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Combinations of Bupivacaine, Fentanyl, and Clonidine for Lumbar Epidural Postoperative Analgesia

A Novel Optimization Procedure

Gorazd Sveticic, M.D., Andrea Gentilini, M.Sc., Ph.D.,† Urs Eichenberger, M.D.,‡ Eleonora Zanderigo, M.Sc.,† Valentina Sartori, M.Sc.,† Martin Luginbühl, M.D.,§ Michele Curatolo, M.D., Ph.D.‖*

Background: **The authors developed and applied a method to optimize the combination of bupivacaine, fentanyl, and clonidine for continuous postoperative lumbar epidural analgesia.**

Methods: **One hundred eighteen patients undergoing knee or hip surgery participated in the study. Postoperative epidural analgesia during 48 h after surgery was optimized under restrictions dictated by side effects. Initially, eight combinations of bupivacaine, fentanyl, and clonidine (expressed as drug concentration in the solution administered) were empirically chosen and investigated. To determine subsequent combinations, an optimization model was applied until three consecutive steps showed no decrease in pain score. For the first time in a clinical investigation, a regression model was applied when the optimization procedure led to combinations associated with unacceptable side effects.**

Results: **The authors analyzed 12 combinations with an allowed bupivacaine concentration range of 0–2.5 mg/ml, a fentanyl concentration range of 0–5 μg/ml, and a clonidine concentration range of 0–5 μg/ml. The best combinations of bupivacaine, fentanyl, and clonidine concentrations were 1.0 mg/ml–1.4 μg/ml–0.5 μg/ml, 0.9 mg/ml–3.0 μg/ml–0.3 μg/ml, 0.6 mg/ml–2.5 μg/ml–0.8 μg/ml, and 1.0 mg/ml–2.4 μg/ml–1.0 μg/ml, respectively, all producing a similarly low pain score. The incidence of side effects was low. The application of the regression model to combinations associated with high incidence of motor block successfully directed the optimization procedure to combinations within the therapeutic range.**

Conclusions: **The results support further study of the combinations of bupivacaine, fentanyl, and clonidine mentioned above for postoperative analgesia after knee and hip surgery. This novel optimization method may be useful in clinical research.**

CONTINUOUS epidural administration of analgesics is a widely used method for the treatment of postoperative pain. Drugs commonly administered for epidural analgesia are local anesthetics, opioids, and α_2 agonists.[1–6] These drugs are variously combined to maximize analgesia and minimize side effects, such as motor block, hypotension, sedation, nausea, vomiting, pruritus, and respiratory depression.[2,6–8] Different combinations have been compared in randomized controlled studies.[2,5–7,9–12] However, when combining drugs at different concentrations, hundreds or thousands of combinations are possible. For example, if five different values for three drugs are considered, $5^3 = 125$ different combinations exist. Clearly, it is impossible to analyze all possible combinations by randomized controlled trials. The choice of the combinations that are compared in such trials is mostly made arbitrarily. As a result, the chosen combinations might be far away from the region of the optimal combinations.

In a previous study,[13] we applied a model[14] to optimize drug combination for thoracic epidural analgesia after major abdominal surgery. Later, we improved the method and applied it to two additional studies: one on intravenous patient-controlled analgesia[15] and the current one. Initially, eight combinations were studied. On the ground of the results observed, further steps were made by investigating new combinations until no further improvement was shown in three consecutive steps. Using this method, optimization may be performed by investigating a limited number of combinations.[13–16]

Epidural local anesthetics frequently cause motor block when administered at a lumbar level.[17] Therefore, the results obtained from the aforementioned study on thoracic epidural anagesia[13] cannot be applied to lumbar epidural analgesia. Motor block prevents patient's mobilization, which is important to avoid postoperative complications, such as thromboembolism. Moreover, it may mask the occurrence of severe complications that lead to permanent neurologic sequel, such as epidural hematoma. Adding clonidine to bupivacaine and fentanyl may reduce the concentration of local anesthetic required to obtain pain relief, thereby reducing the incidence of motor block. However, this practice may also increase side effects. For example, the interaction of clonidine with bupivacaine may increase the incidence of hypotension.[18] Therefore, the right balance of the drug components in the epidural solution is still unclear.

The aim of the current study was to optimize combinations of bupivacaine, fentanyl, and clonidine (ex-

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* Resident, ‡ Staff Member, Division of Pain Therapy, § Head, Orthopedic Anesthesia, ‖ Head, Division of Pain Therapy, Department of Anesthesiology, Inselspital, Bern. † Reader, Swiss Federal Institute of Technology, ETH-Zentrum, Zürich, Switzerland.

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Address reprint requests to Dr. Sveticic: Department of Anesthesiology, Inselspital, 3010 Bern, Switzerland. Address electronic mail to: gorazd.sveticic@insel.ch. Individual article reprints may be purchased through the Journal Web site, www.anesthesiology.org.

pressed as drug concentration in the epidural solution) for continuous postoperative lumbar epidural analgesia after hip and knee surgery.

Materials and Methods

After obtaining the approval from the ethics committee of the University of Bern, Bern, Switzerland, patients undergoing major elective hip or knee surgery (articular capsule opened) were recruited. Written informed consent was obtained from 118 patients. Exclusion criteria were any contraindication to epidural analgesia, age younger than 16 yr, daily intake of opioids for a period greater than 1 week, and lack of patient cooperation. Patients, nurses in charge of perioperative care, and the staff who informed patients, performed anesthesia, and collected postoperative data were not aware of the epidural combination used. Randomization, whenever applied, was performed by drawing lots.

Anesthetic Procedure

Patients were premedicated orally with 7.5 mg midazolam 20–30 min before anesthesia. They were monitored for at least electrocardiogram, noninvasive arterial blood pressure (one measurement every 5 min), and oxygen saturation using pulse oximetry. A urinary catheter was inserted in all patients and left in place during the postoperative study period. Before induction of the epidural block, 6–7 ml/kg lactated Ringer's solution was rapidly infused, followed by 2 ml $\cdot$ kg^{-1} $\cdot$ h^{-1} during the operation.

Combined spinal–epidural block was performed for intraoperative analgesia. The epidural puncture was performed with the median approach at L3–L4. An 18-gauge Tuohy needle was used, and the epidural space was identified by loss of resistance using 0.9% saline. The spinal needle was introduced through the epidural needle into the subarachnoid space, and 15–20 mg plain bupivacaine, 0.5% wt/vol, was injected. The spinal needle was withdrawn, and a catheter was inserted 5 cm cephalad in the epidural space. Epidural boluses of 8–12 ml mepivacaine, 2% wt/vol, were injected hourly until the end of the operation, beginning 1.5–2 h after the spinal block. Blood loss, measured in the suction traps and estimated on the drapes and in the surgical sponges, was replaced 1:1 with gelatin or blood when the hemoglobin values were higher or lower than 9 g/100 ml, respectively (10 g/100 ml for patients with coronary artery disease).

Postoperative Management

The end of the operation was considered as the beginning of the 48-h postoperative study period. When indicated, patients were kept in the recovery room until the morning after the operation. Patients were moved to the ward when cardiocirculatory and respiratory functions were stable. Oxygen, 2–4 l/min, *via* nasal probe was administered to maintain an oxygen saturation of more than 93%. Lactated Ringer's solution, 2,500 ml/24 h, was infused. If the urine output was less than 100 ml/2 h, 500 ml in addition was infused. Blood loss was replaced using the same criteria as in the intraoperative phase. Systolic blood pressure, heart rate, and respiratory rate were monitored and recorded every 2 h during the first 6 h postoperatively and then every 4 h.

The pump for the epidural infusion (CADD-PRIZM®; Deltec, St. Paul, MN) was programmed so that a continuous infusion of 0–15 ml/h was delivered and 5-ml nurse-controlled boluses were administered with a minimum interval of 60 min between two boluses. At the end of the operation, a 5-ml bolus of the postoperative epidural mixture investigated was administered, and the epidural infusion was started at a rate of 7 ml/h. No other analgesics were given during the study period.

Every 2 h during the first 6 h postoperatively and then every 4 h, a verbal descriptor score was recorded by asking patients to rate pain at rest and during mobilization as follows: 0 = no pain, 1 = weak pain, 2 = moderate pain, 3 = strong pain, and 4 = very strong pain. Mobilization was defined as passive turning of patients on the side for nursing procedures. Adequate analgesia was defined as a score of 0 at rest and 2 or less during mobilization. After the initial 6 h, patients were not awakened to give a verbal descriptor score if they were asleep. In that case, a score of 0 at rest and 1 during mobilization was assumed and used for analysis. Patients were instructed to call nurses when pain of any intensity at rest or strong or very strong pain during mobilization occurred. In these cases, the 5-ml epidural bolus was administered by the nurses, and the infusion rate was increased by 2 ml/h to a maximum of 15 ml/h. If the patient did not obtain pain relief (*i.e.*, a score of 0 at rest and 2 during mobilization) at 15 ml/h, 5–20 ml carbonated lidocaine, 2% wt/vol, was injected in 5-ml increments. If no segmental hypoalgesia to cold or a unilateral block involving the side contralateral to the site of operation resulted, failure to provide pain relief was attributed to factors other than the epidural combination (*e.g.*, catheter placement or anatomical factors). These patients were excluded from the analysis. If segmental hypoalgesia on the side of surgery or bilaterally was observed, failure to provide adequate analgesia was attributed to the combination investigated. The epidural combination investigated was discontinued, and the patient remained in the analysis; only data collected before the injection of lidocaine were considered.

Definitions and management of side effects, together with criteria for discontinuing the investigating epidural combination, are presented in table 1. Because all patients received a urinary catheter, urinary retention was not taken into consideration.

Table 1. Definition and Management of Side Effects and Criteria for Discontinuing the Epidural Combination Investigated Because of Side Effects

Side Effect	Measurement and Definition	Management	Criteria for Discontinuing the Epidural Regimen
Motor block	Bromage score[21]: 0 = full flexion of feet and knees; 1 = just able to move knees; 2 = able to move feet only; 3 = unable to move feet or knees	Discontinuation of the epidural regimen investigated if the score was > 0 or the patient could not be mobilized because of motor impairment; regimen then restarted using infusion rate 2 ml/h lower than previous	Motor block not improved (> 0) after reduction of the infusion rate or appearance of pain after reduction of the infusion rate
Hypotension	Systolic blood pressure < 90 mmHg (100 mmHg in patients with coronary artery disease or arterial hypertension), either at rest or during mobilization	Intravenous boluses of 5–10 mg ephedrine administered whenever necessary, and 6–7 ml/kg lactated Ringer's solution rapidly infused every hour	Episodes of hypotension lasting > 2 h despite treatment
Sedation	Score: 0 = alert; 1 = drowsy; 2 = sleeps, easy to arouse verbally, does not fall asleep during or immediately after conversation, can stand up; 3 = sleeps, opens the eyes to verbal command, falls asleep during or immediately after conversation, cannot stand up; 4 = does not open the eyes to verbal command Aim: a level of sedation not impairing an early mobilization and patient's cooperation for physiotherapy	Reduction of the infusion rate by 2 ml/h every hour if score > 3 during the first 12 postoperative hours or > 2 during the subsequent period	Sedation not improved (≤ 2) after reduction of the infusion rate or appearance of pain after reduction of the infusion rate
Nausea	Nausea with or without vomiting	Intravenous administration of 4 mg ondansetron, repeated after 1 h with reduction of epidural solution infusion rate by 2 ml/h if nausea persisted	Nausea not responsive to two doses of ondansetron or appearance of pain after reduction of the infusion rate
Pruritus	Pruritus without cutaneous manifestations	Treatment only if requested by the patient; stepwise intravenous administration of 2 mg clemastin, 10 mg propofol, and, if not effective, reduction of epidural solution infusion rate by 2 ml/h every hour until these symptoms disappeared	Pruritus not responsive to reduction of bolus or appearance of pain after bolus reduction
Bradycardia	Heart rate < 50 beats/min not associated with hypotension for a period longer than 10 min	0.5 mg intravenous atropine with reduction of epidural solution infusion rate by 2 ml/h if bradycardia persisted	Episodes of bradycardia not responsive to atropine or appearance of pain after reduction of the infusion rate
Bradypnea	Respiratory rate < 8/min for a period longer than 10 min	Discontinuation of the epidural study mixture investigated until respiratory rate of 8 breaths/min. Regimen then restarted using infusion rate 2 ml/h lower than previous	Bradypnea not improved (< 8 breaths/min) after reduction of the infusion rate or appearance of pain after reduction of the infusion rate

Motor block was recorded according to the Bromage score[19] (table 1). Motor block was defined as a score greater than 0 or muscle weakness that prevented the patient from lifting the operated leg by 20–30 cm. Motor block was accepted during the first 6 h after the end of the operation, because during this time it may have resulted from the intraoperative administration of epidural local anesthetics. Thereafter, in the presence of motor block, the epidural infusion was interrupted until motor function was restored and then restarted at a rate of 2 ml/h lower than previously.

Interruption of the study resulted from (1) inadequate analgesia (pain score > 0 at rest and > 2 during mobilization at an infusion rate of 15 ml/h) or (2) a side effect that either did not resolve despite reduction in infusion rate or resolved after reduction in infusion rate but with occurrence of inadequate analgesia. Only data collected before interruption of the study were included in the

Table 2. Variables Considered in the Investigation and Restrictions Given to the Optimization Procedure

Variable	Minimum Value	Maximum Value	Minimum Increase	Maximum Increase
Bupivacaine concentration, mg/ml	0	2.5	0.1	0.5
Fentanyl concentration, μg/ml	0	5	0.5	2
Clonidine concentration, μg/ml	0	5	0.5	2

A minimum increase is defined to avoid an increase in the variable produced by the optimization model that would be so small that a high number of steps would be necessary to reach the optimal analgesic effect. The maximum increase aims at preventing an excessive increase in the variable, with possible occurrence of side effects. The increase/decrease is defined as the difference between the new calculated value and the average of the values of "good" combinations (centroid G, see appendix) for each variable investigated.

analyses. Further pain treatment was planed on an individual basis, depending on the reason for interruption.

Data Collection

Perioperative and demographic data collected were sex, age, weight, height, American Society of Anesthesiologists physical status classification, and type and duration of operation. In the postoperative phase, the following data were collected every 2 h during the first 6 h and then every 4 h: pain intensity at rest and during mobilization by verbal descriptor score, systolic blood pressure, heart rate, sedation score, respiratory rate, motor block, and presence of nausea, vomiting, and pruritus. At the end of the study period, occurrence of any postoperative complication, interruption of the study (if any), and reason for interruption were recorded.

Optimization Procedure

The procedure is a modification of the direct search method described by Berenbaum[14] that we previously applied in a clinical study.[13] The aim of the procedure was to increase the analgesic effect, *i.e.*, to minimize the pain score, by sequentially optimizing the combinations of bupivacaine, fentanyl, and clonidine in the epidural solution. Rules of the procedure included minimum and maximum values of drug concentrations in the epidural solution, their minimum and maximum increases between two subsequent optimization steps (table 2), and constraints. Constraint of the search procedure was an unacceptable incidence of side effects. A combination violated a constraint when the study had to be discontinued because of the same side effect in three patients who received that combination, according to the criteria for discontinuing the epidural combination (table 1).

For each combination, six patients were studied. Initially, eight combinations that were expected to provide adequate analgesia and low incidence of side effects were empirically chosen and investigated (table 3, combinations A–H). Patients were randomly allocated to receive one of the combinations. Randomization was stratified according to sex and type of operation.

The investigation consisted of sequential optimization steps. The basic principle is to use the results obtained by the analysis of a group of combinations to create subsequent combinations in a stepwise manner until satisfactory analgesia with an acceptable incidence of side effects is reached. The group of combinations analyzed at each step is named a *complex*. Each complex consisted of eight combinations.

The number of combinations per complex (m = 8) and the number of patients per combination (n = 6) were chosen on a basis of a retrospective analysis of the data published in the previous study,[13,15] whereby the optimal m and n were identified by simulation procedure (see appendix).

The following procedure was used for each complex to calculate the next optimization step.

1. Analgesia and side effects of the combinations included in the complex studied were analyzed.
2. The combination characterized by the worst analgesic effect or associated with an unacceptable incidence of side effects was identified. This combination was not included in the subsequent complexes.
3. A new complex of combinations was created. This complex included the best seven combinations of the previous complex (best analgesia with acceptable incidence of side effects) and a new combination generated from the results obtained with the previous complex. This new combination was identified by applying an improved modification of a previously

Table 3. Epidural Combinations Investigated

Combination	Bupivacaine, mg/ml	Fentanyl, μg/ml	Clonidine, μg/ml
A	1.0	1.4	0.5
B	0.5	2.1	1.0
C	0.3	1.9	0.6
D	0.7	1.5	1.2
E	0.2	2.7	1.5
F	0.9	3.0	0.3
G	0.6	2.5	0.8
H	1.0	2.4	1.0
I	1.5	2.7	0.1
K	0.9	2.7	0.1
L	1.4	2.3	0.5
M	0.9	2.3	0.5

Combinations A–H were empirically chosen as an initial complex, according to the principle of the direct search method. The selection of combinations that are expected to provide adequate analgesia would save unnecessary optimization steps. Combinations I–M resulted from the stepwise optimization procedure. Based on our previous experience, the letter J was not used because it is easily mixed up with the letter I.

Table 4. Patient Characteristics, Type of Operation, and Duration of Operation

Combination	n	Sex, No. F/M	Age, yr	Weight, kg	Height, cm	ASA Physical Status	Type of Operation, No. Hip/Knee	Duration, h:min
A	6	2/4	22–62	63–92	160–180	I	4/2	1:50–3:20
B	6	2/4	18–80	68–96	160–180	I–III	5/1	1:50–4:10
C	6	4/2	30–83	53–102	163–193	I–III	4/2	1:10–3:15
D	6	2/4	26–82	55–102	160–182	I, II	4/2	1:45–3:55
E	6	2/4	30–84	45–104	159–178	I–III	4/2	1:25–3:55
F	6	3/3	19–71	46–93	143–185	I, II	4/2	1:50–4:00
G	6	2/4	25–57	64–100	156–180	I–III	5/1	1:35–3:45
H	6	3/3	28–72	59–85	160–178	I, II	4/2	2:15–3:45
I	4	2/2	26–45	60–110	168–178	I, II	4/0	1:50–3:20
K	6	4/2	40–79	52–90	160–176	I–III	5/1	1:40–2:50
L	4	2/2	19–42	52–83	160–190	I, II	4/0	2:00–2:20
M	6	4/2	17–69	64–130	166–195	I, II	3/3	1:30–6:10
F—retest	6	3/3	28–69	52–90	154–179	I, II	4/2	1:50–3:35
H—retest	6	4/2	23–57	53–110	163–187	I, II	2/4	1:30–3:20

For age, weight, height, American Society of Anesthesiologists (ASA) class, and duration of anesthesia, ranges (minimum–maximum) are reported. Hip surgery: surgical dislocation of the hip, periacetabular osteotomy, total hip replacement. Knee: Proximal tibial osteotomy, total knee replacement, reconstruction of cruciate ligaments. Combinations F and H were tested again (F—retest and H—retest) at the end of the optimization procedure (see Materials and Methods, Optimization Procedure).

n = sample size.

used mathematical model[13] (see appendix). The new combination replaced the one mentioned in point 2. The new combination was studied in a subsequent group of patients.

4. Procedures 1–3 were applied to the new complex.
5. If a combination violated a constraint, a regression model was applied to direct the procedure back to the therapeutic range (see appendix, Logistic Regression).

The optimization procedure was interrupted when the mean pain score obtained with a new combination was not lower than the mean pain score of the previous combination of the sequential procedure at three consecutive steps without violation of constraints.

To minimize the possibility that the best combinations were the result of chance and in conformity with the method adopted in our previous studies,[13,15] at the end of the optimization procedure, we randomly selected two of them to be retested on two additional groups of patients (n = 6/group). Patient allocation to the groups was randomized.

Statistical Analysis

The results of the stepwise procedure were analyzed by descriptive statistics. In sequential optimization methods, tests for statistically significant differences between groups are not used.[14] Therefore, it cannot be concluded that any combination is statistically significantly different from other ones. Rather, the method focuses on the trend of the optimization procedure and avoids excessive weight on any individual combination.[14] The identified optimal combinations must be investigated in further randomized controlled trials. This practice reproduces the one of the other two clinical studies in which this model was applied.[13,15]

Results

Of the 118 patients enrolled, 38 were not included in the analyses for the following reasons: unexpected postoperative use of indomethacin for ectopic ossification prophylaxis (9 patients), catheter dislocation (8), change of type of anesthesia (6), unilateral spread of analgesia postoperatively (6), type of operation different then planed (3), pain other then surgical pain that needed additional analgesics (2), perforation of the dura during the insertion of the epidural catheter (2), complications (1), and randomization error (1). Therefore, 80 patients completed the study. Twelve epidural regimens were investigated (table 3). Demographic and perioperative data are shown in table 4.

The combinations analyzed at each optimization step are shown in figure 1. Figure 2 shows an initial decrease in the mean pain score at the first step that remained low during the rest of the optimization procedure.

Figure 3 shows a decrease in the incidence of insufficient analgesia during the four optimization steps (complexes 2–5). The increase in the incidence of motor block reported in figure 3 at complexes 2 and 4 corresponds to the violation of a constraint, *i.e.*, the study was discontinued in three patients because of motor block in combinations I (complex 2) and L (complex 4). At these points, the regression procedure could successfully bring the search out of the toxic range back to the therapeutic range at complexes 3 and 5, respectively (see appendix, Logistic Regression). The incidence of other side effects remained low and constant (fig. 3).

The average concentration of fentanyl in the epidural solution increased during the optimization procedure, whereas clonidine concentration decreased at the first step but remained stable thereafter (fig. 4). The increase

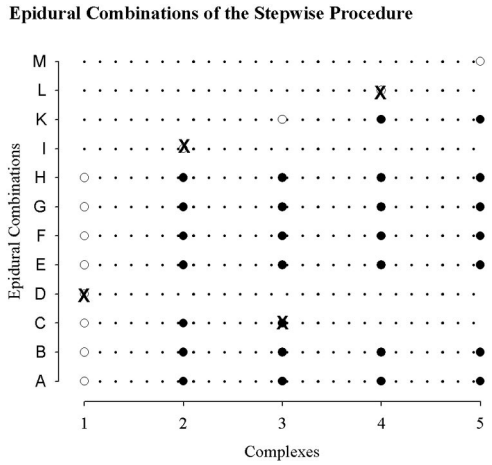

Fig. 1. Combinations of the sequential optimization procedure. Each combination is described in table 1. Initially, eight combinations were analyzed (complex 1). Thereafter, the worst combination of the complex (D) was discarded, and a new combination was identified by an optimization model (combination I of complex 2) and tested on an additional group of patients. This procedure was repeated at each subsequent step. *White points* represent new combination of a complex. Combinations marked as *X* represent the worst combination of each complex and were therefore not included in subsequent complexes. *Black points* indicate combinations that were tested at previous steps.

in bupivacaine concentration was limited by the occurrence of motor block: The regression model identifies a bupivacaine concentration as the determinant of motor block (see appendix, Logistic Regression).

There was no violation of constraints because of side effects other than motor block. Insufficient data prevented us from calculating the occurrence probability of other side effects.

At the end of the optimization procedure, the "good" combinations of the final complex were A (1.0 mg/ml bupivacaine, 1.4 μg/ml fentanyl, 0.5 μg/ml clonidine), F (0.9 mg/ml bupivacaine, 3.0 μg/ml fentanyl, 0.3 μg/ml clonidine), G (0.6 mg/ml bupivacaine, 2.5 μg/ml fentanyl, 0.8 μg/ml clonidine), and H (1.0 mg/ml bupivacaine,

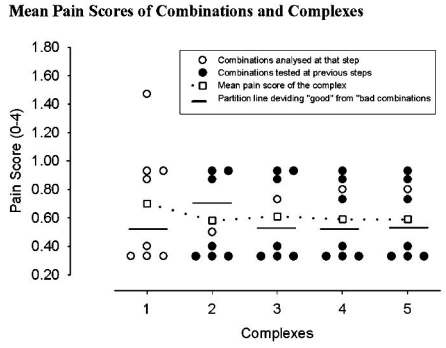

Fig. 2. Mean pain scores of each combination (*black circles*) and mean pain scores of each complex (*open squares*) of the sequential optimization procedure. Calculation of the mean pain score is described in the appendix. For each complex, the partition line (*horizontal line*) divides the "good" from the "bad" combinations.

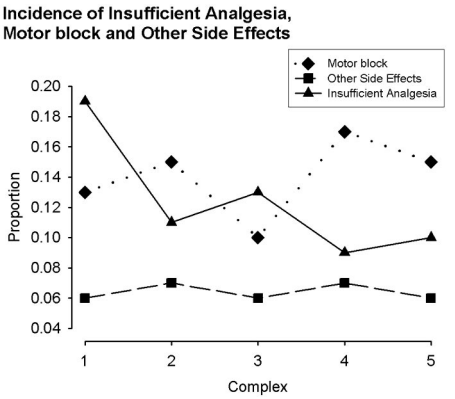

Fig. 3. Incidence of insufficient analgesia, motor block, and other side effects in the complexes analyzed. Insufficient analgesia and side effects are reported as the proportion of patients in which the epidural combination had to be discontinued because of insufficient analgesia or any side effect, respectively (table 7).

2.4 μg/ml fentanyl, 1.0 μg/ml clonidine). Good combinations are defined the ones with an average pain score below the partition line that separates the good from the bad combinations (fig. 2 and appendix, Partitioning). Among these combinations, F and H were randomly selected and retested on two additional groups of patients (n = 6). After retesting, these combinations were ranked again in the subgroup of good combinations of the last complex (pain scores of 0.47 and 0.33, respectively).

In table 5, respiratory and cardiocirculatory parameters pertaining to the good combinations of the last complex are reported. Table 6 shows the analgesic effect and consumption of drugs used in these combinations. The incidences of inadequate analgesia and side effects for all combinations are reported in table 7.

In one patient (combination B), nerve damage of unclear etiology (surgical damage, toxicity) occurred, resulting in paresis that partly recovered at follow-up 6 months after the surgery. The patient was excluded from

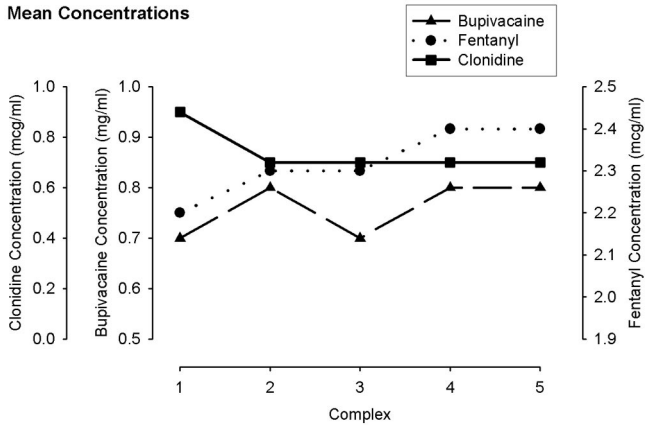

Fig. 4. Mean concentrations of bupivacaine, fentanyl, and clonidine in the epidural solution of each complex.

Table 5. Respiratory and Cardiocirculatory Parameters in the "Good" Combinations of the Final Complex

Combination	n	RR	HR	SBP	Spo_2
A (1.0–1.4–0.5)	6	14.7 (2.0)	80.3 (10.2)	109.9 (12.6)	97.1 (1.5)
F (0.9–3.0–0.3)	6	14.4 (2.5)	87.5 (15.1)	110.0 (12.7)	97.1 (1.6)
G (0.6–2.5–0.8)	6	14.7 (2.2)	74.5 (12.8)	110.0 (14.1)	96.9 (1.6)
H (1.0–2.4–1.0)	6	16.4 (2.4)	85.2 (9.5)	107.0 (13.4)	96.7 (2.7)
F—retested	6	15.5 (2.6)	81.1 (13.3)	108.2 (14.0)	96.2 (2.7)
H—retested	6	14.7 (1.8)	68.7 (9.3)	110.6 (15.8)	96.6 (2.3)

For each combination, bupivacaine concentration (mg/ml), fentanyl (μg/ml), and clonidine (μg/ml) concentrations, respectively, are given in parentheses in the left column. Means (SDs) of respiratory rate (RR), heart rate (HR), systolic blood pressure (SBP), and oxygen saturation using pulse oximetry (Spo_2) are given. To minimize the possibility that combinations were ranked as the best or worst ones as a result of chance, we randomly selected and retested combinations F and H on six additional patients per combination.

the analysis. Otherwise, no other complications were observed.

Discussion

A "direct search" model was applied to optimize combinations of bupivacaine, fentanyl, and clonidine for postoperative lumbar epidural analgesia. Previously, this method has been used in only two clinical trials.[13,15] To our knowledge, the regression model to deal with occurrence of side effects had not been used in human studies. During the study period, an initial decrease in pain score (fig. 2) and a continuous decrease in incidence of insufficient analgesia (fig. 3) were observed. A low incidence of motor block and other side effects was achieved at the end of the direct search procedure (fig. 3 and table 7).

Clinical Aspects

Among the good combinations of the final complex (combinations A–F–G–H), no clinically significant difference in the pain scores was observed (table 6). Therefore, the procedure did not lead to only one satisfactory regimen, but rather to a group of combinations characterized by a similar efficacy. This reproduces the findings of the previous two studies that employed this methodology.[13,15]

An increase in fentanyl concentration in the epidural solution was observed during the four optimization steps, whereas the concentrations of bupivacaine and clonidine showed minor changes (fig. 4). This may suggest that, in the range investigated, bupivacaine and clonidine concentrations were within the optimal area, while the initial fentanyl concentration was too low. This is in accordance with the principle of the direct search: The concentration of the drug investigated increases at each step if the average concentration in the good group of the complex is higher than in the bad group (see appendix, Method 1).

Clonidine was present in each of the good combinations of the final complex (table 6). Addition of 4.5 μg/ml clonidine to the combination of 0.625 mg/ml bupivacaine and 2 μg/ml fentanyl in a randomized controlled trial improved the quality of analgesia during labor.[6] In the previous study, applying the direct search model to combinations of the same three drugs for thoracic epidural anesthesia identified a combination of 9 mg/h bupivacaine, 21 μg/h fentanyl, and 5 μg/h clonidine as one of the best three combinations.[13] In the other two best combinations, clonidine was not present in the epidural solution. In a clinical trial on thoracic epidural, the addition of higher doses of clonidine (20 μg/h) to bupivacaine and fentanyl improved the quality of postoperative analgesia but induced hypotension that increased vasopressor requirement.[20] It is possible that clonidine in a low concentration is a useful additive for lumbar epidural postoperative analgesia in that it allows a reduction in bupivacaine concentration and therefore reduces the incidence of motor block. This is probably less important in thoracic epidural an-

Table 6. Analgesic Effect and Consumption of Drugs for the "Good" Combinations of the Final Complex

Combination	n	Pain Score	Bupivacaine, mg/h	Fentanyl, μg/h	Clonidine, μg/h
A (1.0–1.4–0.5)	6	0.33 (0.21)	9.87 (2.24)	13.82 (3.14)	4.94 (1.12)
F (0.9–3.0–0.3)	6	0.33 (0.21)	8.98 (1.57)	29.93 (5.25)	2.99 (0.52)
G (0.6–2.5–0.8)	6	0.40 (0.33)	6.29 (1.03)	26.20 (4.31)	8.38 (1.38)
H (1.0–2.4–1.0)	6	0.33 (0.21)	9.22 (2.07)	22.12 (4.97)	9.22 (2.07)
F—retested	6	0.47 (0.21)	8.55 (1.74)	28.51 (5.79)	2.85 (0.58)
H—retested	6	0.33 (0.21)	8.63 (2.03)	20.71 (4.86)	8.63 (2.03)

For each combination, bupivacaine (mg/ml), fentanyl (μg/ml), and clonidine (μg/ml) concentrations, respectively, are given in parentheses in the left column. The pain score of each combination was calculated by computing the mean for each patient, using all observations on pain at rest and during mobilization and calculating the average pain score from the individual means of all patients. Data for pain score are presented as mean (SD) because the ranking was done using mean values (see appendix). Mean values and SD of total dose (mg/h) are reported.

Table 7. Incidence of Side Effects and Pain Requiring an Early Discontinuation of the Epidural Combination

Combination	n	Motor Block	Pain	Pruritus	Sedation	Bradypnea
A (1.0–1.4–0.5)	6	2 (13, 21)	0	0	0	0
B (0.5–2.1–1.0)	6	0	2 (3, 4)	0	0	0
C (0.3–1.9–0.6)	6	0	2 (6, 6)	0	0	0
D (0.7–1.5–1.2)	6	2 (23, 9)	4 (5, 6, 4, 6)	0	0	0
E (0.2–2.7–1.5)	6	0	1 (15)	1 (26)	0	1 (34)
F (0.9–3.0–0.3)	6	0	0	0	1 (45)	0
G (0.6–2.5–0.8)	6	0	0	0	0	0
H (1.0–2.4–1.0)	6	2 (12, 22)	0	0	0	0
I (1.5–2.7–0.1)	4	3 (17, 34, 32)	0	0	0	0
K (0.9–2.7–0.1)	6	1 (29)	1 (3)	0	0	0
L (1.4–2.3–0.5)	4	3 (19, 23, 43)	0	0	0	0
M (0.9–2.3–0.5)	6	2 (29, 23)	1 (8)	0	0	0
F—retest	6	0	0	0	0	0
H—retest	6	2 (32, 25)	0	0	0	0

For each combination, bupivacaine (mg/ml), fentanyl (μg/ml), and clonidine (μg/ml) concentrations, respectively, are given in parentheses in the left column. Data are expressed as the number of patients in which the combination was discontinued. In brackets, the time from the beginning of the study to discontinuation of the epidural combination because of side effects or pain is reported (h). See table 1 for a description of the criteria for discontinuing the therapy. In combination D, there are four patients with insufficient analgesia because the two last patients were studied simultaneously, both resulting in discontinuation because of insufficient analgesia. In no patient was the combination discontinued because of nausea. Combinations F and H were reanalyzed in six patients (see Materials and Methods, Optimization Procedure).

algesia, in which motor block due to administration of local anesthetic is unlikely to occur. However, the nature of the direct search method does not allow the conclusion that adding clonidine to bupivacaine and fentanyl is advantageous. Rather, the study identifies combinations that must be compared to a bupivacaine–fentanyl mixture in a randomized controlled trial.

In general, the use of lumbar epidural postoperative pain therapy after major hip and knee surgery is increasingly limited. One reason is the revival of peripheral nerve blockade, which avoids the risk of epidural hematoma, abscess, and urinary retention. An additional reason for using less lumbar epidural analgesia is the increasing practice of fast-track surgery with early patient discharge. Nevertheless, lumbar postoperative epidural analgesia remains a common practice in many institutions, particularly because of its high analgesic efficacy, its low failure rate, and the fact that fast-track surgery is not yet widely used in several countries.

There are many potentially useful fields of use optimization methods in medicine. Apart from dose-finding studies combining two or more drugs, they can be used to optimize a variety of interventions, such as the best balance between different anesthetic techniques or the optimal use of technological tools, *e.g.*, monitoring. In this respect, optimization procedures remain potentially useful but probably underused methodologies in medicine.

Methodologic Aspects

We used this improved optimization model simultaneously in our intravenous patient-controlled analgesia study[15] and in the current one. This study was completed later than a patient-controlled analgesia study because of longer patient recruiting. The method not used before, even in the patient-controlled analgesia study, is the regression model (see appendix, Logistic Regression). None of the combinations of morphine and ketamine for patient-controlled analgesia violated a constraint, so there was no need to use logistic regression in that study.

Via logistic regression, we calculated the probability that each of the three variables investigated (concentrations of bupivacaine, fentanyl, and clonidine) has led to the specific side effect. After identifying bupivacaine as responsible for motor block, we recalculated the new combination that would bring the search out of the toxic range: Bupivacaine concentration was recalculated as the average concentration among the good combinations of the complex that violated a constraint, whereas fentanyl and clonidine concentrations remained the same. The method proved successful in identifying combinations that did not violate the constraint *motor block* in subsequent steps.

The combinations of the good group were already present in the initial complex. This indicates that the empirical choice of combinations may effectively identify the range of optimal combinations. This suggests that the use of optimization procedures may be particularly indicated for treatment modalities for which there is not large clinical experience, which is not the case in lumbar epidural analgesia. However, in our previous studies on thoracic epidural analgesia[13] and intravenous patient-controlled analgesia,[15] most good combinations were not present in the initial complex but resulted from the optimization procedure.

Several issues must be specially considered when the proposed method is used. The first one is the choice of number of combinations per complex (m) and number of patients per combination (n). High values of m and n

Table 8. Distribution of Pain Classes, Average Pain Score, and Ranking of Initial Complex

	Pain Classes						
	1	2	3	4	5		
	Pain Score						
	0.2	0.6	1	1.4	1.8		
Combination	Distribution in Pain Classes, No. of Patients/Category					Average Pain Score	Rank
A	4	2	0	0	0	0.33	1
B	2	1	1	0	2	0.93	6
C	2	1	1	0	2	0.93	7
D	0	1	1	0	4	1.47	8
E	1	2	2	0	1	0.87	5
F	4	2	0	0	0	0.33	2
G	4	1	1	0	0	0.40	4
H	4	2	0	0	0	0.33	3

The pain classes are derived by dividing the highest pain score in the original classification (*i.e.*, 4) by the highest pain score reported during the test of the first combination (*i.e.*, 2). The new classes are defined by the ranges (values in brackets) 1 (0–0.4), 2 (0.4–0.8), 3 (0.8–1.2), 4 (1.2–1.6), and 5 (1.6–2.0). The new pain scores of the normalized classes are chosen as the midpoints of the new classes.

may improve the direction of the search but result in a higher cost of the study or even make the study unfeasible. However, low values of m and n reduce the time to test the complex but may prolong the time to reach the endpoint, because the search direction may be deviated by outlying patients. We chose the m = 8 and n = 6 based on a simulation procedure that used data collected in our first optimization study[13] (see appendix). We cannot say whether these m and n values would be optimal also for investigations other then the one that we performed.

The second issue is the procedure to partition the complex. According to Berenbaum,[14,21] at each optimization step, the new combination is calculated by partitioning the complex in two halves, *i.e.*, good and bad clusters— combinations. Using that principle in our case, four combinations would be good and four would be bad. However, cutting the ranked list at its half is purely arbitrary. For example, the worst combination of the good subgroup and the best combination of the bad subgroup could be characterized by similar and clinically indistinguishable pain scores. In this case, it would be more logical and more productive for the optimization procedure if these two combinations belonged to the same cluster, either the good or the bad one. In this study, we used a more rational algorithm to define clusters. In brief, to avoid the limitation of using the average pain score, we considered the distribution of pain to allocate combinations into good and bad groups. For example, two combinations whose average pain scores differ from each other markedly may still belong to the same cluster if the distributions of pain scores among the patients are such that they significantly overlap.

To compute the probability density function of pain scores for each combination, the concept of pain classes was introduced. Pain scores could assume the integer values in the range 0–4, so five different pain score classes could be defined. In table 8, distribution of patients into pain classes, pain score values per class, average pain score per combination, and ranking of the initial complex are presented. Because an analysis of the experimental results showed that not the whole interval of pain score values was covered, the five pain score classes were *a posteriori* rescaled in the experimentally significant range 0–2. (For further details on the rescaling and computing methods, refer to the appendix.)

Third, the value of coefficient α (appendix, equation 5) defines the length of the step away from the bad combinations in the direction of the good ones when identifying the new optimized combination. The optimal value of α is undetermined, somewhat arbitrary, and likely to depend on the type of the experiment. Low values of α, which cause small changes, should be used in experiments where severe toxicity is anticipated but may prolong the study. Higher values of α may result in more rapid conclusion of the study but also in overshooting the target, which would miss the optimum. We chose a value of α of 1.3 based on experience of the previous studies.[13,14]

Fourth, it is possible that the response surface has more than one optimum. In that case, the procedure could lead to a local optimum (statistically, a set of parameters that produces a good result but not the optimal one) instead of a global optimum. The problem could be minimized by starting the procedure from two or more differently located starting points and testing whether the procedure leads to the same endpoint. However, multiplying the number of combinations tested would reduce the main advantage of the direct search method: investigating few combinations to reach a desired result. In this study, we assumed that we were dealing with a biologic response surface with one single optimum. Because we cannot exclude the possibility of more than one optimum, the term *optimization* must be taken with caution. It is used as a description of a stepwise process of improving the endpoint, rather than the indicator of a certain identification of the best combination.

Fifth, the safety of a therapeutic regimen cannot be demonstrated by investigations conducted on a low number of patients. Prospective observational studies analyzing the proposed combinations on a large patient population are necessary to detect the incidence and severity of uncommon side effects. This may be the case of clonidine-containing mixtures, for which no large trials have been published.

Conclusions

This further experience with a direct search method, using a logistic regression for the first time in a clinical

setting, confirmed the usefulness of optimization methods to identify potentially useful clinical regimens. Further validation and improvements of the model are needed.

Combinations of bupivacaine, fentanyl, and clonidine concentrations of 1.0 mg/ml–1.4 μg/ml–0.5 μg/ml, 0.9 mg/ml–3.0 μg/ml–0.3 μg/ml, 1.0 mg/ml–2.4 μg/ml–1.0 μg/ml, and 0.6 mg/ml–2.5 μg/ml–0.8 μg/ml, respectively, showed similar analgesic effect with low incidence of side effects. We recommend these regimens to be further investigated and compared in randomized controlled trials.[22]

Appendix

The Direct Search Procedure

Direct search procedures may be effectively used for medical purposes to optimize combinations of a therapeutic regimen.[15] In the current study, combinations of bupivacaine, fentanyl, and clonidine concentration in the epidural solution were optimized. In a previous study,[15] we used the direct search method by Berenbaum[14] to optimize combinations of bupivacaine, fentanyl, clonidine and infusion rate for postoperative epidural analgesia. We will further refer to the algorithm adopted in this early study as *method 1*. For the current study and a recently published study,[17] we developed and tested an improved direct search method, to which we will refer as *method 2*. This method does address the major considerations of method 1 mentioned in the Discussion.

First, we recall the main steps of the algorithm of method 1. Second, we discuss the modifications, which were introduced in method 2. Before applying it in our study, method 2 was tested retrospectively on the data set obtained in the previous study where method 1 was applied.[15] Method 2 was designed to improve the efficiency of the clinical investigation because it aims at using the minimum number of patients that is required to reach the endpoint.

Method 1

A complex consists of a series of m different combinations of independent variables $\{c_1, c_2, \ldots, c_m\}$. In our case, the variables in each combination are bupivacaine, fentanyl, and clonidine concentrations in the epidural solution. Precisely, $c_i = (b_i, f_i, cl_i)$, where b_i, f_i, and cl_i are the bupivacaine, fentanyl, and clonidine concentrations in that particular combination ($i = 1, \ldots, m$). Let us define as n_i as the number of patients testing combination i. According to the study protocol, this number was constant ($n_i = n$) for all combinations. Let us denote as PS_{ij} as the pain score reported by patient j when testing the combination i. PS_{ij} represents the average pain score reported by patient j in the 48-h study period. The pain score of the combination i is defined as the average pain score across the patients who tested the combination:

$$PS_i = \frac{1}{n_i}\sum_{j=1}^{n_i} PS_{ij}. \quad (1)$$

Let us rank the combinations within each complex $\{c_1, c_2, \ldots, c_m\}$ according to their average pain score from the lowest to the highest. Namely,

$$PS_1 < PS_2 < \ldots < PS_m. \quad (2)$$

Assume without loss of generality that m is even. Let us define the group of "good" and "bad" combinations as the first and last m/2 combinations in the ranked list, respectively. The centroids G and B of the good and bad m/2 combinations are computed as

$$G = \sum_{i=1}^{m/2} \frac{c_i}{m/2} \quad (3)$$

$$B = \sum_{i=m/2+1}^{m} \frac{c_i}{m/2}. \quad (4)$$

For example, if the bupivacaine concentrations in the four good combinations are 0.6, 0.9, 1.0, and 1.0, G_b would be $(0.6 + 0.9 + 1.0 + 1.0)/4 = 0.9$. B_b is calculated for bupivacaine in the same fashion, by considering the bupivacaine concentrations of the four bad combinations. The same procedure is applied to fentanyl and clonidine concentrations.

The new combination N to be tested is obtained as

$$N = G + \alpha(G - B), \quad (5)$$

where α is constrained to be a positive number (see Discussion). Minimum and maximum values of drug concentrations in the epidural solution and their minimum and maximum increases between two subsequent optimization steps were predefined (table 2).

Equation 5 shows the basic principle of the direct search method. If, for example, the average bupivacaine concentration of the four good combinations is higher than the average bupivacaine concentration of the four bad combinations, the new combination of the optimization procedure will contain a higher bupivacaine concentration.

Method 2

Choosing m and n. By analyzing the data published in the previous study retrospectively,[15] we concluded that the optimal values in the optimization algorithm to be used are $m = 8$ and $n = 6$. In that study, a direct search procedure was applied to combinations of bupivacaine, fentanyl, and clonidine and infusion rate to minimize the pain score and the side effects. By using data of the previous study to modify the search procedure of the current one, we implicitly assume that the interindividual variabilities among the subjects with regard to the drugs used in the two studies are comparable and the optimal m and n values are the same. The data from the previous study was used uniquely to determine the optimal values of m and n.

Eleven combinations were considered in the previous study. We investigated what the search direction would have been with m varying in the range 6–11. For every m, we assumed that n patients tried each combination with n in the range 1–8. We extracted m combinations at random from the initial set and n patients at random among the ones who tried the m combinations. For every set of combinations selected and a fixed n, we repeated the random extraction of the n patients within each combination 15 times. Then, we divided the observations into clusters with the new partition algorithm (see appendix, Partitioning the Complexes) and computed the new combination according to equation 5. The higher m and n are, the more stable the search direction will be, because the interindividual variability will be smoothed by averaging over a larger set of data. However, by increasing m and n excessively, we may exceed the resources available for the study without having performed the necessary steps to reach the endpoint. We increased m and n until there was no further significant decrease in the variability of the search direction. For a fixed m and n, we denoted as δ^2_1, δ^2_2, δ^2_3, and δ^2_4 the variabilities of the four independent variables in the previous study (1 = bupivacaine, 2 = fentanyl, 3 = clonidine, 4 = infusion rate). As an example, δ^2_3 is plotted in figure 5 as a function of the number of patients per combinations (n). All the variabilities except δ^2_4 decrease with increasing n and m. A significant reduction in variability is obtained for $n = 6$ and $m = 8$. Higher values for both n and m do not result in significant

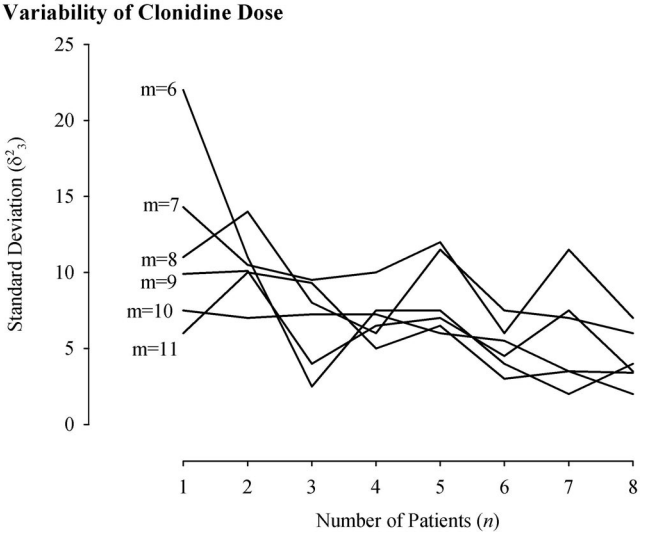

Fig. 5. Simulation procedure conducted on the data of the previous study[15] to find the optimal number of combinations per complex (m) and the optimal number of patients per combination (n) for the current study. Variability of the clonidine concentration in the new combination to be tested is shown. On the x-axis, the number of patients testing a single combination is depicted. On the y-axis, the SD of the clonidine concentration in the solution investigated is depicted. Different curves in the plot correspond to different numbers of combinations in the complex.

improvements. Based on these data, we included six patients per combination and eight combinations per complex in the current study.

Partitioning the Complexes. If we consider the average pain score of a particular combination as a random variable, the ranking in equation 2 is also random. We chose to partition the complexes with the maximum estimated probability that the highest pain score in the group G is lower than the lowest in the group B.

To show how this can be done, let us first define the average pain score of a specific combination i as

$$PS_i = \frac{1}{n_i}\sum_{h=1}^{h_{max}} g(h) \cdot N_{ih}, \quad (6)$$

where h is the index denoting the pain score classes, ranging from 1 to h_{max}; g(h) is the pain score value associated with pain class h, and N_{ih} is the number of individuals having received combination i falling into pain class h. The number of subjects investigated per combination is constant ($n_i = n$), so we can define $PS_{i,t}$ as

$$PS_{i,t} = n \cdot PS_i = n \cdot \frac{1}{n}\sum_{h=1}^{h_{max}} g(h) \cdot N_{ih} = \sum_{h=1}^{h_{max}} g(h) \cdot N_{ih}, \quad (7)$$

where pedix t stands for *total*.

Note that PS_i as defined in equation 6 does coincide with PS_i defined in equation 1: In equation 1, the sum is over the different patients, whereas in equation 6, the sum is over the different pain classes.

As described in the study protocol, the pain score ranged from 0 (no pain) to 4 (maximal pain), according to the standard verbal analog scale. However, because all of the data recorded in the study fell in the interval 0–2, we rescaled our range by constructing five equally spaced intervals: 0–0.4, 0.4–0.8, 0.8–1.2, 1.2–1.6, and 1.6–2. The pain score associated with each of these new five classes is its mean value: 0.2, 0.6, 1, 1.4, and 1.8, respectively.

The rescaling we adopted does not influence either the mathematical treatise or the decision process about optimization steps.

For example (see table 8),

Table 9.

	Pain Class: h				
	1	2	3	4	5
	Pain Score: g(h)				
	0.2	0.6	1	1.4	1.8
No. of patients in each class for combination A	4	2	0	0	0
No. of patients in each class for combination B	2	1	1	0	2

Given five pain classes (h) with their pain scores g(h) and given two sets of patients, receiving combinations A and B, respectively, we can calculate the associated average and total pain score $_i$ and $PS_{i,t}$ as follows:

$$PS_A = (4 \cdot 0.2 + 2 \cdot 0.6 + 0 \cdot 1 + 0 \cdot 1.4 + 0 \cdot 1.8)/6 = 0.33$$

$$PS_{A,t} = (4 \cdot 0.2 + 2 \cdot 0.6 + 0 \cdot 1 + 0 \cdot 1.4 + 0 \cdot 1.8) = 1.98$$

$$PS_B = (2 \cdot 0.2 + 1 \cdot 0.6 + 1 \cdot 1 + 0 \cdot 1.4 + 2 \cdot 1.8)/6 = 0.93$$

$$PS_{B,t} = (2 \cdot 0.2 + 1 \cdot 0.6 + 1 \cdot 1 + 0 \cdot 1.4 + 2 \cdot 1.8) = 5.6.$$

If N_{ih} is a random variable, PS_i is also random. The probability that the number of patients testing combination i falling into the first pain class ($N_{i,1}$) is equal to n $_{i,1}$, that the number of patients falling into the second pain class ($N_{i,2}$) is equal to $n_{i,2}$, and so on, $P(N_{i,1} = n_{i,1}, \ldots, N_{i,h_{max}} = n_{i,h_{max}})$ is described by a multinomial distribution[22] and can therefore be expressed as

$$P(N_{i,1} = n_{i,1}, \ldots, N_{i,h_{max}} = n_{i,h_{max}}) = \frac{n_i!}{n_{i,1}!n_{i,2}! \ldots n_{i,h_{max}}!}\pi_{i,1}^{n_{i,1}} \cdot \pi_{i,2}^{n_{i,2}} \ldots \pi_{i,h_{max}}^{n_{i,h_{max}}}, \quad (8)$$

where $\pi_{i,h}$ are the probabilities that a patient testing the combination i will fall into pain class h. Each patient might have a different probability to fall into a specific pain class h having received a certain combination i. However, because no *a priori* knowledge is available about the individual probabilities of every single patient, we can assume them to be equal and estimate them using the maximum likelihood method

$$\hat{\pi}_{i,h} = \frac{n_{i,h}}{n_i}. \quad (9)$$

$PS_{i,t}$, as defined in equation 7, is a discrete variable; therefore, its probability density function can be calculated by summing the probability of all possible distributions of patients across the pain score classes, such that $PS_{i,t}$ is equal to r:

$$f_i(r) = P(PS_{i,t} = r) = \sum_{(n_{i,1}, \ldots, n_{i,h_{max}}) \in S_{i,r}} P(N_{i,1} = n_{i,1}, \ldots, N_{i,h_{max}} = n_{i,h_{max}})$$

$$\text{for } r = g(1) \cdot n_i, g(1) \cdot (n_i - 1) + \Delta r, g(1) \cdot (n_i - 2) + 2 \cdot \Delta r, \ldots, g(h_{max}) \cdot n_i, \quad (10)$$

where $S_{i,r}$ is defined as the set of all possible patient distributions into pain classes resulting for combination i in a $PS_{i,t}$ of value r:

$$S_{i,r} = \left\{ (n_{i,1}, \ldots, n_{i,h_{max}}) \text{ such that } \sum_{h=1}^{h_{max}} n_{i,h} \cdot g(h) = r \right\}. \quad (11)$$

Note that r can assume a finite number of values, deriving from the different distributions of patients into the pain classes. r ranges from $r_{min} = g(1) \cdot n_i$ to $r_{max} = g(h_{max}) \cdot n_i$ with a step size of $\Delta r = 0.4$. Let us denote as k (from 1 to k_{max}) the index running from r_{min} to r_{max}.

According to equations 8 and 9, equation 10 allows direct calculation of how probable it is that the total pain score for the combination

i, $PS_{i,t}$, assumes the value r for every possible r, from a given realization $\{n_{i,1}, \ldots, n_{i,hmax}\}$.

Let us rank the combinations $\{c_1, c_2, \ldots, c_m\}$ by increasing pain scores as in equation 2. Let us define the two groups

$$G = \{c_1, c_2, \ldots, c_q\}$$

$$B = \{c_{q+1}, c_{q+2}, \ldots, c_m\}$$

for a given q. We chose the discriminating index $\bar{q}$to maximize the estimated probability of having the highest total pain score in the group G ($PS_{q,t}$) lower than the lowest pain score in the group B ($PS_{q+1,t}$), *i.e.*,

$$\bar{q} \text{ is defined such that } P(PS_{q+1,t} > PS_{q,t}) \text{ is maximum.}$$

The above probability can be calculated as

$$P(PS_{q,t} - PS_{q+1,t} < 0) = \sum_{K=-(k_{max}-1)}^{0} \sum_{k=1}^{k_{max}-1} f_q(r(k+K)) \cdot f_{q+1}(r(k)). \quad (12)$$

For example (see table 8), let us calculate the partitioning resulting from the first set of initial combinations. Table 8 reports the number of patients falling in the different pain classes for the combinations A, . . . , H, the average pain score, and the ranking for each combination. The following ranking holds for the combinations A–H:

$$PS_{A,t} < PS_{F,t} < PS_{H,t} < PS_{G,t} < PS_{E,t} < PS_{B,t} < PS_{C,t} < PS_{D,t}.$$

We computed the probability of each pair of subsequent inequalities ($PS_{A,t} < PS_{F,t}$, $PS_{F,t} < PS_{H,t}$, $PS_{H,t} < PS_{G,t}$, $PS_{G,t} < PS_{E,t}$, $PS_{E,t} < PS_{B,t}$, $PS_{B,t} < PS_{C,t}$, $PS_{C,t} < PS_{D,t}$) according to equation 12, and we chose the highest probability as the cutting point for the partitioning of the complexes. The highest probability occurs between the combination G and E with $P(PS_{G,t} < PS_{E,t}) = 0.97$.

The rules presented in table 3 were followed. It can happen that new combinations provided by a given optimization step lead to unacceptable side effects (*i.e.*, violate the toxicity constraint). That happened in our study when combination I of complex 2 and combination L of complex 4 were tested. In these two cases, it was necessary to apply the regression model proposed by Berenbaum[14] to perform a step back from the toxicity into the therapeutic response surface.

Logistic Regression

Possibly, the new combination should be heading in the direction dictated by the optimization step while not leading to side effects. To do so, we adopted a two steps approach. First, we used the logistic regression to calculate which among the three variables in the new combination—concentration of bupivacaine, fentanyl, and clonidine—has significantly led to side effects. Second, we recalculated the concentration of such variable as the average concentration among the good combinations of the previous complex while keeping the other two variables the same as in the previous step.

We assumed the following logistic model to estimate the probability of occurrence of a side effect:

$$P = \frac{e^{\alpha_1 \cdot x_1 + \alpha_2 \cdot x_2 + \alpha_3 \cdot x_3}}{1 + e^{\alpha_1 \cdot x_1 + \alpha_2 \cdot x_2 + \alpha_3 \cdot x_3}}, \quad (13)$$

where *P* is the probability of side effect, x_1, x_2, and x_3 are the concentrations of bupivacaine, fentanyl, and clonidine, respectively, and α_1, α_2, and α_3 are the corresponding regression coefficients. By explicitating the regressors in equation 13, we obtain

$$\ln\frac{P}{1-P} = \alpha_1 \cdot x_1 + \alpha_2 \cdot x_2 + \alpha_3 \cdot x_3,$$

where ln indicates the logarithmic operator with base e.

The regression coefficients α_1, α_2, and α_3 can be calculated *via* linear regression by replacing x_1, x_2, and x_3 with the concentrations of bupivacaine, fentanyl, and clonidine in each of the combinations investigated. For each combination, *P* can be substituted with an estimate of the probability of side effects π:

$$\pi = \frac{P_S}{P_S + P_N}, \quad (14)$$

where Ps/Pn is the number of patients who reported/did not report side effects after administration of the given combination. We have computed α_1, α_2, and α_3 by using combinations A–I and the occurrence of motor block as reported in table 7. Only bupivacaine proved to be a statistically significant regressor ($\alpha_1 = 1.0$ with significance $P = 0.01$, $\alpha_2 = \alpha_3 = 0.0$), which is consistent with the notion that only bupivacaine, among the drugs investigated, produces motor block. Therefore, we averaged bupivacaine concentration in the good combinations for identifying the new combination in the optimization procedure.

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