀ implies that estimates for effectiveness at the 95th percentile (ED₉₅), which is clinically more relevant, are less precise. However, using the ED₅₀ to show dose-sparing effects raises the definite possibility that similar effects may occur at ED₉₅ doses. In addition, because ED₅₀ corresponds to the greatest inflection point on the dose-response curve, its estimation is a more sensitive research tool than estimating ED₉₅.

In this study, an effective dose was defined as achiev-

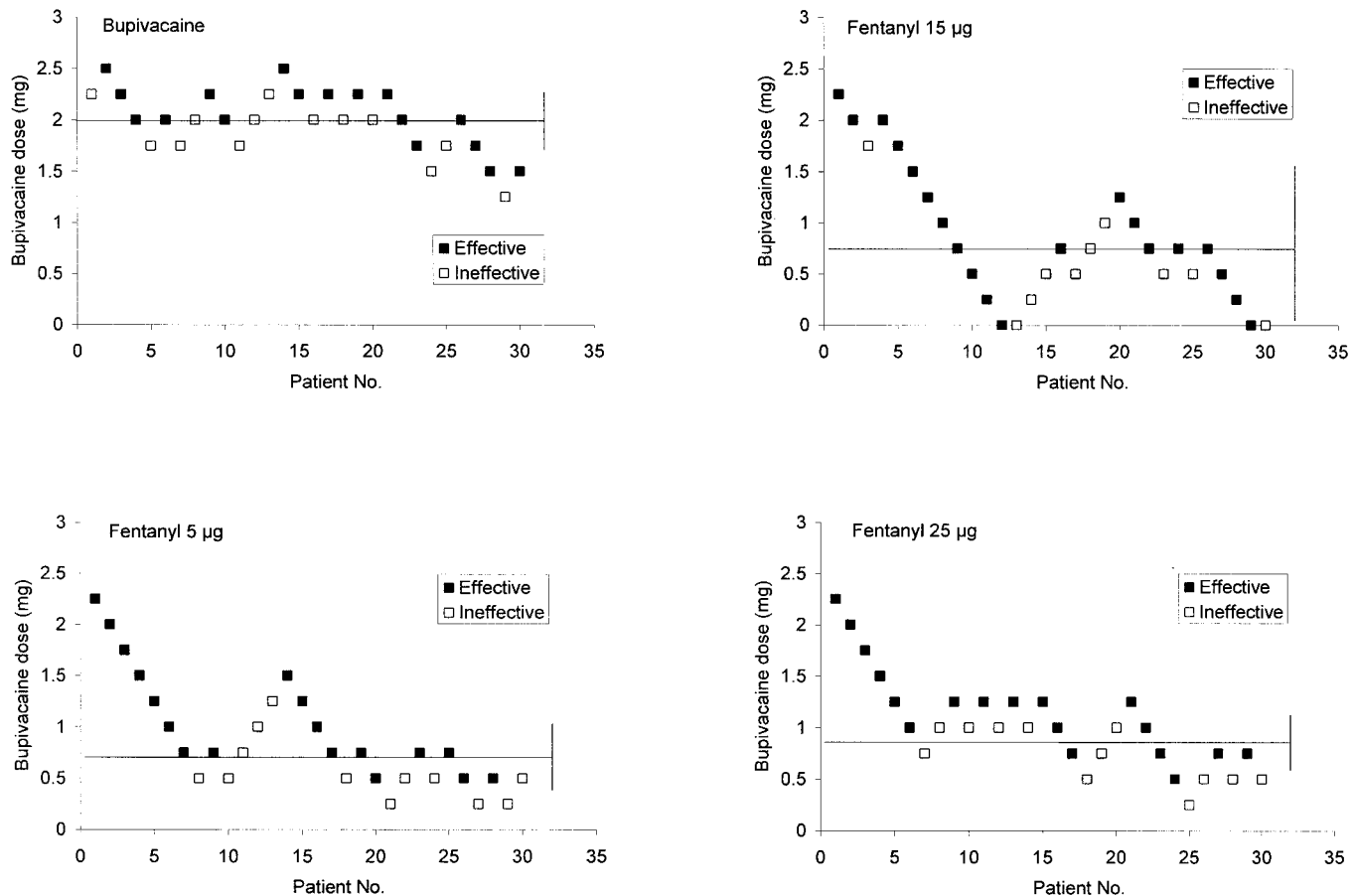


Fig. 1. The minimum local analgesic dose (MLAD) of intrathecal bupivacaine and with addition of 5, 15, or 25 µg fentanyl as determined by the technique of up-down sequential allocation. Error bars represent 95% confidence intervals. The testing interval was 0.25 mg.

ing a VAPS of 10 mm or less within 15 min of the spinal injection. Using a longer study period may possibly have allowed more time for an ineffective dose to become effective, but we think that this is unlikely. A dose-response study using intrathecal fentanyl alone showed that VAPS with even the lowest dose of fentanyl (5 µg) was maximally reduced within 15 min.¹¹ We also thought that if a longer study period had been chosen, the onset time would then have approached that expected for epidural analgesia, thus losing the clinical advantage of rapid onset of intrathecal analgesia.

Table 2. Bupivacaine Requirements and Effect of Fentanyl

Group (n = 30)	MLAD (95% CI, mg)	Dunn P Value*
Bupivacaine-control	1.99 (1.71, 2.27)	
Bupivacaine-5 µg fentanyl	0.69 (0.35, 1.02)	< 0.001
Bupivacaine-15 µg fentanyl	0.71 (0.00, 1.53)	< 0.001
Bupivacaine-25 µg fentanyl	0.85 (0.58, 1.13)	< 0.001

* P value compared with bupivacaine-control. Kruskal-Wallis, $P < 0.0001$.
MLAD = minimum local analgesic dose; CI = confidence interval.

Baseline VAPS Difference

The difference in baseline VAPS between groups might have been expected to lead to an increased MLAD in the 5-µg bupivacaine-fentanyl group. However, in this study, there is no evidence to support this, and analysis of 14 minimum local analgesic concentration studies (involving 620 cases) revealed that opioid usage and cervical dilatation had an overriding influence in determining epidural bupivacaine requirements.¹² In the current study, there was no difference between groups in terms of cervical dilatation.

Table 3. Onset Time and Duration of Spinal Analgesia for Women with Effective Analgesia

Group	Onset (min)	Duration of Analgesia (min)*
Bupivacaine-control (n = 17)	8.8 (4.16)	43.1 (19.81)
Bupivacaine-5 µg fentanyl (n = 18)	10.2 (4.01)	56.1 (17.26)
Bupivacaine-15 µg fentanyl (n = 20)	10.2 (4.13)	68.5 (33.43)
Bupivacaine-25 µg fentanyl (n = 18)	8.6 (3.35)	77.2 (25.95)

Results are expressed as mean (SD).

* Dose-dependent increase of duration of analgesia with fentanyl ($P < 0.0001$).

Table 4. Maximum Height of Sensory Block, Motor Block, and Incidence of Pruritus

Group (n = 30)	Cold	Pin Prick	Bromage	Pruritus*
Bupivacaine-control	T7 [T8 to T6]	T9 [T10 to T8]	5 [4-5]	0 (0)
Bupivacaine-5 μ g fentanyl	T7 [T8 to T6]	T8 [T10 to T7]	5 [4-5]	12 (40)
Bupivacaine-15 μ g fentanyl	T7 [T8 to T6]	T8 [T9 to T7]	5 [4-5]	18 (60)
Bupivacaine-25 μ g fentanyl	T7 [T8 to T6]	T9 [T10 to T7]	5 [5]	22 (73)

Results are expressed as median [interquartile range] and count (%).

* Dose-dependent increase in incidence of pruritus with fentanyl ($P < 0.0001$).

Dose-Response Relation of Intrathecal Bupivacaine with Fentanyl

Dose-response studies for intrathecal drugs used in labor have been conducted for sufentanil alone^{13,14} and in combination with neostigmine¹⁵ and for fentanyl.^{11,16} Bupivacaine with fentanyl has been shown to increase duration and speed of onset of analgesia compared with fentanyl alone,^{4,17} but very little is known regarding the dose-response relations of these drugs when used in combination.

We have shown that the addition of 5, 15, or 25 μ g fentanyl results in a similar bupivacaine dose-sparing effect. We were unable to show a dose-dependent reduction in bupivacaine requirements, which implies that to establish a dose-dependent effect of fentanyl on MLAD, dosages lower than 5 μ g fentanyl would need to be studied.

The popular combination of 2.5 mg bupivacaine with 25 μ g fentanyl is associated with high success rates for provision of analgesia in labor.^{1,3} Our findings suggest that 2.5 mg bupivacaine represents 3 times the ED₅₀ of bupivacaine in this combination (table 2), and, although ED₉₅ doses cannot be reliably estimated, this dosage combination may be at the upper flatter part of the dose-response curve. These findings are further supported by two studies comparing 25 μ g fentanyl in combination with 2.5 or 1.25 mg bupivacaine.^{4,5} Both doses produced effective analgesia, but the 1.25-mg bupivacaine group did have a shorter duration of action.

Pruritus

We have shown that the incidence of pruritus increases from 40% in the 5- μ g bupivacaine-fentanyl group to 73% in the 25- μ g bupivacaine-fentanyl group (table 4), and that this is a dose-dependent effect of fentanyl. Palmer *et al.*,¹⁶ using intrathecal fentanyl alone in doses ranging from 5 to 45 μ g, reported similar incidences of pruritus, suggesting that there is a very low threshold for fentanyl-induced pruritus. Interestingly, however, they were not able to demonstrate a dose-dependent effect, and it may be that the addition of bupivacaine to fentanyl leads to an alteration of the fentanyl dose-response relation for pruritus. It has been shown that intrathecal bupivacaine reduces the incidence of pruritus, but the mechanism is unclear. It may involve neuronal blockade or direct modulation of the

opioid receptor.¹⁷ It is also interesting that this dose-dependent relation for pruritus was not shown for analgesia. This suggests that the dose-response curves are separate, with the pruritus curve to the right of the analgesia curve. Although our data for the entire dose-response relation of bupivacaine with fentanyl is incomplete, our findings suggest that it may be possible that a fentanyl dosage of less than 5 μ g may contribute to analgesia without causing pruritus.

Onset and Duration of Action

In the current study, the time of onset of analgesia was unaffected by the addition of fentanyl. However, Palmer *et al.*⁴ have shown that higher doses of fentanyl significantly speed up the onset of analgesia. In their study, they used a time interval of 2.5 min to measure VAPS, whereas we used a 5-min interval. It is possible that differences in onset time could occur within the first 5 min and that our study may therefore not have detected this.

In our study, the duration of analgesia ranged from 43 to 77 min (table 3). This is shorter than can be achieved by spinal regimens currently used in clinical practice, which can produce in excess of 90 min of analgesia.^{1,3} We have demonstrated that fentanyl has a dose-dependent effect on duration of analgesia (table 3). The values for duration of analgesia in this study are mean values derived from groups of women who had lower doses of bupivacaine and fentanyl than commonly used, and, therefore, it is to be expected that duration of action will be shorter. We also defined the duration of effective analgesia as the time until the first uncomfortable contraction was felt, but in clinical practice many women may choose to ask for further analgesia at a later time, thus prolonging the duration.

In conclusion, for the patients in the current study, the MLAD of intrathecal bupivacaine was estimated to be 1.99 mg. The addition of 5 μ g intrathecal fentanyl offers a similar significant bupivacaine dose-sparing effect as 15 and 25 μ g. These findings suggest that analgesia in the first stage of labor can be achieved using lower doses of fentanyl. However, although the incidence of pruritus was reduced with lower doses of fentanyl, the duration of action of spinal analgesia was also reduced. No patients in our study requested treatment for pruritus, suggesting that this side effect was well tolerated. Many clinicians may therefore accept an increase in pruritus

for the advantage of a longer duration of action. Further studies are necessary to determine ED₉₅ dosages for this combination.

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