Anesthesiology
2000; 92:325-37

A Direct Search Procedure to Optimize Combinations of Epidural Bupivacaine, Fentanyl, and Clonidine for Postoperative Analgesia

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Background: **The authors applied an optimization model (direct search) to find the optimal combination of bupivacaine dose, fentanyl dose, clonidine dose, and infusion rate for continuous postoperative epidural analgesia.**

Methods: **One hundred ninety patients undergoing 48-h thoracic epidural analgesia after major abdominal surgery were studied. Combinations of the variables of bupivacaine dose, fentanyl dose, clonidine dose, and infusion rate were investigated to optimize the analgesic effect (monitored by verbal descriptor pain score) under restrictions dictated by the incidence and severity of side effects. Six combinations were empirically chosen and investigated. Then a stepwise optimization model was applied to determine subsequent combinations until no decrease in the pain score after three consecutive steps was obtained.**

Results: **Twenty combinations were analyzed. The optimization procedure led to a reduction in the incidence of side effects and in the mean pain scores. The three best combinations of bupivacaine dose (mg/h), fentanyl dose (μg/h), clonidine dose (μg/h), and infusion rate (ml/h) were: 9-21-5-7, 8-30-0-9, and 13-25-0-9, respectively.**

Conclusions: **Given the variables investigated, the aforementioned combinations may be the optimal ones to provide postoperative analgesia after major abdominal surgery. Using the direct search method, the enormous number of possible combinations of a therapeutic strategy can be reduced to a small number of potentially useful ones. This is accomplished using a scientific rather than an arbitrary procedure. (Key words: Constraints; function minimization; linear programming; simplex method.)**

This article is accompanied by an Editorial View. Please see: Fisher DM: The direct search procedure: A new approach to evaluating clinical regimens. ANESTHESIOLOGY 2000; 92:301-3.

EPIDURAL administration of local anesthetics, opioids, and the α_2-agonist clonidine is effective for the treatment of postoperative pain.[1-6] However, side effects are frequently observed. Local anesthetics may cause hypotension[1,7] and motor block.[8] Opioid-related side effects include nausea, vomiting, pruritus, sedation, and respiratory depression.[9] Clonidine may be responsible for hypotension and sedation.[10] Most side effects of epidural local anesthetics,[11,12] opioids,[9] and clonidine[10,13] are dose-dependent. These drugs produce analgesia but do not share most side effects. This provides a rationale for coadministering low doses of two or three drugs to provide satisfactory analgesia and minimize side effects.

Combining drugs for postoperative epidural analgesia is common practice.[8,14,15] Combinations of local anesthetics with opioids,[1,2,7,16,17] opioids with clonidine,[4,18-20] and local anesthetics with clonidine[21] have been studied. Different combinations have been compared by randomized controlled studies.[1,2,13,18,20] However, randomized controlled studies can only analyze a very small proportion of all possible combinations. For instance, if four variables (*e.g.*, the dose of three drugs and the rate of infusion) and four different values for each variable are considered, then 256 (4^4) different combinations

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Received from the Department of Anesthesiology, Division of Pain Therapy, University of Bern, Inselspital, Switzerland. Submitted for publication February 26, 1999. Accepted for publication September 29, 1999. Supported by the Department of Anesthesiology of the University of Bern, Bern, Switzerland. Presented at the 9th World Congress on Pain, Vienna, Austria, August 22-27, 1999.

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Table 1. Definition and Management of Side Effects. Criteria for Discontinuing the Epidural Regimen Investigated because of Side Effects

Side effect	Measurement and Definition	Management	Criteria for Discontinuing the Epidural Regimen
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 ephedrine 5–10 mg administered whenever necessary, and lactated Ringer's solution 6–7 ml/kg 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, can not 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.	Discontinuation of the epidural regimen investigated if score = 4 until the morning after operation or if ≥ 3 during the subsequent period.	See Management (left).
Bradypnea	Respiratory rate < 8 breaths/min for a period longer than 10 min.	Discontinuation of the epidural regimen investigated.	See Management (left).
Motor block	Bromage score:[27] 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 ≥ 1 or the patient could not be mobilized because of motor impairment.	See Management (left).
Nausea		Stepwise intravenous administration of: 10 mg metoclopramide and 4 mg ondansetron, repeated after 1 h if nausea persisted.	Nausea not responsive to two doses of ondansetron.
Pruritus	Pruritus without cutaneous manifestations.	Treatment only if requested by the patient. Stepwise intravenous administration of 2 mg clemastin, 10 mg propofol, and 40 μg naloxone.	Pruritus requiring the administration of naloxone.

Modifications in the drug concentration or the infusion rate are considered as discontinuation of the epidural regimen investigated.

exist. Clearly, an investigation conducted on such a high number of combinations is not feasible. As a result, there is no scientifically based agreement on the optimal regimen for epidural analgesia.[22] Different mixtures and infusion rates are used on an empirical basis.[8]

A possible approach to this problem is represented by direct search optimization methods.[23–26] Initially, few combinations are empirically chosen and examined. On the basis of the results obtained, new combinations are created in a stepwise manner and investigated. The concept is to use the information obtained at each step to move toward the optimal combination. In this way, the optimum can be identified by testing a small number of combinations. To our knowledge, this method had never been used in human studies.

We hypothesized that a direct search method[24] could be used to find the optimal combination of bupivacaine dose, fentanyl dose, clonidine dose, and infusion rate for continuous postoperative epidural analgesia after major abdominal surgery. The target and restrictions of the optimization procedure were analgesia and side effects, respectively.

Materials and Methods

The study was approved by the local ethics committee. All consecutive patients undergoing elective upper

Table 2. Variables Considered in the Investigation and Restrictions Imposed to the Optimization Procedure, *i.e.*, Minimum and Maximum Values and Minimum and Maximum Increases When a New Regimen is Identified by the Optimization Procedure

Variable	Minimum Value	Maximum Value	Minimum Increase	Maximum Increase
Bupivacaine dose (mg/h)	0	25	2.5	10
Fentanyl dose (μg/h)	0	40	5	15
Clonidine dose (μg/h)	0	60	3	6
Infusion rate (ml/h)	5	15	0	5

The figures concern the basal epidural infusion and do not consider the extra epidural boluses given in case of inadequate analgesia. Increases were defined for each variable as the difference between the new calculated value in the optimization procedure and the average of the values of the three best regimens. A minimum increase was 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 was aimed at preventing an excessive increase in the variable, with possible occurrence of complications. See Methods section and Appendix for a description of the optimization procedure.

(stomach, pancreas, liver) and lower (colon, rectum) abdominal surgery performed by median xiphoid-pubic laparotomy were considered. Exclusion criteria were any contraindication to epidural analgesia, age < 16 yr, an additional surgical access (*e.g.*, thoracoabdominal or abdominoperineal operations), daily intake of opioids for a period > 1 week, and lack of patient's cooperation. Two hundred eleven patients were enrolled and gave written informed consent.

Patients, nurses in charge for the perioperative care, and staff who informed patients, performed anesthesia, and collected postoperative data were not aware of the epidural regimen used. All randomizations were performed by drawing lots.

Anesthetic Procedure

Patients were premedicated orally with midazolam 7.5 mg. The epidural puncture was performed at T7–T9 and T9–T11 for upper and lower abdominal surgery, respectively. The epidural space was identified by loss of resistance using 0.9% saline. A catheter was inserted 5 cm cephalad in the epidural space. After a negative test dose with 3 ml carbonated lidocaine, 2%, with freshly added epinephrine 5 μg/ml, 3-ml bolus doses of the same solution were injected every 10 min until a bilateral hyposensitivity to pin prick (21-gauge sharp-beveled needle) covering at least 4 dermatomes between T6 and T12 was recorded.

The epidural catheter was connected to a CADD-PCA-R-5800 Pump (SIMS Deltec, St. Paul, MN). The epidural mixture was prepared by the pharmacy of the hospital and contained two or three of the following drugs: bupivacaine, fentanyl, and clonidine. A 5-ml bolus dose of the investigated epidural mixture was administered, and the epidural infusion was started at the rate pertaining to the regimen investigated. The pump was programmed so that the infusion rate could not be changed and 4-ml nurse-controlled bolus doses with a lockout time of 15 min could be administered four times per hour.

General anesthesia was induced with intravenous fentanyl 3 μg/kg, thiopental 5–7 mg/kg, and pancuronium 0.1 mg/kg. After intubation, a mixture of oxygen, air, and 3–4 vol% desflurane (end-tidal concentration) was delivered (monitor Hellige AG, Freiburg, Germany). In the presence of signs of inadequate analgesia, intravenous bolus doses of 1 μg/kg fentanyl were administered.

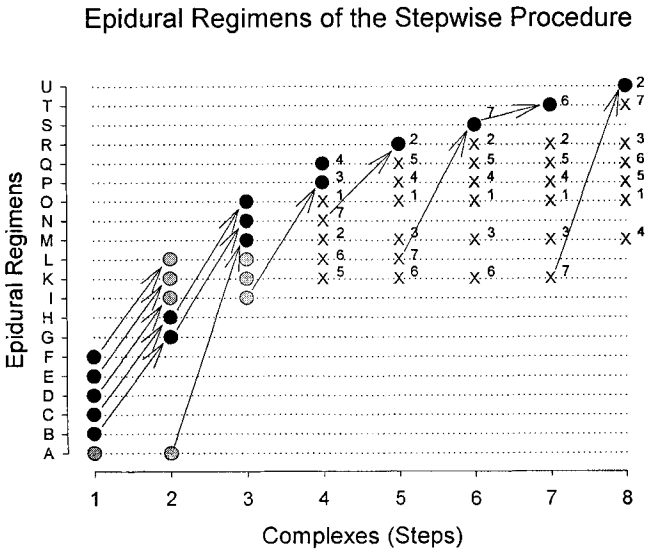

Fig. 1. The graph shows the epidural regimens of each complex during the stepwise optimization procedure. Black points are defined as regimens completed during the corresponding step, gray points as regimens completed during multiple steps, and X symbols as regimens already completed. For instance, regimen K was first applied to patients during step 2. At this step, regimens A, G, and H were stopped early because of side effects, and complex 3 was created. At step 3 there were still patients receiving regimen K. Therefore, regimen K was applied to patients at both step 2 and 3 (gray points). At step 4, there was no patient receiving regimen K (X symbols). The numbers to the right of the symbols indicate the ranking of the regimens within each complex according to the analgesic effect (1 = best, 7 = worst). The arrows indicate a change of the regimens from one complex to the next one. The reasons for changing were side effects (steps 1–4) or inadequate analgesia (steps 4–8). Data obtained by the repeated analysis of regimens O and R in the validation phase (see appendix) are not included. See Methods and the appendix for a detailed explanation.

Table 3. Epidural Regimens Investigated

Regimen	N	Bupivacaine D (C) mg/h (mg/ml)	Fentanyl D (C) μg/h (μg/ml)	Clonidine D (C) μg/h (μg/ml)	Infusion Rate ml/h
A	9	0 (0)	30 (4.3)	24 (3.4)	7
B	3	4 (0.5)	12 (1.5)	60 (7.5)	8
C	4	8 (0.9)	0 (0)	48 (5.3)	9
D	4	12 (1.2)	6 (0.6)	36 (3.6)	10
E	5	16 (1.5)	24 (2.2)	12 (1.1)	11
F	3	20 (1.7)	18 (1.5)	0 (0)	12
G	2	4 (0.5)	12 (1.5)	24 (3.0)	8
H	2	8 (0.9)	0 (0)	24 (2.7)	9
I	8	12 (1.7)	6 (0.9)	12 (1.7)	7
K	12	4 (0.5)	24 (3.0)	12 (1.5)	8
L	12	8 (0.9)	18 (2.0)	0 (0)	9
M	12	0 (0)	30 (4.3)	12 (1.7)	7
N	8	12 (1.5)	12 (1.5)	0 (0)	8
O	24	8 (0.9)	30 (3.3)	0 (0)	9
P	12	12 (1.7)	6 (0.9)	6 (0.9)	7
Q	12	0 (0)	38 (4.8)	14 (1.8)	8
R	24	9 (1.3)	21 (3.0)	5 (0.7)	7
S	10	5 (0.7)	34 (4.9)	3 (0.4)	7
T	12	8 (1.0)	32 (4.0)	2 (0.3)	8
U	12	13 (1.4)	25 (2.8)	0 (0)	9

The figures concern the basal epidural infusion and do not consider the extra epidural boluses given in case of inadequate analgesia.
C = drug concentration in the epidural mixture; D = dose of drug per hour; N = sample size.

Extra bolus doses of the epidural solution were not allowed before extubation. The trachea was extubated as soon as patients opened their eyes to verbal command. If extubation was not performed within 2 h after the end of the operation, the patient was excluded from the study.

Postoperative Management

Extubation was considered as the beginning of the postoperative study period, which included the first 48 h. The epidural mixture used intraoperatively was administered at the same infusion rate. No systemic analgesic was given.

Patients remained in the recovery room for at least 24 h. Electrocardiogram, oxygen saturation using pulse oximetry (Sp_{O_2}; continuously), and noninvasive blood pressure (every 15–30 min) were monitored. Oxygen 2–4 l/min was administered *via* nasal probe to maintain a $Sp_{O_2} \geq 95\%$. Lactated Ringer's solution 2,500–3,500 ml/24 h according to body weight was infused. All patients had an indwelling urinary catheter. Patients were mobilized on the morning after operation by inviting them to sit at bed for 3–5 min and then to stand up and walk. Blood pressure was measured every 2–5 min during mobilization.

Patients were asked to rate pain at rest and after cough (verbal descriptor score) as follows: 0 = no pain, 1 = weak pain, 2 = moderate pain, 3 = strong pain, and 4 = very strong pain. Pain during cough was measured by asking patients to cough twice. Adequate pain treatment was defined as a score of 0 at rest and ≤ 1 during cough. This was chosen to provide pain relief at rest and allow mobilization and physiotherapy with minimal discomfort. Patients were instructed to call nurses whenever they felt pain of any intensity at rest or moderate, strong, or very strong pain during cough. In these cases, a 4-ml bolus dose of the epidural mixture was administered by the nurses. After 15 min, the patient was asked to rate pain again. If scores of 0 at rest and ≤ 1 during cough were not achieved, another 4-ml bolus dose was administered. If four bolus doses had to be administered every 15 min, 6–18 ml carbonated lidocaine, 2%, was injected to test the position of the epidural catheter. If bilateral hypoalgesia to pin prick covering less than the dermatomes corresponding to the laparotomy wound (T6–T12) was observed, failure to provide pain relief was attributed to factors other than the epidural regimen (*e.g.*, catheter placement). These cases were excluded from the analysis. If bilateral hypoalgesia covering at least T6–T12 was observed, failure to provide adequate analgesia was attributed to the epidural regimen. A more concentrated solution was administered and/or the infusion rate was increased. Failure of epidural analgesia completed the study for a patient. The patient was not

Table 4. Patient Characteristics, Type of Operation, Duration of Operation, and Intraoperative Amount of Intravenous Fentanyl

Regimen	N	Sex (No. F/M)	Age (yr)	Weight (kg)	Height (cm)	Type of Operation (No. upper/lower)	Duration (h:min)	Intravenous Fentanyl μg/h
A	9	4/5	58 ± 15	71 ± 18	168 ± 9	7/2	4:26 ± 1:27	117 ± 74
B	3	2/1	37–64	62–103	163–187	3/0	3:10–6:35	0–75
C	4	3/1	59–81	54–84	154–182	3/1	3:45–10:30	0–20
D	4	2/2	50–71	60–70	156–176	3/1	3:15–6:00	0–17
E	5	1/4	41–77	51–88	156–179	4/1	1:30–6:20	0–200
F	3	0/3	51–72	53–71	157–175	3/0	3:45–5:35	18–27
G	2	1/1	59–74	63–76	169–173	0/2	4:30–4:55	20–167
H	2	0/2	60–79	82–88	172–178	2/0	7:20–7:25	27–157
I	8	5/3	54 ± 7	80 ± 21	168 ± 8	7/1	4:55 ± 2:44	110 ± 117
K	12	5/7	55 ± 17	77 ± 24	167 ± 10	9/3	4:44 ± 1:45	103 ± 146
L	12	4/8	57 ± 21	75 ± 33	169 ± 6	10/2	4:27 ± 1:15	105 ± 53
M	12	8/4	52 ± 15	85 ± 34	168 ± 9	9/3	4:47 ± 2:12	86 ± 68
N	8	6/2	42 ± 22	85 ± 30	165 ± 7	7/1	3:15 ± 1:07	120 ± 104
O	24	12/12	59 ± 15	80 ± 28	167 ± 7	20/4	4:32 ± 1:37	76 ± 76
P	12	8/4	53 ± 15	86 ± 32	164 ± 9	9/3	4:30 ± 1:46	39 ± 57
Q	12	5/7	61 ± 13	69 ± 11	169 ± 11	11/1	6:09 ± 3:08	57 ± 51
R	24	11/13	63 ± 11	74 ± 18	168 ± 11	16/8	5:27 ± 2:15	55 ± 66
S	10	2/8	50 ± 13	83 ± 37	171 ± 7	7/3	5:15 ± 1:40	63 ± 53
T	12	5/7	60 ± 17	84 ± 22	170 ± 13	10/2	5:09 ± 2:08	73 ± 67
U	12	5/7	51 ± 18	77 ± 19	168 ± 5	9/3	4:40 ± 2:27	53 ± 30

For age, weight, height and duration of operation mean values ± SD are reported, unless for regimens investigated in fewer than six patients, in which ranges (minimum–maximum) are reported.

Upper abdominal surgery: stomach, pancreas, liver. Lower abdominal surgery: colon, rectum.

For fentanyl, the total intraoperative amount (excluding the intubation dose) was divided by the duration of operation.

No statistically significant differences in any of these variables among the different regimens were found. The chi-square test performed on sex and type of operation may not be fully accurate because some of the expected values of the contingency table were less than 1, and more than 20% of the expected values were less than 5.

N = sample size.

excluded from the analysis, but only data collected before the injection of lidocaine were considered.

Table 1 shows definition and management of the side effects and the criteria investigated for discontinuing the epidural regimen. Urinary retention was not considered because all patients received a urinary catheter. The occurrence of any other side effect was recorded. When the epidural regimen was discontinued because of side effects, patients were treated further by either decreasing the infusion rate or administering a less concentrated solution. A side effect requiring the discontinuation of the epidural regimen completed the study for a patient. Only data collected before discontinuation of the epidural regimen under investigation were included in the analyses.

Data Collection

The intraoperative dose of intravenous fentanyl was recorded. In the postoperative phase, the following data were collected every 2 h during the first 6 h, and then every 4 h: verbal descriptor pain score at rest and during cough, systolic blood pressure, heart rate, sedation score (table 1), respiratory rate, motor block[27] (table 1), presence of nausea, and pruritus. Forty-eight hours after extubation or after discontinuation of the regimen investigated, total number of epidural bolus doses administered and occurrence of any additional side effect or postoperative complication were recorded.

Optimization Procedure (Direct Search)

In this section, the main aspects of the optimization procedure are presented. The method is described in detail in the appendix.

The aim of the direct search procedure was to optimize the analgesic effect, *i.e.*, to minimize the pain score. To this purpose, the optimal combination of bupivacaine dose, fentanyl dose, clonidine dose, and infusion rate was sought (table 2). Each combination of these four variables defined an epidural regimen. Constraint of the search procedure was an unacceptable incidence of side effects. An epidural regimen violated a constraint when it had to be discontinued because of the same side effect in four patients who received that regimen (table 1).

For each regimen, 12 patients were studied. If an

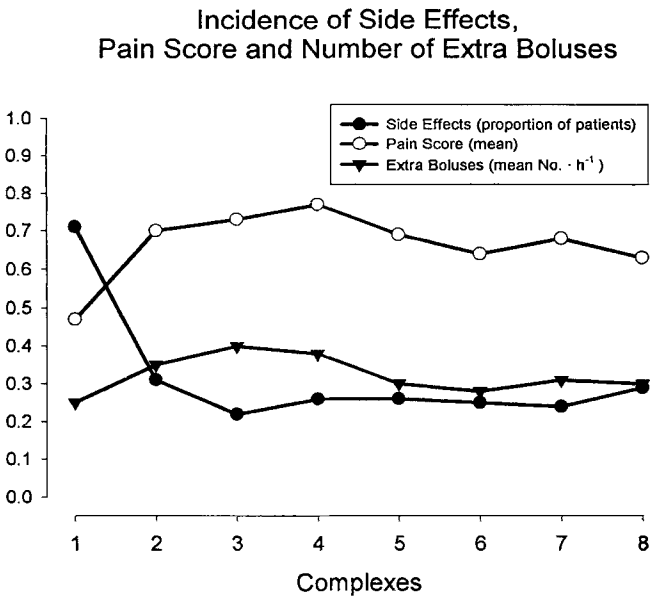

Fig. 2. The graph illustrates the incidence of side effects, the mean pain score, and the mean number of extra epidural bolus doses of each complex during the optimization procedure. Side effects are represented as the proportion of patients in which the epidural regimen investigated had to be discontinued because of any side effect (table 6). The pain score of each complex was calculated by computing the mean for each patient, using all observations on pain at rest and during cough, and calculating the average pain score for each regimen from the individual means of all patients. The mean pain score of each complex was then calculated from the mean scores of the corresponding regimens (fig. 1). The number of extra epidural bolus doses per hour was calculated by dividing the total number of bolus doses by the time during which the epidural mixture was infused.

epidural regimen had to be discontinued because of pain in 5 patients or because of the same side effect in 4 patients (table 1), the regimen was considered unacceptable even if < 12 patients had been studied.

The investigation consisted of sequential optimization steps (fig. 1). The basic principle was to use the results obtained by the analysis of a group of regimens to create subsequent regimens in a stepwise manner until optimal analgesia with an acceptable incidence of side effects was reached. The group of regimens analyzed at each step was named a "complex." The following procedure was used for each complex.

1. Analysis of analgesia and side effects of the regimens included in the complex studied.
2. Identification of the regimens characterized by the worst analgesic effect or associated with an unacceptable incidence of side effects (see appendix for the criteria used). These regimens were not included in the subsequent complexes.
3. Creation of a new complex of epidural regimens. This complex included the best regimens of the previous complex (best analgesia with acceptable incidence of side effects) and new regimens generated from the results obtained with the previous complex (see appendix for the method adopted). The new regimens replaced the ones mentioned in point 2 (fig. 1, arrows). Each of the new regimens was studied in a subsequent group of patients.
4. Application of the procedure 1–3 to the new complex.

The optimization procedure was characterized by two phases. During the first phase (fig. 1, steps 1–4), the regimens to be investigated were determined in an empirical manner. The aim was to identify a group (complex) of regimens that did not violate any constraint. In the second phase (fig. 1, steps 4–8), the regimens to be investigated were determined using a mathematical model (see appendix). This model was not used at the beginning of the study because it can only be applied when no regimen violates any constraint. The aim of the second phase was to optimize the analgesic effect.

The optimization procedure was interrupted when no further improvement in the mean pain score was achieved after three consecutive steps.

Statistical Analysis

Differences in patients' age, weight, height, duration of operation, and amount of intraoperative intravenous fentanyl among the groups receiving the different epidural regimens were analyzed by one-way analysis of variance (for normally distributed data) or Kruskal-Wallis one-way analysis of variance on ranks (when data were not normally distributed). The groups were compared for gender and type of operation using the chi-square test.

The results of the direct search were analyzed by descriptive statistics. We did not test for statistically significant differences between the outcomes in successive steps, in conformity with the relevant literature on the sequential optimization methods.[24,28] It is not required that the difference in the effect among the combinations is statistically significant. The method that we used avoids placing excessive reliance on any individual combination and instead looks at the average trend that emerges from the search procedure.

Results

Of the 211 patients enrolled, 21 were not included in the analyses for the following reasons: inability to identify the epidural space (n = 2), perforation of the dura during the insertion of the epidural catheter (n = 2), unexpected thoracotomy or insertion of a thoracic drainage (n = 2), delayed extubation because of intraoperative complications (n = 4), catheter dislocation (n = 6), unilateral spread of analgesia postoperatively (n = 2), removal of the epidural catheter because of catheter infection (n = 1), reoperation because of bleeding (n = 1), and postoperative administration of acetaminophen because of fever (n = 1). The study was therefore completed in 190 patients. Twenty epidural regimens were investigated (table 3). In two patients (regimens L and U), only one pain assessment was performed because of early discontinuation of the epidural regimen. Pain scores and number of epidural bolus doses pertaining to these patients were therefore not included in the calculations for the optimization procedure. Summary statistics of patient characteristics, type and duration of surgery, and amount of intraoperative fentanyl is reported in table 4.

During steps 1-4, a dramatic decrease in the incidence of side effects was observed (fig. 2). When the mathematical model for optimizing the analgesic effect was applied (steps 4-8), a decrease in the mean pain score and in the mean number of extra epidural bolus doses was observed (fig. 2). Changes in the variables analyzed during the optimization procedure are illustrated in figure 3. In figure 4 and table 5, the main outcome variables pertaining to the three best regimens are shown. The incidence of side effects for all regimens is reported in table 6.

Discussion

We applied an optimization model to postoperative epidural analgesia. To our knowledge, this method had never been used in human studies. During the study period, a decrease in the pain scores and the incidence of side effects was observed (fig. 2). Very low pain scores at rest and during cough and a low incidence of side effects was achieved at the end of the direct search procedure (fig. 4 and tables 5 and 6).

The optimal combinations were identified by investigating 20 of several hundreds or thousands of possible combinations. We therefore found that direct search methods may be useful in medical problems. The enormous number of possible combinations of a therapeutic strategy can be reduced to a limited number of potentially useful ones. We believe that these scientific-based methods should be preferred to procedures conducted on a purely arbitrary or empirical basis.

There are inherent limitations in direct search methods. An expectation that the results may improve at each step might influence the evaluation of the outcome. Therefore, the method should be used with caution when the measurements are strongly dependent on the observer evaluation. Alternatively, methods of internal validation can be introduced. Although the partition method minimizes the weight given to single combina-

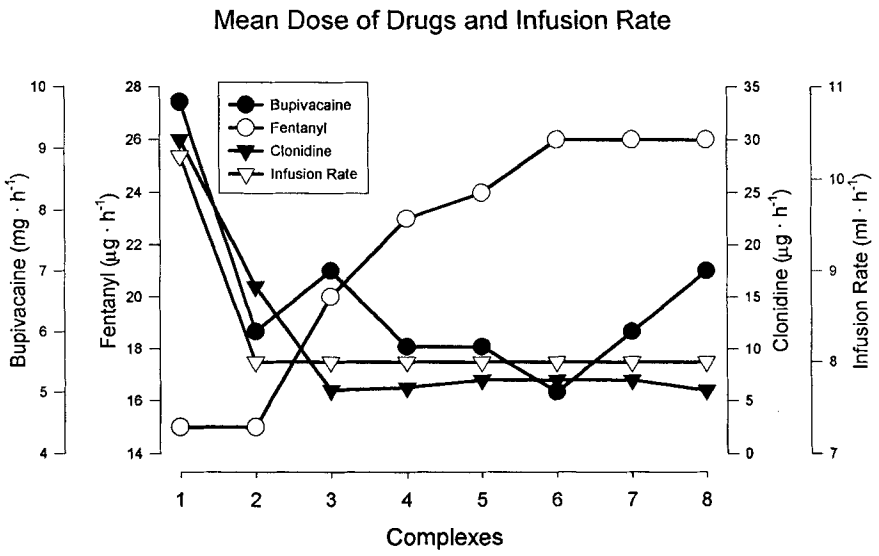

Fig. 3. The graph shows the mean doses of bupivacaine, fentanyl, and clonidine, and the mean infusion rate of each complex during the optimization procedure. The epidural regimens of each complex are represented in figure 1 and are described in table 3. The mean values of doses and infusion rates of the continuous infusion are shown. The extra epidural bolus doses are not considered.

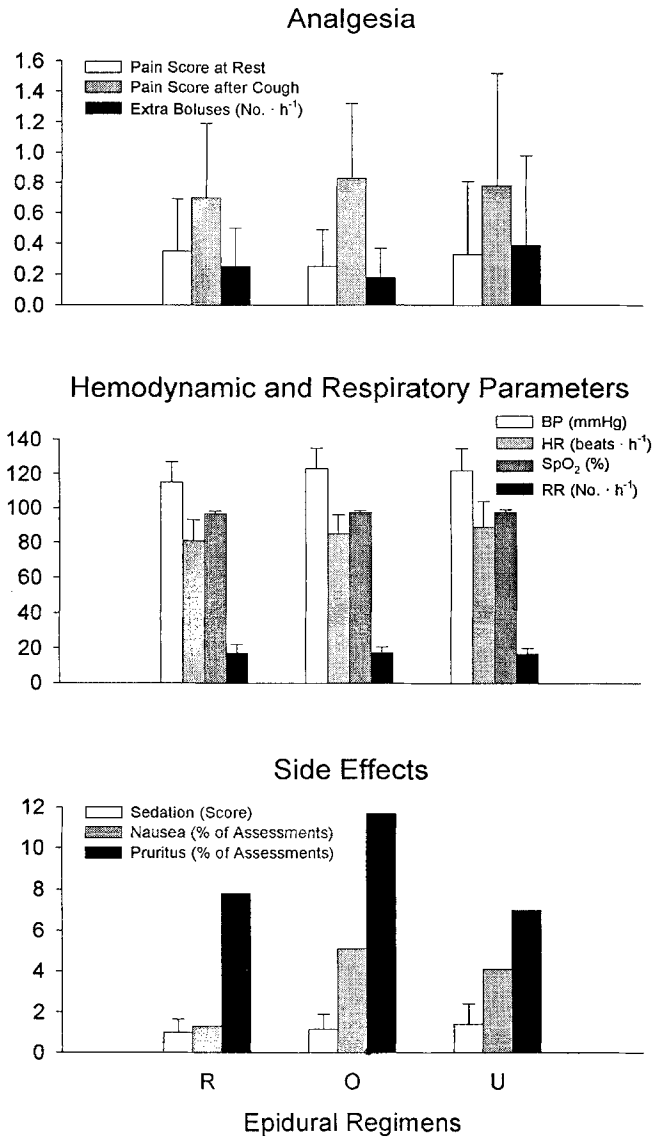

Fig. 4. The graph shows the main outcome variables of the best three regimens. (*Top*) Means and SDs of pain score and number of epidural bolus doses administered in case of inadequate analgesia. (*Middle*) Means and SDs of systolic blood pressure (BP), heart rate (HR), oxygen saturation using pulse oximetry (Sp_{O_2}), and respiratory rate (RR). (*Bottom*) Means and SDs of sedation score and percentage of assessments at which nausea and pruritus were recorded. See table 6 for side effects requiring discontinuation of the epidural regimen.

tions (figs. 5 and 6), it is still possible that combinations are ranked as the best or worst as a result of extreme chance. We minimized this problem by retesting two of the best regimens at the end of the optimization procedure. Additional limitations of this method in biological experiments have been previously addressed by Berenbaum.[24] We hope that the current study will encourage additional research to improve the optimization models for medical problems.

We suggest that the final group of combinations resulting from optimization procedures should be investigated by randomized controlled trials to detect significant differences in the outcome variables. Prospective observational studies, investigating the best combinations on large sample sizes, should be conducted to assess the incidence of rare complications and demonstrate the safety of the therapies.

The variable composition (*i.e.*, drug doses and infusion rates) of the best three epidural regimens, R-O-U, was relatively homogeneous (table 5). No clinically significant difference in the pain scores among these regimens was observed (fig. 4 and table 5). Therefore, the procedure did not lead to one optimal regimen, but rather to a group of optimal regimens characterized by a similar efficacy.

The fact that equally good analgesia was achieved by different epidural mixtures suggests that the doses of the individual drugs can be adapted within the aforementioned ranges to the needs of individual patients. For instance, the occurrence of motor block might be treated by decreasing the bupivacaine dose and increasing the fentanyl or clonidine dose of the epidural regimen, without impairing analgesia. The high variability of the pain scores (fig. 4) indicates that even the best regimens cannot guarantee an optimal pain relief in all patients. It is conceivable that some patients may benefit from increases in the doses of the epidural drugs.

Bupivacaine and fentanyl were present in each of the three best regimens (table 5). This emphasizes the importance of combinations of local anesthetics with opioids for postoperative analgesia. In these regimens, an extremely low incidence of side effects was observed (table 6 and fig. 4). It has recently been shown that the analgesic efficacy of bupivacaine–fentanyl mixtures for thoracic epidural analgesia can be markedly enhanced by the addition of epinephrine, with concomitant reduction in the incidence of side effects.[29]

Clonidine was present in a dose of 5 μg/h in one of the best three regimens (table 5). The addition of 20 but not 10 or 15 μg/h clonidine to an epidural mixture of bupivacaine 0.125% and fentanyl 2 μg/ml improved the quality of postoperative analgesia in a randomized controlled trial.[13] However, a decrease in blood pressure and an increase in vasopressor requirement was observed. Pain relief and incidence of side effects with regimen R, which included all three drugs, were very

Table 5. Analgesic Effect, Dose of Drugs, and Infusion Rate of the Best Three Regimens

Regimen	N	Pain Score	Extra Boluses (No/h)	Bupivacaine (mg/h)	Fentanyl (μg/h)	Clonidine (μg/h)	Infusion Rate (ml/h)
R	24	0.53 ± 0.39	0.25 ± 0.24	9 (10.3 ± 1.3)	21 (24.0 ± 2.9)	5 (5.7 ± 0.7)	7 (8.0 ± 1.0)
O	24	0.54 ± 0.34	0.18 ± 0.19	8 (8.7 ± 0.7)	30 (32.4 ± 2.5)	0	9 (9.7 ± 0.8)
U	12	0.55 ± 0.60	0.39 ± 0.59	13 (15.2 ± 3.3)	25 (29.3 ± 6.6)	0	9 (10.6 ± 2.3)

The pain score of each regimen was calculated by computing the mean for each patient, using all observations on pain at rest and during cough, and calculating the average pain score from the individual mean of all patients.

For dose of drugs and infusion rate, the first value refers to the continuous infusion. Mean values and SD of the total dose and infusion rate, *i.e.*, including the extra boluses, are reported in brackets.

N = sample size.

Mean values ± SD are reported.

close to those observed for regimens O and U, which included only bupivacaine and fentanyl (fig. 4 and tables 5 and 6). It therefore seems that adding small doses of clonidine is either not effective or can be compensated by slightly increasing the doses of other drugs. The incidence and severity of local anesthetic-induced hypotension and opioid-induced sedation may be enhanced by the coadministration of clonidine. These side effects were particularly frequent and severe at the beginning of the study, when clonidine doses up to 60 μg/h were administered. Mixtures of clonidine 12–14 μg/h and fentanyl 30–38 μg/h without bupivacaine (regimens M and Q) were included in the final complex (fig. 1). The mean (SD) pain scores of regimens M and Q were 0.61

Table 6. Incidence of Side Effects and Pain Requiring Early Discontinuation of the Epidural Regimen

Regimen	N	B-F-C (R)	Hypotension	Sedation	Motor Block	Pruritus	Pain	Time (h)
A	9	0-30-24 (7)	0.33	0.11	0	0	0.22	1–40
B	3	4-12-60 (8)	0	1.00	0	0	0	11–46
C	4	8-0-48 (9)	0	0.50	0	0	0.25	5–11
D	4	12-6-36 (10)	0.75	0.75	0	0	0	4–20
E	5	16-24-12 (11)	0.60	0.20	0	0	0	7–18
F	3	20-18-0 (12)	0.67	0	0.67	0	0	6–12
G	2	4-12-24 (8)	0	0	0	0	0.50	19–19
H	2	8-0-24 (9)	0.50	0	0.50	0	0	10–10
I	8	12-6-12 (7)	0.25	0.5	0	0	0	5–42
K	12	4-24-12 (8)	0	0.08	0	0	0.33	12–33
L	12	8-18-0 (9)	0.08	0.08	0	0.08	0.33	1–40
M	12	0-30-12 (7)	0	0.17	0	0	0.25	19–46
N	8	12-12-0 (0)	0.12	0	0	0	0.62	3–28
O	24	8-30-0 (9)	0.17	0.04	0	0	0.08	6–25
P	12	12-6-6 (7)	0.25	0.08	0.08	0	0.17	11–42
Q	12	0-38-14 (8)	0.25	0.17	0	0	0.08	5–46
R	24	9-21-5 (7)	0.12	0.04	0.04	0.04	0.08	10–41
S	10	5-34-3 (7)	0.20	0	0	0.1	0.50	16–27
T	12	8-32-2 (8)	0	0	0	0.08	0.17	5–41
U	12	13-25-0 (9)	0.17	0.17	0.17	0	0.17	2–16

Modifications in the drug concentration or the infusion rate are considered as discontinuation of the epidural regimen investigated.

B = dose of bupivacaine (mg/h); C = dose of clonidine (μg/h); F = dose of fentanyl (μg/h); N = number of patients; R = infusion rate of the epidural mixture (ml/h).

Data are expressed as the proportion of patients in which the regimen was discontinued. See table 1 and Methods section for a description of the criteria for discontinuing the therapy. In the last column, the time from extubation to discontinuation of the epidural regimen because of side effects or pain is reported in ranges (minimum–maximum).

In some patients, more than one side effect requiring discontinuation of the regimen occurred.

In addition to the data presented, bradypnea requiring the discontinuation of the epidural regimen was observed 41 h postoperatively in one patient who received regimen T. The respiratory rate did not increase after intravenous administration of 0.2 mg naloxone, and slowly increased during the subsequent 3 days. In one patient receiving regimen Q, persisting bradycardia (heart rate < 50 beats/min) without hypotension developed. As a precaution, the infusion rate of the epidural solution was decreased 10 h postoperatively. Nausea was not a reason for discontinuation in any case. No other side effect or complication was observed during the postoperative study period.

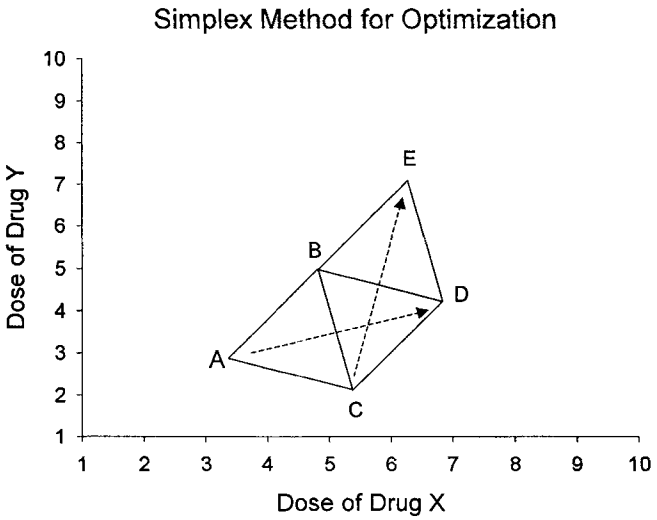

Fig. 5. The graph shows the simplex method for optimization. This method was not used in our study and is presented to facilitate the comprehension of the principles of optimization models. For a problem of *n* variables, an initial complex of n + 1 empirically chosen combinations is analyzed. To combine two drugs, X and Y, n + 1 = 3 combinations that form the vertices of an equilateral triangle are chosen (combinations A, B, and C). After analyzing these combinations, the one characterized by the worst therapeutic effect (*i.e.*, combination A) is discarded. A new combination, D, is determined by reflecting the triangle A-B-C on the axis B-C of the initial complex. Combination D of the new complex, B-C-D, is analyzed, the worst combination of the complex, B-C-D (*i.e.*, combination C), is discarded, and the new combination, E, is determined. The procedure is stopped when no further improvement in the therapeutic effect is obtained. In this way, information obtained in each step is used to move toward the optimum, and a very small proportion of all possible combinations has to be analyzed. The simplex method has been applied in mathematical and industrial problems. Its main disadvantage for applications in medical problems is the excessive weight given to the results obtained by each combination.[25] Measurements performed in a medical setting are usually characterized by a large variability. Thus, a certain combination can be found to be the worst one merely as a result of chance. Because the direction of the steps is given by the position of the worst combination, a wrong estimation would direct the optimization procedure toward a wrong point.

(0.33) and 0.74 (0.69), respectively. These regimens may be useful alternatives to mixtures of local anesthetics with opioids in particular cases, for instance, in the presence of motor block.

The safety of the bupivacaine and fentanyl doses used in regimens including only these two drugs (O and U) has been proven.[8,15] This information is not available for mixtures including fentanyl and clonidine, with or without bupivacaine, which have been investigated on small sample sizes.[13,18,30]

The results from studies that investigated the influence of the infusion rate (volume per hour) at constant drug doses (amount of drug per hour) are controversial.[17,31] The application of the direct search model produced an increase in the bupivacaine and fentanyl doses, whereas the infusion rate remained constant (fig. 3, steps 4–8). This suggests that the amount of drug may be more important than the volume of solution administered per unit of time, at least for the drugs that we have investigated and the spinal level where the epidural solution was administered.

Epidural analgesia may prevent or minimize perioperative physiologic perturbations such as respiratory, cardiovascular, and coagulation changes.[22] It is not known whether and to which extent these effects are caused by improved analgesia and whether they result in a decrease in the incidence of postoperative complications.[22] On the basis of the current knowledge, it is not possible to conclude that an optimal analgesic effect is associated with the best patient outcome.

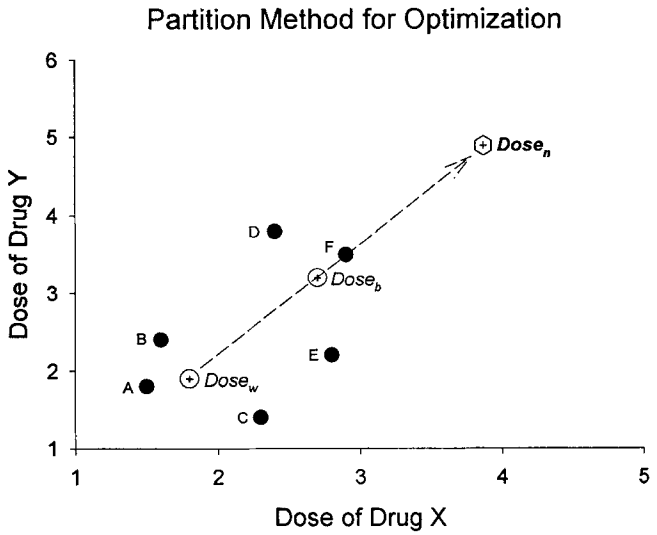

Fig. 6. The graph shows the Berenbaum's partition method for direct search.[24] The main rationale is to avoid the excessive weight given to the worst combination by the simplex method (fig. 5). This minimizes the potential bias resulting from the large variability that characterizes biological experiments. In the example illustrated, a complex of six combinations (A–F) of two drugs (X and Y) is represented. These combinations are ranked from best to worst according to their therapeutic effect. The combinations are then partitioned between the best and the worst halves. If $Dose_w$ and $Dose_b$, are the mean doses of the drugs in the worst three (A-B-C) and best three (D-E-F) combinations, respectively, the doses of the new combination are given by the equation $Dose_n = Dose_b + \alpha(Dose_b - Dose_w)$, where α is a positive number. In this way, the relative position of the three worst combinations in the ranking does not influence the direction of the next step.

Conclusions

Given the variables investigated, the combinations identified by the direct search procedure (table 5) may be the optimal ones to provide postoperative analgesia after major abdominal surgery. The direct search method may be a valuable model in clinical research. The enormous number of possible combinations of a therapeutic strategy can be reduced to a small number of potentially useful ones.

Appendix: Optimization Procedure

Phase 1: Empirical Procedure

This phase included steps 1–4 of the direct search procedure (fig. 1).

Initially, six regimens were investigated for complex 1 (table 3, regimens A–F). The number of regimens included in the complex was based on the previous literature on the method that we used,[24] according to which the number of regimens of the complex should be > 4 + 1 (where 4 is the number of variables investigated; table 2). The aim of the selection of the initial regimens was to identify effective combinations so that the optimum could be reached after a few number of optimization steps. Therefore, doses that were expected to provide adequate analgesia on the basis of previous investigations and pilot studies were empirically[23,24,28] chosen. The doses were also selected so that for each variable, a wide range of doses in regimens A–F was investigated. For instance, the bupivacaine dose in regimens A–F was 0–20 mg/h. Each patient was randomly assigned to one of the six regimens.

A very high incidence of side effects requiring discontinuation of the epidural regimens of complexes 1–3 was observed (table 6). For most regimens, the cutoff number of four cases required to define the incidence of side effects as unacceptable was not reached. However, because of the frequency and severity of the side effects, we were strongly concerned that the regimens may produce serious adverse effects. Therefore, the use of most regimens was stopped even if the side effects occurred in less than four patients for each regimen.

The method used to identify the new regimens in the empirical phase is explained by the following example. During the analysis of complex 1 (fig. 1), sedation and hypotension required discontinuation of the epidural regimen in 8 and 9 of the 19 patients receiving regimens B–F, respectively (table 6). Too high a dose of clonidine was probably responsible for sedation. Fentanyl did not seem to be primarily responsible for unacceptable sedation because it was administered in very low doses in regimens associated with this side effect (*i.e.*, B–D, table 6). Regimen E was characterized by a high incidence of hypotension, and regimen F was characterized by both hypotension and motor block (table 6). Too high a dose of bupivacaine was probably responsible for these effects. Therefore, when determining the regimens of complex 2 (fig. 1), the clonidine dose was reduced for regimens B, C, and D (to create regimens G, H, and I, respectively), and the bupivacaine dose was reduced for regimens E and F (to create regimens K and L, respectively). In addition, when changing regimens B–F to regimens G–L, the infusion rates were reduced because most side effects occurred with infusion rates of 10–12 ml/h (table 6). As for the initial complex, the criteria to choose the specific doses were to create regimens that would still provide adequate analgesia and were characterized by a wide range of the doses across the different regimens of complex 2 (table 3, regimens A, G–L). At the time when complex 2 was created, three patients had received regimen A. Hypotension requiring discontinuation of the regimen was observed in one of them. Because it was not yet clear whether regimen A was unacceptable, it was incorporated in complex 2 and further investigated together with regimens G–L (fig. 1).

During steps 1–4, the drug doses of the regimens were reduced until a complex that did not violate any constraint was identified (complex 4, fig. 1 and table 6). To investigate better the fentanyl–clonidine combination, we introduced an additional regimen, Q, in complex 4 (table 3). This is an acceptable practice during optimization procedures.[25] Therefore, each of the complexes 4–8 included seven regimens.

Phase 2: Application of the Mathematical Model

General Aspects. This phase included steps 4–8 of the optimization procedure (fig. 1).

As in phase 1, the results obtained by analyzing each complex were used to determine the subsequent regimens. However, a mathematical model rather than an empirical procedure was used. The model that we used is a modification of the simplex method proposed by Spendley *et al.*[28] The simplex method was not used in the current study but is described in figure 5 to facilitate the comprehension of the principles of optimization models. We used the direct search partition method developed by Berenbaum.[24] The principle underlying this method is explained in figure 6.

The aim of the optimization procedure in this phase was to optimize the analgesic effect. Restrictions imposed were minimum and maximum value of variables, minimum and maximum increase of variables at each step (table 2), and constraints. No constraint was violated by the regimens of complexes 4–8, *i.e.*, no regimen was discontinued in > three patients because of the same side effect.

In the following sections we describe the mathematical model used to optimize the analgesic effect. To facilitate the comprehension of the method, we explain how this model was applied to complex 4 for generating complex 5.

Ranking of the Regimens of Each Complex. At each step, the regimens within each complex were ranked from the best to the worst according to the pain score (fig. 1, complexes 4–8). The mean pain score for each patient, using all observations on pain at rest and during cough, was computed. The average pain score for each regimen was calculated from the individual means of all patients. Independent of the pain score, a regimen was ranked as the worst if the drug concentration or the infusion rate had to be changed because of pain in > four patients or if an average number of extra epidural bolus doses > 2 per hour was administered. The data pertaining to pain scores and number of extra epidural bolus doses were not considered for patients in whom the drug concentration or the infusion rate were changed before at least two measurements (*i.e.*, 2 and 4 h postoperatively) were made. According to these criteria, the seven regimens of each complex were ranked as r_{1-7}, where r_1 was the regimen giving the best and r_7 the one giving the worst analgesic effect (fig. 1).

Example. In complex 4, regimen N was discontinued in five patients because of inadequate analgesia (table 6). It was therefore ranked as the worst one of the complex. The other regimens of complex 4 were ranked from the best to the worst according to the average pain score (fig. 1).

Partitioning of the Complex. Each complex (r_{1-7}) was partitioned into two sets, r_{1-3} and r_{4-7} (*i.e.*, the regimens giving the best and the worst analgesic effect, respectively). The mean values C_b and C_w of each variable (*i.e.*, bupivacaine dose, fentanyl dose, clonidine dose, and infusion rate) for these sets were calculated by vector analysis:

$$C_b = (c_1 + c_2 + c_3)/3 \text{ and } C_w = (c_4 + c_5 + c_6 + c_7)/4 \quad (1)$$

where c_{1-7} are the values of each variable for the regimens, r_{1-7}.

Example. The seven regimens of complex 4 were partitioned into sets O-M-P (the best three regimens) and Q-K-L-N (the worst four regimens). The bupivacaine dose of the best three (O-M-P) and the worst four regimens (Q-K-L-N) of complex 4 was 8-0-12 and 0-4-8-12 mg/h, respectively (table 3). The mean bupivacaine dose of these two sets was $(8 + 0 + 12)/3 = 6.7$ and $(0 + 4 + 8 + 12)/4 = 6.0$ mg/h, respectively. The mean fentanyl dose, clonidine dose, and infusion rate of the best three and worst four regimens were calculated in the same fashion.

Identification of the New Regimen for the Subsequent Complex. The new regimen (*N*) to be studied was generated by the equation:

$$N_i = C_b\alpha(C_b - C_w) \quad (2)$$

where $\alpha = 1.3$ (see fig. 6). In general, the only formal requirement for α is that it must be a positive number. The role of this coefficient is to determine the speed of convergence to the optimal combination. Too small a value for α would yield a very slow convergence to the optimal combination, whereas too large a value could be responsible for the iteration to "overshoot" its target. *Ex ante*, the exact choice of α is inevitably somewhat arbitrary. We chose the particular value $\alpha = 1.3$ in conformity with a previous study using the partition method.[24]

The new regimen was then studied in a subsequent group of patients. If no constraint was violated, the new regimen was accepted in the subsequent complex and the worst one, r_7, was discarded.

Example. For complex 4, the bupivacaine dose of the new regimen to be investigated was calculated according to equation 2: $6.7 + 1.3(6.7 - 6.0) = 7.6$ mg/h. Thus, the calculation resulted in an increase in the bupivacaine dose from 6.7 (mean of the best three regimens) to 7.6 mg/h. This increase was less than the predefined minimum increase of 2.5 (table 2). Therefore, the bupivacaine dose of the new regimen was $6.7 + 2.5 = 9$ mg/h (rounded). The fentanyl dose, the clonidine dose, and the infusion rate of the new regimen were calculated in the same fashion. This resulted in the generation of the regimen R (table 3). Regimen R was included in complex 5, where it replaced the worst regimen, N, of the previous complex (fig. 1). In this way, a new complex of seven regimens was obtained, wherein six regimens were in common with the previous complex and had been already completed. Regimen R was then investigated in 12 patients. The regimens of complex 5 were ranked according to the analgesic effect, and the procedure continued as previously described.

In the last optimization step, we modified the calculation by partitioning the seventh complex of the optimization procedure (fig. 1) into the best two and the worst five regimens (instead of the best three and the worst four, as previously made). This was done because in the sixth and seventh complexes, the new regimens identified by the direct search model were either equally or only slightly more effective than the regimens that were discarded. The inhomogeneous composition of the variables of the three best regimens, O-R-M, may have been responsible for lack of optimization. In particular, M was strongly different from O and R in the bupivacaine and clonidine dose (table 3). Changing the rules of the direct search procedure during the experimental phase is an acceptable practice.[25] The new regimen, U, that resulted from the last step was ranked among the best three regimens (fig. 1).

End of the Optimization Procedure. No improvement in the pain score was achieved in the last three steps. The mean pain scores of the best three regimens—O, U, and R—were 0.51, 0.55, and 0.58, respectively. These values were close to the score of 0.5 (mean of 0 at rest and 1 during cough) defined as adequate analgesia. We therefore stopped the direct search procedure.

To check the robustness of the ranking procedure, we reanalyzed regimens O and R (randomly selected among the three best ones of the final complex; fig. 1) in two additional groups of 12 patients. The aim was to minimize the likelihood that the best regimens were ranked as the best as a result of chance. Twenty-four consecutive patients received either regimen O or R in a randomized fashion. The mean pain scores of regimens O and R in this phase were 0.56 and 0.47, respectively (0.51 and 0.58 in the optimization phase, respectively). By reranking the regimens on the basis of these additional data, regimens O and R were ranked again among the three best ones (table 5).

The authors thank Dr. Spencer S. Liu (Virginia Mason Medical Center, Seattle, WA) for reviewing the manuscript, and the staff of the hospital pharmacy for their cooperation.

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