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On the ropivacaine-reducing effect of low-dose sufentanil in intrathecal labor analgesia

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Background: Combining ropivacaine with sufentanil for intrathecal (i.t.) analgesia in labor is well recognized, but information on dosing is limited. This study aimed to determine the ED 50 of i.t. ropivacaine and to assess the effect of adding defined low doses of sufentanil.
Methods: This was a two-phase, double-blind, randomized and prospective study. One hundred and fifteen parturients receiving combined spinal epidural analgesia were allocated to one of four groups to receive ropivacaine or sufentanil alone or in combination. In phase one, sufentanil dose–response was calculated using logistic regression. In phase two, ED 50 of ropivacaine and of the combination with a fixed dosage of sufentanil at ED 20 and ED 40 was evaluated using the technique of up–down sequential allocation. Analgesic effectiveness was assessed 15 min after injection using a 100 mm visual analog scale, with <10 mm lasting for 45 min defined as effective. Furthermore, side effects and duration were recorded.
Results: The ED 50 of i.t. ropivacaine was 4.6 mg [95% confidence intervals (95% CI) 4.28, 5.31]. Adding sufentanil at ED 20 significantly decreased the ED 50 of i.t. ropivacaine to 2.1 mg (95%CI 1.75, 2.5) ($P < 0.005$); at ED 40, the reduction was similar ($P < 0.005$). Combining sufentanil with ropivacaine resulted in a dose-independent prolongation of analgesia. Besides pruritus, which was well tolerated, there were no differences in side effects.
Conclusion: Adding sufentanil at ED 20 results in a more than 50% dose-sparing effect of ropivacaine and considerably prolongs analgesia. Increasing dosage implicates no clinical benefit.

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Neuroaxial analgesia is the method of choice for analgesia in labor, according to the consensus statement of the American College of Obstetricians and Gynecologists.[1] A popular technique is combined spinal–epidural (CSE) analgesia.[2] It is an alternative to epidural analgesia for labor and delivery,[3] with a more rapid onset of analgesia and higher patient satisfaction rates.[4–6] Duration of effective analgesia, the minimum effective, and the minimum motor-blocking dose are the key characteristics of local anesthetics in intrathecal (i.t.) labor analgesia. The combination with an opioid allows a reduction of local anesthetic, resulting in reduced motor blockade and increased duration of analgesia.[7–14] For this purpose, sufentanil is a favorable opioid due to its high lipid solubility and analgesic potency. I.t. dosages, however, have been arbitrarily chosen.[8,15–18] Available data on i.t. sufentanil are restricted to ED 50 (= dosage at which 50% of patients have effective analgesia) and ED 95. Furthermore, the described ED 50 shows a wide variation from 1.8 to 2.6 μg,[17,19,20] mainly explained by differing authors' definitions of effective analgesia. No data are available on dose–response below ED 50, but lower dosages of sufentanil could be especially favorable in order to reduce ropivacaine dosage, the incidence of side effects and to increase the duration of analgesia. The effect of very low-dose sufentanil on i.t. ropivacaine dosing has not been examined so far. Therefore, the aim of this study was to determine the i.t. dose-dependent effect of sufentanil on ED 50 of ropivacaine in labor analgesia. We wished to achieve this aim by applying a clinical model that estimates the ED 50 of ropivacaine. We then combined ropivacaine with the ED 20 and ED 40 of sufentanil. By determining its effect on the ED 50 of ropivacaine, we could quantify the ropivacaine dose-sparing effect. As literature is contradictory regarding the dose–response curve of i.t.

sufentanil,[17,20] we estimated the ED 20 and 40 in a phase one study group using a logistic regression model. Furthermore, we wanted to study the incidence of side effects and to measure the duration of action.

Methods

After obtaining approval from the local ethics committee (Medical University Vienna) and written informed consent, parturients who requested labor analgesia were enrolled consecutively in this prospective, double-blind, parallel-group, randomized study. In phase one, dose–response of i.t. sufentanil was estimated using the technique of random allocation; in phase two, ED 50 of i.t. ropivacaine with and without sufentanil was calculated by up–down sequential allocation.

All women were between the 36th and 41st gestational week, nulli- or multiparous status, at 2–6 cm of cervical dilatation in induced or spontaneous labor. They were classified as American Society of Anesthesiologists physical status I and II.

We excluded women who received opioids or sedative medication within 6 h before requesting regional analgesia.

In phase one, an arbitrary 25 patients received randomly 1,2,3,4 or 5 μg of i.t sufentanil to determine ED 20 and ED 40 by logistic regression. ED 20 was defined as the dosage at which 20% of patients had effective analgesia, ED 40 as the dosage with 40% effective analgesia. Effective analgesia was defined as visual analog pain scale (VAS) of 10 mm or less by 15 min with a duration of at least 45 min. Drug dosage was randomly allocated by a computer and sealed in an envelope.

In phase two, women were randomly allocated to one of three groups. Patients received ropivacaine alone or in combination with sufentanil. To investigate a dose effect, it was chosen at ED 20 or ED 40 as determined in phase one. The first patient in each group received 2.0 mg ropivacaine. This dose was chosen, as it lies between the ED 50 s of ropivacaine, as estimated in former studies.[21,22] Thereafter, the dose of ropivacaine received by a particular subject was determined by the analgesic response of the previous subject within the group. This resulted in the administration of either a higher or a lower dose of ropivacaine according to the up–down sequence. The testing interval was set at 0.25 mg ropivacaine. All the drug solutions were prepared according to a standardized protocol at an equal volume of 2.5 ml using preservative-free saline by a research fellow not involved in patient assessment. We used 0.2% w/v plain ropivacaine (AstraZeneca Austria, Vienna, Austria) with or without sufentanil (Hameln Pharmaceuticals, Hameln, Germany).

After intravenous prehydration with 500 ml lactated Ringer's solution, women underwent a CSE technique administered in the flexed sitting position. The epidural space was identified using loss of resistance to saline at the L3–L4 or L4–L5 intervertebral space using a 16 G Tuohy needle (EpiStar CSE-Set, RUESCH Lab. Pharmaceutiques, Betschdorf, France). After placing an 18 G epidural catheter, a 25 G, a 127 mm Pencil Point spinal needle (EpiStar CSE-Set, RUESCH Lab. Pharmaceutiques) was then placed through the Tuohy needle until the cerebro-spinal fluid was visible. Immediately, the drug solution was administered and the women were then placed at an estimated 45° head-up position with left uterine displacement, and routine maternal cardiovascular and fetal monitoring was performed. Time zero was defined as the end of the i.t. injection.

Pain intensity was assessed using a 100 mm VAS, where 0 represented 'no pain' and 100 represented the 'worst pain ever,' at 5-min intervals until 15 min after injection and after 30, 45 and 60 min. An effective dose was defined as a VAS of 10 mm or less within 15 min and a minimum duration of analgesia of 45 min. End of duration was defined as the first uncomfortable uterine contraction, in accordance with the guidelines suggested by Morgan and Kadim.[23] Women were informed about the possibility of additional epidural analgesia. Women with ineffective analgesia or weakening analgesia at the end of the study period were administered 15 ml ropivacaine, 0.2% w/v as an epidural rescue bolus. Other data collected at the same time points included sensory level, the degree of motor block, changes in arterial blood pressure and the incidence of pruritus, nausea and vomiting. Sensory level was determined by a reduced temperature sensation to a cold stimulus of 4C°. 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. Arterial hypotension was defined as a 20% decrease in the mean arterial pressure after time zero. The presence of pruritus and nausea were ascertained by questioning, and

the incidence of vomiting was recorded. Pruritus and nausea were scored using a scale where 0 = no symptoms, 1 = mild symptoms and 2 = symptoms requiring treatment (= severe symptoms).

For all women, age, weight, height, gestation, parity, cervical dilatation and use of oxytocin for induction were recorded.

Patient and obstetric data were collected and are presented as mean, standard deviation (SD), median, interquartile range and count, as appropriate.

The ED 20 and 40 for sufentanil in the phase one study group was estimated by logistic regression, and 95% confidence intervals (95% CI) were computed based on Fieller's theorem.[24] Similarly, the ED 50 for ropivacaine was estimated based on separate logistic regressions for each of the groups: ropivacaine-control, ropivacaine with sufentanil at ED 20 and ropivacaine with sufentanil at ED 40, with a dependent variable as effective analgesia and an independent variable as ropivacaine dose. To investigate a possible effect of oxytocin treatments, the logistic regressions were repeated with the additional independent variable oxytocin. To investigate pair-wise differences between the no sufentanil, 1.6 and 2.2 μg sufentanil dose groups, logistic regressions with independent variables sufentanil dose group and ropivacaine dose were performed. To investigate the robustness of statistical analysis, the ED 50s and 95% CI for ropivacaine were calculated using the formula of Dixon and Massey. According to this method, a sample size of 30 patients yields a CI with width 0.5 mg ropivacaine for the ED 50 Dixon estimate, if SD of the effective dose is 0.5 mg ropivacaine. The 95% CI were calculated using the following equation: 95% CI = dosing increment $\times$ ($\sqrt{}$l(2/n)) $\times$ 1.96, in which n is the last n trials and 1.96 indicates the 0.05 α level of the normal distribution (Dixon and Massey, 1969).[25]

For comparing side effects, only patients receiving a ropivacaine dose within ± 10% of the estimated ED 50 have been considered. In the phase-one group, only patients receiving ± 30% of the estimated ED 50 have been considered. Additionally, the mean duration of analgesia in patients having effective analgesia only was calculated and compared separately. Binary variables were compared between groups using Fisher's exact tests, and metric variables were compared using Wilcoxon's tests. For each variable we adjusted for the multiple group comparisons using the Bonferroni–Holm method. The two-sided significance level was set at 0.05 if not indicated otherwise.

Analyses were performed using the following software: R Development Core Team (2007): A Language and Environment for statistical Computing, (R Foundation for Statistical Computing, Vienna, Austria. ISBN 3-900051-07-0).*

Results

Of the 120 women enrolled, five were excluded, three patients delivered before the end of the study period and two were excluded because of protocol violation.

One hundred and fifteen patients remained eligible for further analysis. The demographic characteristics and baseline VAS scores are shown in Table 1. Sufentanil response rates and dose–response curve with a 95% CI are presented in Fig. 1. ED 20 amounted to 1.6 μg (95% CI, 0.0, 2.3), ED 40 to 2.2 μg (95% CI, 0.68, 3.0) and ED 50 to 2.5 μg (95% CI, 1.3, 3.4).

The dose-dependent sequences of effective and ineffective analgesia, respectively, are shown in Fig. 2. The ED 50s and CIs of ropivacaine alone, of ropivacaine with sufentanil at ED 20 and ED 40 are shown in Table 2. The ED 50 of the ropivacaine–control group is significantly different compared with the ED 50s of the ropivacaine–ED 20 sufentanil and the ropivacaine–ED 40 sufentanil groups, as there is no intersection in the two-sided 95% CI.

After adjusting for the ropivacaine dose, logistic regression showed a difference between the ropivacaine–control group and the ropivacaine–ED 20 ($P = 0.005$) and ED 40–sufentanil groups (0.005). However, no difference in effect between the ropivacaine–ED 20 and the ropivacaine–ED 40–sufentanil groups was identified ($P = 0.13$). This result is emphasized by their widely overlapping CIs.

Comparing the data for all women with effective analgesia, duration of spinal analgesia increased dose independently with the addition of sufentanil: in average, it was 64 min in the ropivacaine–control group, 104 min in the ropivacaine–ED 20–sufentanil group ($P < 0.0155$) and 95 min in the ropivacaine–ED 40–sufentanil group ($P < 0.045$). There was no difference in the duration of analgesia between the ropivacaine–ED 20–sufentanil and the ropivacaine–ED 40–sufentanil groups.

Pruritus occurred more frequently in the sufentanil group and the ropivacaine–ED 20–sufentanil group than in the ropivacaine–control group ($P = 0.013$ and 0.042) Incidence rates were 50%,

*http://www.R-project.org

Table 1

Demographic characteristics and baseline VAS-Score of patients included into the sufentanil dose–response group or the sequential up–down analysis group, receiving intrathecal ropivacaine alone or combined with intrathecal sufentanil at ED 20 (1.6 μg) and ED 40 (2.2 μg).

	Sufentanil-group ($n = 25$)	Ropivacaine–control ($n = 30$)	Ropivacaine+ED 20 sufentanil ($n = 30$)	Ropivacaine+ED 40 sufentanil ($n = 30$)
Age (years)	28.8 (5.9)	28.8 (4.9)	29.9 (3.8)	28.2 (4.1)
Height (cm)	166.8 (6.5)	167.3 (5.7)	167.4 (4.3)	164.7 (5.8)
Weight (kg)	82.5 (14.9)	77.6 (13.9)	76.7 (9.7)	76.0 (15.8)
Gestation (weeks)	39.8 [1.0]	39.5 [1.1]	39.4 [1.0]	39.6 [1.2]
Cervical Dilatation (cm)	4.3 [1.2]	4.2 [1.2]	3.6 [1.0]	3.8 [1.0]
Nulliparous	16	20	16	21
Oxytocin use	6	15	10	11
Initial VAS	75 [62–95]	84.5 [75–94]	77.0 [70–85]	87.5 [80–93]

Results are expressed as mean (SD), median [interquartile range], and count, as appropriate.
No statistically significant differences between the groups were detected.
VAS, visual analog pain scale (mm).

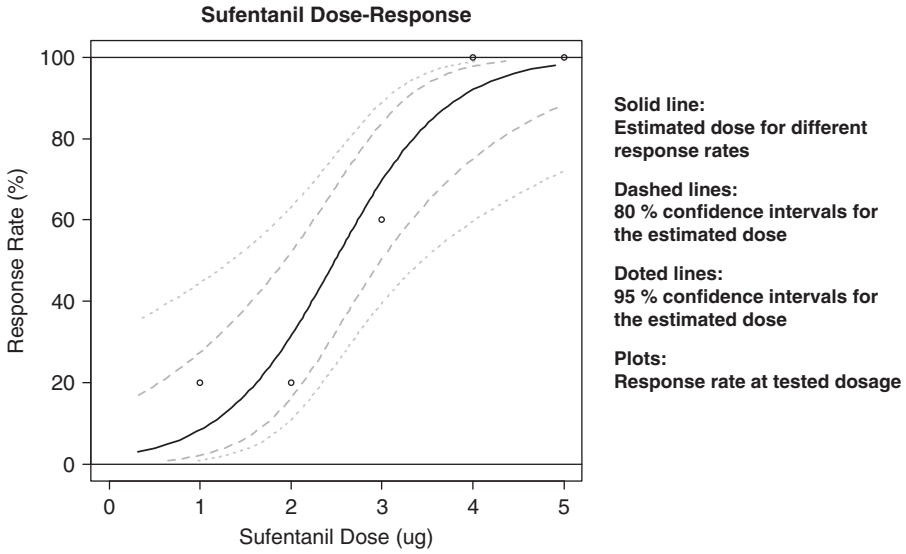

Fig. 1. Dose–response of 25 patients randomly receiving 1, 2, 3, 4 or 5 μg of intrathecal sufentanil during study phase one. Effective analgesia was defined as VAS of 10 mm or less by 15 min with a duration of at least 45 min after drug application.

34% and 0%, respectively. In the ropivacaine–ED 40–sufentanil group, 24% of parturients had pruritus ($P = 0.277$). Pruritus was well tolerated, and no woman required treatment.

Five women had motor block with a Bromage of 4 at 2.25 mg ($n = 1$) in the ropivacaine–ED 20–sufentanil group, at 1.75 mg ($n = 1$) and 2.25 mg ($n = 1$) in the ropivacaine–ED 40–sufentanil group and at 4.5 mg ($n = 2$) in the ropivacaine–control group. All other patients had a Bromage of five.

Four patients in the sufentanil and in the ropivacaine–ED 20–sufentanil group, three patients in the ropivacaine–ED 40–sufentanil group and five patients in the ropivacaine group were suffering from arterial hypotension. No patient suffered from nausea and vomiting. No difference was observed in the onset of analgesia. Clinical review was never triggered by a change in the fetal heart rate during the study. Oxytocin had no effect on analgesia, except in the ropivacaine–ED 40–sufentanil group. In this group, oxytocin was marginally associated with effective analgesia ($P = 0.04$).

Discussion

This study quantified the dose-reducing effect of sufentanil on i.t. ropivacaine for labor analgesia. By

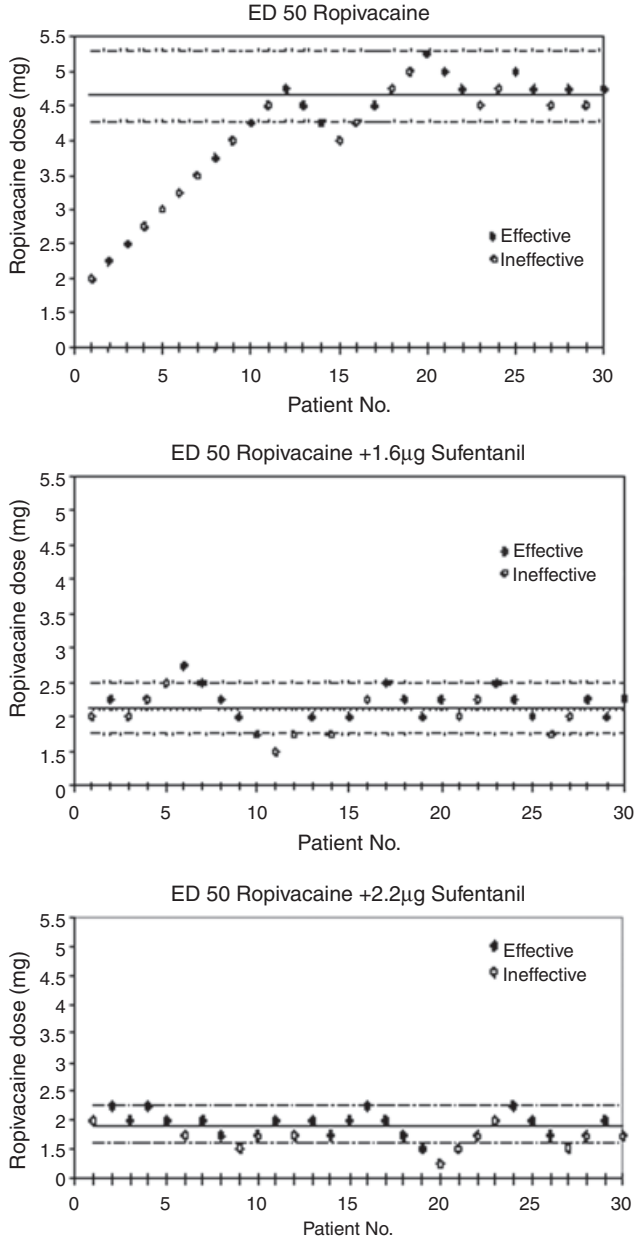

Fig. 2. The median analgesic dose (ED 50) of intrathecal ropivacaine alone and with the addition of intrathecal sufentanil at ED 20 (1.6 μg) and ED 40 (2.2 μg) as determined by the technique of up–down sequential allocation, calculated by logistic regression analysis. The testing interval was 0.25 mg. Lines represent ED 50 and confidence intervals.

combining with a relatively low dose of 1.6 μg sufentanil, we could reduce the ED 50 of ropivacaine by more than 50%. We determined the dose–response of sufentanil alone and the effect of low-dose sufentanil on ropivacaine in the same population. We demonstrated a prolongation of analgesia by this combination. Interestingly, no dose-dependent difference on analgesia was observed and typical opioid-related side effects

Table 2

The median analgesic dose (ED 50) of intrathecal ropivacaine alone and with the addition of intrathecal sufentanil at ED 20 (1.6 μg) and ED 40 (2.2 μg) as determined by the technique of up–down sequential allocation, calculated by logistic regression analysis or by the Dixon and Massey method.

Sufentanil	Logistic regression	Dixon and Massey method
0 ($n = 30$)	4.6 mg (4.28–5.31)	4.6 mg (4.34–4.96)
1.6 μg (ED 20) ($n = 30$)	2.1 mg (1.75–2.50)	2.1 mg (1.91–2.34)
2.2 μg (ED 40) ($n = 30$)	1.9 mg (1.62–2.26)	1.9 mg (1.67–2.04)

between ED 20 and ED 40 of sufentanil were observed. A dose of 1.6 μg sufentanil in combination with ropivacaine, therefore, seems to be highly suitable as a combination dosage.

The ED 50 for i.t. ropivacaine alone in labor analgesia has been determined by several groups before, but varies considerably. Different methodological approaches may explain this. In our study, the ED 50 was 4.6 mg, whereas other studies estimated ED 50 at 3.6 mg (3.3–3.9, 95% CI)[22] or at 1.4 mg (1.2–1.6, 95% CI).[21] However, study populations differed: cervical dilatation was below 4 or 5 cm, respectively, and the use of oxytocin was prohibited. Furthermore, analgesic effectiveness was defined with an absolute VAS <10 mm after 30 min. In our study, stronger criteria of effectiveness required analgesia after 15 min and a duration of at least 45 min. Additionally, our inclusion criteria allowed greater cervical dilatation, oxytocin use and multiparous women, as these inclusion criteria best reflect the population in our department. When applying comparable inclusion criteria, consistent results were found, despite different study designs. Our ED 50 of 2.1 mg (1.75–2.50, 95% CI) ropivacaine combined with 1.6 μg sufentanil is in agreement with the finding of Van de Velde et al.,[15] who reported an ED 50 of ropivacaine combined with an arbitrarily chosen dosage of 1.5 μg sufentanil at 2.2 mg (1.8–2.6, 95% CI).

By adding a low dose of 1.6 or 2.2 μg sufentanil to i.t. ropivacaine, a remarkable prolongation of analgesia could be achieved. However, no relationship to sufentanil dosage could be observed. This is in accordance with other findings,[11] where increasing i.t. sufentanil dosage added to a constant dosage of i.t. bupivacaine did not increase the duration of labor analgesia.

The most distinctive side effect of i.t. opioids is pruritus. Using low dosage of sufentanil, we could

keep the pruritus incidence rate low and tolerable, with no patient requiring treatment. Our incidence rates are well consistent with published data[12]in which drug combination and dose level were comparable. Higher dosages of sufentanil up to 10 μg lead to a pruritus rate up to 95%.[26] Using dosages below 5 μg, however, result in mild pruritus not necessitating any treatment.[11,27] Thus, according to our results, it seems advisable to use a low dosage of sufentanil.

With the exception of pruritus, the addition of sufentanil in ED 20 and 40 to i.t. ropivacaine causes a comparable incidence of side effects. We could not observe any differences in the onset of nausea, vomiting and maternal hemodynamic variables. Despite reducing the ED 50 of ropivacaine by >50%, motor block was surprisingly not reduced. I.t. ropivacaine exhibits a greater sensory motor separation than bupivacaine.[22,28,29] However, compared with epidural application, this is less marked.[30] Furthermore, the change of motor block potency by combining an opioid with local anesthetic in labor analgesia is insufficiently studied.

Up–down sequential allocation is an efficient and widely used method to define dose-sparing properties and potency ratios of drugs and drug combinations.[12,22,31–33] As stated above, different inclusion criteria affect resulting ED 50s. We have chosen wide inclusion criteria to better reflect the population in our department. This limits the comparability to ED 50 estimates in previous studies. However, dose-sparing effects are unaffected as inclusion criteria are equal in the compared groups.

The primary purpose of this methodology is not to determine side effects and measure the duration of action, as drugs are not used in a clinical dose range and doses vary. As a dose relationship to side effects can be expected, only patients receiving a ropivacaine dose within ±10% of the estimated ED 50 have been considered. A 10% range guarantees a sufficient number of observations, while keeping the dosing sufficiently homogeneous. Effects on secondary outcome by adding different dosages of sufentanil to i.t. ropivacaine are important qualitative observations. Similar effects may occur at ED 95, at which a reliable estimation of doses in the flat saturation region of the dose–response curves requires prohibitively large sample sizes.

We have chosen 2 mg of i.t. ropivacaine as the starting dose as it lies in the range of the published ED 50 estimates.[21,22] Furthermore, as a low starting point, it reduces the probability of side effects. Even though a low starting point may reduce the efficiency of up–down sequential allocation, our CIs were similar to comparable studies.[2,15,21,22]

As the combination dosage, we have chosen sufentanil at ED 20 and ED 40. ED 20 was selected as it is widely used in pharmacodynamic assessments in medicinal products. Similar to ED 50 and ED 80, ED 20 is thus available for the majority of medicines. ED 20 also reflects a dose that produces a clinically meaningful effect. In order to investigate a dosing effect, ED 40 was chosen, as it lies in an acceptable distance from ED 20 on the dose–response curve and not above ED 50, which would have interfered with the ED 50 estimation of ropivacaine.

In conclusion, the ED 50 of i.t. ropivacaine was determined to be 4.6 mg. For the first time, the effective dose of sufentanil alone was determined in the same population. The respective ED 20 and ED 40 of 1.6 and 2.2 μg of sufentanil added to ropivacaine resulted in a >50% decrease of ED 50 to 2.1 and 1.9 mg ropivacaine, respectively. Moreover, we found a dose-independent increase in the duration of analgesia. Besides pruritus, which was only mild, no differences in the occurrence of side effects were observed. Our results indicate that it is favorable to add sufentanil at a low dose of 1.6 μg to ropivacaine for i.t. labor analgesia.

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