Anesthesiology 2003; 98:1195–205

Combinations of Morphine with Ketamine for Patient-controlled Analgesia

A New Optimization Method

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

Background: **According to previous studies, the addition of ketamine to morphine for intravenous patient-controlled analgesia (PCA) may be beneficial. The authors developed and applied a new model to optimize the combination of morphine, ketamine, and a lockout interval for PCA after lumbar spine and hip surgery.**

Methods: **One-hundred two patients undergoing lumbar spine or hip surgery participated in the study. The analgesic effect of PCA during 48 h after surgery was optimized under restrictions dictated by side effects. Initially, eight combinations of morphine, ketamine (expressed as drug concentration in the solution administered), and a lockout interval (*i.e.*, minimal allowed time between two consecutive PCA boluses) were empirically chosen and investigated. To determine subsequent combinations, an optimization model was applied until three consecutive steps showed no decrease in pain score.**

Results: **The authors analyzed 12 combinations with an allowed morphine and ketamine range in a PCA solution of 0–2 mg/ml and a lockout interval range of 5–12 min. During the optimization procedure, a reduction in mean pain scores with a low incidence of side effects was observed. The procedure converged to a morphine-to-ketamine ratio of 1:1 and a lockout interval of 8 min.**

Conclusions: **Using a novel method to analyze drug combinations, the study supports combinations of morphine with ketamine in a ratio of 1:1 and a lockout interval of 8 min for postoperative PCA following spine and hip surgery.**

INTRAVENOUS patient-controlled analgesia (PCA) with morphine is commonly used for postoperative analgesia after major surgery. Opioids, however, frequently cause side effects such as nausea and heavy sedation.[1] Respiratory depression,[1] although rare, is a concern. Tolerance to the analgesic effect may develop during opioid therapy, even at a very early stage.[2]

This article is featured in "This Month in Anesthesiology." Please see this issue of ANESTHESIOLOGY, page 5A.

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

Received from the Division of Pain Therapy, Department of Anesthesiology, University of Bern, Inselspital, Bern, Switzerland. Submitted for publication December 21, 2001. Accepted for publication December 11, 2002. Supported by the Department of Anesthesiology, University of Bern, Bern, Switzerland.

Address reprint requests to Dr. Sveticic: Department of Anesthesiology, Inselspital, 3010 Bern, Switzerland. Address electronic mail to: gorazd.sveticic@insel.ch.

Nociceptive stimulation produces spinal cord hyperexcitability *via* activation of the *N*-methyl-D-aspartate (NMDA) receptor.[3–5] Spinal cord hyperexcitability is involved in the pathophysiology of acute pain.[6] High doses opioids may activate NMDA pain facilitatory processes, which causes hyperalgesia and could enhance postoperative pain.[7] Therefore, the NMDA antagonist ketamine may have a role in the treatment of postoperative pain. The concomitant administration of an NMDA antagonist and an opioid may result in a synergistic or additive analgesic effect in animals.[5,8–10] This may allow a reduction in the doses of both drugs, which could result in a lower incidence of side effects. Animal studies have shown that NMDA antagonists prevent the development of tolerance to continuous exposure to morphine[8] and attenuate and reverse opioid-induced tolerance.[9] These data are consistent with clinical investigations showing that adding ketamine to opioids improves postoperative analgesia and reduces side effects.[10,11] On the other hand, the results of other studies did not confirm these findings and question the usefulness of adding ketamine to morphine for PCA.[12–14] Thus, while basic pain research clearly favors the combination of opioids with NMDA antagonists, the results of clinical research are still equivocal.

Although the addition of ketamine to morphine for PCA may be advantageous, the optimal combination of these two drugs and the optimal lockout time (*i.e.*, the minimal allowed time between two consecutive boluses) is not known. When two drugs are combined at different concentrations in the PCA solution and different lockout times are investigated, hundreds of combinations of PCA regimens are possible. For example, if 5 different values for each variable are considered, 5^3 (= 125) different combinations exist. Therefore, the optimal combination is unlikely to be identified by randomized controlled studies, since a very small proportion of all possible combinations is analyzed.

In a previous study,[15] we applied a "direct search" model[16] for the first time in a clinical investigation to optimize drug combinations for thoracic epidural analgesia after major abdominal surgery. The main advantage of this method is that a limited number of combinations have to be investigated.[15–17]

The aim of the current study was to optimize combinations of morphine, ketamine (expressed as drug con-

centration in the PCA solution), and a lockout interval for PCA after major lumbar spine or hip surgery, using a modification of the previously used model. Initially, we studied eight combinations. On the ground of the results observed, further steps were made by investigating new combinations until a point was reached at which no further improvement was made.

Materials and Methods

The ethics committee of the University of Bern (Bern, Switzerland) approved the study. Patients undergoing major spine surgery (lower thoracic and lumbar spine decompression and stabilization performed by median approach) or major hip surgery (articular capsule opened) were studied. Written informed consent was obtained from 102 patients. Exclusion criteria were any contraindication to ketamine or morphine, age less than 16 yr, intake of psychotropic drugs, daily intake of opioids for a period longer than 1 week, and lack of the patient's cooperation. Patients; the nurses in charge of perioperative care; and the staff members who informed the patient, performed anesthesia, and collected postoperative data were not aware of the PCA regimen used. Randomization was performed by drawing lots.

Anesthetic Procedure

The anesthetic procedure used was the routine procedure of our hospital. Patients were premedicated orally with 7.5 mg midazolam 20–30 min before anesthesia. Monitoring included at least an 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 study period.

General anesthesia was induced with 0.15–0.2 mg intravenous fentanyl, 5–7 mg/kg thiopental, and 0.1 mg/kg vecuronium. After intubation, a mixture of oxygen (30% inspired concentration) and nitrous oxide and isoflurane (0.3–0.5 vol% end-tidal concentration) was delivered. In the presence of signs of inadequate analgesia, intravenous boluses of 0.1–0.2 mg fentanyl and 1.0–2.0 mg vecuronium were administered at the discretion of the attending anesthesiologist. At the end of surgery, residual neuromuscular blockade was antagonized with neostigmine and glycopyrrolate.

The trachea was extubated as soon as patients opened their eyes to verbal command. If extubation was not performed within 1 h after the end of the operation, the patient was excluded from the study.

Postoperative Management

Patients were instructed on the use of PCA both on the day before surgery and after the end of surgery. The PCA pump was installed immediately after extubation and initially programmed to deliver a 1-ml bolus on demand with a maximum of 6 boluses per hour. The lockout time (*i.e.*, the minimum time allowed between two boluses) was one of the independent variables of the study and therefore depended on the regimen analyzed (table 1). Patients were instructed to press the PCA button when pain of any intensity at rest or moderate, strong, or very strong pain during mobilization occurred. If adequate analgesia was not obtained after six subsequent bolus requests (counting also demands below the lockout time, whereby no drug was delivered), the PCA bolus was permanently increased by 0.2 ml, to a maximum of 2 ml per bolus.

Table 1. Patient-controlled Analgesia Combinations Investigated

Combination	Morphine, mg/ml	Ketamine mg/ml	Lockout, min
A	0.9	0.7	8
B	1.0	0.6	9
C	0.7	0.4	8
D	0.5	0.6	6
E	0.7	0.7	7
F	0.7	1.0	9
G	0.4	0.8	9
H	0.4	1.0	7
I	1.0	1.0	8
K	1.1	1.2	8
L	1.3	1.3	8
M	1.4	1.4	11

Combinations A–H were empirically chosen as an initial complex. According to the principle of the 'direct search' method, choosing the initial combinations is not very important, keeping in mind the fact that wise selection of the initial complex would save us unnecessary optimization steps. Eventually, the endpoint should be reached regardless of the initial complex. Combinations I–M resulted from the stepwise optimization procedure.

In the first postoperative hour, 2.5-mg boluses of intravenous morphine were given as a rescue drug during the time in which the pump did not deliver bolus (*i.e.*, lockout time). After each morphine injection, the PCA bolus was increased by 0.2 ml. After the first hour postoperatively, no supplemental analgesia or sedation was administered. One hour after extubation was considered the beginning of the postoperative study period, which included the following 48 h. Thus, data pertaining the first postoperative hour were not used for the optimization model.

When indicated, patients were kept in the recovery room until the next morning after surgery. During this time, oxygen saturation using pulse oximetry was continuously measured. Patients were moved to the ward when cardiocirculatory and respiratory function were stable. Oxygen, 2–4 l/min *via* nasal probe, was administered to maintain an oxygen saturation of more than 93%. 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.

A verbal descriptor score was recorded every 2 h during the first 6 h postoperatively and then every 4 h by asking patients to rate pain at rest and during mobiliza-

Table 2. Definition and Management of Side Effects: Criteria for Discontinuing the PCA Combination Investigated Because of Side Effects

Side Effect	Measurement and Definition	Management	Criteria for Discontinuing the PCA Combination
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.	Reduction of PCA bolus by 0.2 ml every hour, if score $>$ 3 during the first 12 postoperative hours or $>$ 2 during the subsequent period.	Sedation not improved ($\leq$ 2) after reduction of bolus or appearance of pain after bolus reduction.
Bradypnea	Respiratory rate $<$ 8 /min for a period longer than 10 min.	Discontinuation of the PCA study mixture investigated till respiratory rate of 8 /min. PCA then restarted using 0.2 ml lower bolus than the previous one.	Bradypnea not improved ($<$ 8 /min) after reduction of bolus or appearance of pain after bolus reduction.
Dreams or hallucinations	Categorized as pleasant or unpleasant dreams or any sensation that is not caused by an external event.	In the presence of unpleasant dreams or hallucinations, reduction of PCA bolus by 0.2 ml every hour, until these symptoms disappeared.	Symptoms not eliminated after reduction of bolus or appearance of pain after bolus reduction.
Nausea	Intolerable nausea with or without vomiting.	I.v. administration of: 4 mg ondansetron, repeated after 1 h with reduction of PCA bolus by 0.2 ml if nausea persisted.	Nausea not responsive to two doses ondansetron.
Pruritus	Pruritus without cutaneous manifestations.	Treatment only if requested by the patient. IV administration of 2 mg clemastin; if not effective, reduction of PCA bolus by 0.2 ml every hour, until these symptoms disappeared.	Pruritus not responsive to reduction of bolus or appearance of pain after bolus reduction.

PCA = patient-controlled analgesia.

tion as follows: 0 = no pain, 1 = weak, 2 = moderate, 3 = strong, and 4 = very strong pain. Mobilization was defined as passive turning of patients on their side for nursing procedures. Adequate analgesia was defined as a score of 0 at rest and 2 or less during mobilization.

The study was interrupted because of (1) inadequate analgesia (pain score $>$ 0 at rest and $>$ 2 during mobilization after 2-ml PCA boluses repeated 6 times in 1 h); or (2) side effects that did not disappear despite reduction in PCA bolus or disappeared after reduction in PCA bolus, with inadequate analgesia occurring. Definition and management of side effects, together with criteria for discontinuing the PCA combination investigated, are presented in table 2. Only data collected before interruption of the study were included in the analyses. Further pain treatment was planed on an individual basis, depending on the reason for interruption.

Data Collection

Demographic and perioperative data were age, weight, American Society of Anesthesiologists physical status, type of operation, amount of fentanyl administered intraoperatively, duration of anesthesia (from intubation to extubation), and amount of rescue morphine administered in the first postoperative hour.

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, sedation score, presence of dreams and hallucinations, respiratory rate, and presence of nausea, vomiting, and pruritus. At the end of the study, duration of the study period, morphine and ketamine consumption, interruption of the study (if any), reason for interruption, and occurrence of any postoperative complication were recorded.

Optimization Procedure

The main aspects of the optimization procedure are presented in this section. A detailed description is given in the Appendix.

The procedure is a modification of the "direct search" method described by Berenbaum[16] that we previously

Table 3. Variables Considered in the Investigation and Restrictions Given for Direct Search

Variable	Minimum Value	Maximum Value	Minimum Increase	Maximum Increase
Morphine concentration, mg/ml	0	2	0.1	0.5
Ketamine concentration, mg/ml	0	2	0.1	0.5
Lockout interval, min	5	12	2 (decrease)*	

When identifying a new combination in the optimization procedure, a minimum increase in morphine and ketamine concentrations in patient-controlled analgesia solution was defined to avoid an increase in the dose produced by the optimization model that would be so small that a high number of steps would be necessary to reach the endpoint of the procedure. The maximum increase aimed at preventing an excessive increase in the drug doses 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.

* For lockout interval, no limits in increase were defined. As an extreme, decrease of 2 min was defined in order to avoid an excessive decrease in the interval between two doses with possible drug accumulation.

applied in a clinical study.[15] The aim of the procedure was to increase the analgesic effect, *i.e.*, to minimize the pain score, by sequentially optimizing the combination of morphine concentration in PCA solution, ketamine concentration in PCA solution, and lockout interval. Rules of the procedure included minimum and maximum value of independent variables, their minimum and maximum increase between two subsequent optimization steps (table 3), 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 PCA combination (table 2).

For each combination, six patients were studied. Initially, eight combinations that were expected to provide adequate analgesia and a low incidence of side effects were chosen and investigated (table 1, combinations A–H). Patients were randomly allocated to 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 utilize 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 rationale for choosing the number of patients in a combination group (*i.e.*, six) and the number of combinations in a complex (*i.e.*, eight) is explained in the Appendix.

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

1. Analysis of analgesia and side effects of the combinations included in the complex studied.
2. Identification of the combination characterized by the worst analgesic effect or associated with an unacceptable incidence of side effects. This combination was not included in the subsequent complexes.
3. Creation of a new complex of combinations. 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 used mathematical model[15] (see Appendix). The new combination replaced the one mentioned in point 2. The new combination was studied in a subsequent group of patients.
4. Application of the procedures 1–3 to the new complex.

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.

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

Statistical Analysis

The results of the direct search were analyzed by descriptive statistics. In sequential optimization methods, tests for statistically significant differences between groups are not used.[16] The method focuses on the trend of the optimization procedure and avoids excessive weight on any individual combination.[18] The optimization model to identify new combinations was based on a statistical method that is described in the Appendix.

Results

Of the 102 patients enrolled, 18 were not included in the analyses for the following reasons: intraoperative protocol violation (2 patients), change of operation planned (2), postoperative use of indomethacin for ectopic ossification prophylaxis (6), pain other then surgical pain that necessitated additional analgesics (3), post-

Table 4. Patients' Characteristics, Type of Operation, Intraoperative Amount of Intravenous Fentanyl, Duration of Anesthesia, and Amount of Intravenous Morphine as Rescue Drug During the First Hour after Extubation

Combination	n	Sex, No. F/M	Age, yr	Weight, kg	ASA	Type of Operation, No. hip/spine	IV Fentanyl, μg/h	Duration of Anesthesia, h:min	Rescue Morphine, mg
A	6	3/3	22–72	52–94	1–3	4/2	124–171	3:30–6:30	0–5
B	6	3/3	24–66	54–85	1–3	3/3	100–183	4:30–6:00	0–5
C	6	3/3	25–66	58–100	1–2	3/3	107–248	4:00–6:00	0–10
D	6	4/2	30–72	62–118	1–2	4/2	111–200	4:00–5:00	0–10
E	6	3/3	48–68	57–95	1–2	3/3	57–200	3:30–5:40	0–7.5
F	6	3/3	17–76	56–75	1–2	4/2	100–232	3:40–8:00	0
G	6	3/3	35–81	60–103	1–2	3/3	86–140	3:40–6:00	0–10
H	6	3/3	20–69	74–95	1–3	3/3	90–236	4:00–5:30	5–12.5
I	6	4/2	18–80	52–105	1–2	4/2	89–193	2:30–5:35	0–5
K	6	3/3	27–68	62–82	1–2	4/2	119–196	4:05–6:45	0–17.5
L	6	4/2	29–64	57–76	1–2	4/2	92–168	3:00–5:45	0–12.5
M	6	2/4	28–76	60–95	1–3	3/3	120–191	3:40–5:45	2.5–17.5
E-retest	6	4/2	19–76	55–83	1–2	4/2	29–150	3:45–6:50	0–7.5
K-retest	6	4/2	23–67	60–94	1–2	3/3	91–165	3:40–6:30	0–10

For age, ASA class, weight, duration of anesthesia, amount of fentanyl administered intraoperatively, and amount of rescue morphine administered in the first hour postoperatively, ranges (minimum–maximum) are reported. Hip surgery: surgical dislocation of the hip, periacetabular osteotomy, total hip arthroplasty. Lumbar spine surgery: decompression and stabilization, internal fixation using Dynesys© (Sulzer Orthopedics Ltd., Baar, Switzerland). For fentanyl, the total intraoperative amount was divided by the duration of anesthesia. Combinations E and K were tested again (E-retest and K-retest) due to retesting at the end of the optimization procedure (see Methods, Optimization Procedure).

operative protocol violation (1), lack of patient compliance (3), and randomization error (1). The study was therefore completed in 84 patients. We investigated 12 PCA regimens (and studied additional patients in 2 of these groups) (table 1). Demographic and perioperative data are shown in table 4.

Figure 1 illustrates combinations analyzed at each optimization step. During the four optimization steps (complexes 2–5), a decrease in the mean pain score and in the proportion of patients with insufficient analgesia was observed (fig. 2). The incidence of side effects remained low (fig. 2). Changes in the variables analyzed during the optimization procedure are illustrated in figure 3: the average concentration of both morphine and ketamine in the PCA solutions increased during the four steps, whereas the average lockout interval remained constant. At the end of the optimization procedure, the three best combinations were I (1.0 mg/ml morphine, 1.0 mg/ml ketamine, 8-min lockout interval), E (0.7 mg/ml morphine, 0.7 mg/ml ketamine, 7-min lockout interval), and K (1.1 mg/ml morphine, 1.2 mg/ml ketamine, 8-min lockout interval). 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 E and K on six additional patients per combination. After retesting, these combinations were ranked again in the subgroup below the partitioning line of the last complex (defined as "good" combinations; see Appendix) with average pain scores of 0.77 and 0.83, respectively (fig. 2, top). In table 5, pain scores, PCA bolus dose, and drug consumption pertaining to the "good" combinations of the last complex are shown. The incidences of side effects and insufficient analgesia requiring an early discontinuation of the study are reported in table 6.

None of the combinations investigated violated any constraint, *i.e.*, the study was not discontinued in more than two patients because of the same side effect in any combination. No complication occurred.

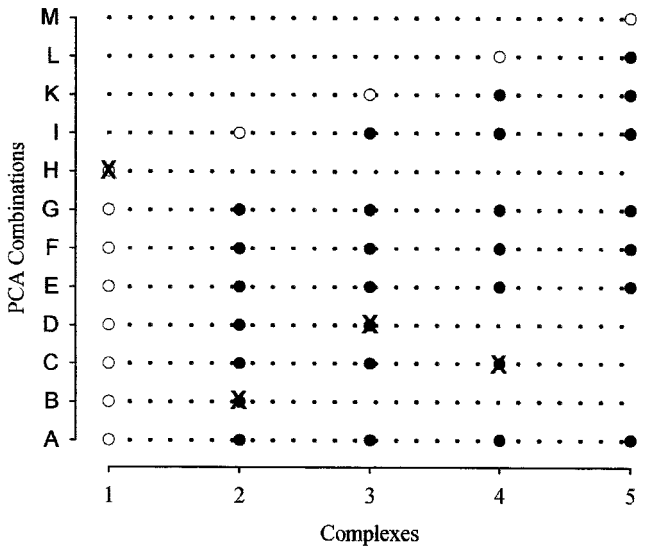

Fig. 1. Combinations of the sequential optimization procedure. Each combination is described in table 1. Initially, eight combinations were analyzed (complex 1). Thereafter, the worst combination of the complex (x) was discarded, and a new combination was identified by optimization model (combination I of complex 2) and tested on an additional group of patients (white points). This procedure was repeated at each subsequent step. Black points indicate combinations that were tested at previous steps.

Discussion

Clinical Aspects

We applied a stepwise optimization model to postoperative PCA. During the study period, we observed a decrease in pain scores associated with an increase in

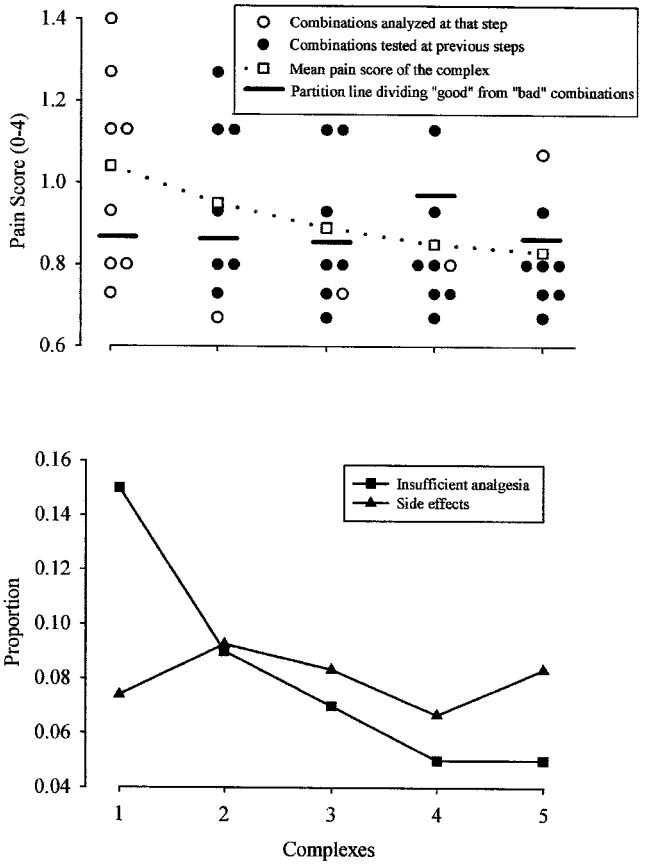

Fig. 2. (*Top*) Mean pain scores of each combination and mean pain score of each complex of the sequential optimization procedure. Calculation of the mean pain score is described in the Appendix. For each complex, the partition line (horizontal line) divides the "good" from the "bad" combinations. The progressive deterioration in performance of the added combinations from complex 2 onward suggests that the optimization procedure has passed the peak and is moving from the desired end point. (*Bottom*) Incidence of insufficient analgesia and side effects in the complexes analyzed. Insufficient analgesia and side effects are reported as the proportion of patients in which the PCA combination had to be discontinued because of insufficient analgesia or any side effect, respectively (table 6).

morphine and ketamine concentrations in the PCA solution of the combinations analyzed (figs. 2 and 3). At the end of the procedure, the best combinations were characterized by very low pain scores and a low incidence of side effects (tables 5 and 6 and fig. 2).

The benefit of adding ketamine to morphine for PCA has been demonstrated by randomized controlled studies.[10,11] However, other investigations on major abdominal surgery did not confirm this finding.[12,13] In the current study, the application of the optimization model produced an increase in the morphine and ketamine concentrations in the PCA solutions analyzed (fig. 3). According to the principle of the optimization method employed, new combinations identified by the stepwise procedure contain more ketamine than the previous ones if the average ketamine concentration of the "good" combinations is higher than the average ketamine concentration of the "bad" combinations (fig. 2 top; see Appendix for details). Therefore, the increase in ketamine concentration in the PCA solutions analyzed during the four optimization steps is indirect evidence that very low concentrations of ketamine in the PCA solution have a clinically detectable analgesic effect when combined with morphine. The lockout interval displayed minimal changes (fig. 3). This suggests that the lockout interval, in the range investigated, might have been within the optimal area. Within this range, the lockout interval is probably less sensitive than changes in the drug concentrations in the PCA solution. Furthermore, because of the relatively slow onset of the drugs studied, differences in lockout time may not have an impact on the pain score over a fairly broad range.

The drug concentrations in the PCA solutions of the "good" group of the final complex (table 5) shows a morphine-to-ketamine ratio converging to 1:1. The variable magnitude of the bolus dose was probably the result of the well-known interindividual variability in drug requirement to achieve satisfactory analgesia. The lockout interval was 8 min in four of the "good" combinations and 7 and 9 min in the remaining two combinations (table 5). No clinically significant difference in the pain scores among these six combinations was observed (fig. 2 and table 5). Therefore, a satisfactory setting seems to be a morphine-to-ketamine ratio of 1:1, delivered at PCA boluses of 0.9–1.8 mg for each drug, with a lockout interval of 8 min. We emphasize that the magnitude of the PCA bolus may need to be adapted to the individual patient, according to analgesic efficacy and side effects.

The analysis of the remaining "bad" combinations (B, C, D, G, H, and M; table 1) reveals characteristics that may explain unsatisfactory analgesia. In combinations B, C, G, D, and H, the concentration of one or both drugs in the solution was lower than 0.7 mg/ml. Although the volume of the PCA bolus was increased in the presence of inadequate analgesia, the 0.2-ml increase every hour did not allow rapid achievement of satisfactory pain relief, with a consequently high average pain score. In

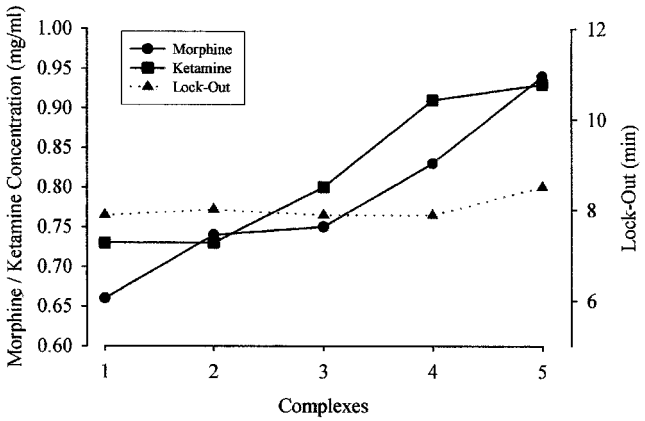

Fig. 3. Mean concentrations of morphine and ketamine in the PCA solution and mean lockout interval of each complex.

Table 5. Pain Score, Patient-controlled Analgesia Bolus Dose, and Drug Consumption in the 'Good' Combinations of the Final Complex

			Patient-controlled Analgesia Bolus Dose, mg		Consumption, mg/h	
Combination	n	Pain Score	Morphine	Ketamine	Morphine	Ketamine
I (1.0, 1.0, 8)	6	0.67 (±0.39)	1.6 (1.0–2.0)	1.6 (1.0–2.0)	3.1 (0.5–3.6)	3.1 (0.5–3.6)
E (0.7, 0.7, 7)	6	0.73 (±0.21)	1.1 (0.7–1.4)	1.1 (0.7–1.4)	2.1 (0.3–2.9)	2.1 (0.3–2.9)
K (1.1, 1.2, 8)	6	0.73 (±0.21)	1.7 (1.1–2.0)	1.8 (1.2–2.2)	2.1 (0.5–3.6)	2.3 (0.6–3.6)
F (0.7, 1.0, 9)	6	0.80 (±0.22)	1.2 (0.7–1.4)	1.7 (1.0–2.0)	1.3 (0.9–3.6)	1.9 (1.2–5.2)
L (1.3, 1.3, 8)	6	0.80 (±0.55)	1.6 (1.3–2.6)	1.6 (1.3–2.6)	3.1 (1.4–5.7)	3.1 (1.4–5.7)
A (0.9, 0.7, 8)	6	0.80 (±0.61)	1.2 (0.9–1.8)	0.9 (0.7–1.4)	1.9 (0.5–6.0)	1.5 (0.4–4.6)

For each combination, morphine concentration in patient-controlled analgesia solution (mg/ml), ketamine concentration in patient-controlled analgesia solution (mg/ml) and lockout interval (min) are given in brackets. 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) since the ranking was done using mean values (see Appendix). Patient-controlled analgesia bolus dose represents the median (range) of the drug dose reached after adjusting the bolus delivered in individual patients according to analgesia and side effects. Drug consumption (median and ranges) was calculated by dividing the total consumption by the duration of the study period.

combination M, the main problem may have been the particularly high lockout interval (11 min), which may have prevented the achievement of an adequate plasma drug concentration in some patients. Alternatively, the presence of one or more outliers may have accounted for the disappointing effect of combination M, despite high drug concentrations in the PCA solution.

Methodological Aspects

In the current study, we improved the optimization model previously used.[15–17] We developed a more effective method to identify the new combinations at each step of the optimization. Based on a simulation procedure that used the data collected in a previous study,[15] we minimized the number of patients per combination and optimized the number of combinations in each complex, assuming that the interindividual variability in the two studies is similar (see Appendix). In this way, we rendered the procedure more efficient by reducing the number of patients investigated. In fact, the final combinations were identified by investigating 12 out of several hundreds of possible combinations after only five steps enrolling only 102 patients.

The new method that we propose addresses three major issues of the one employed in the previous study.[15] First, as it stands in its original version,[16] the algorithm does not provide guidelines to choose the parameters m (*e.g.*, number of combinations per complex) and n (*e.g.*, number of patients per combination). Choosing excessively low values of m and n may reduce the time necessary to test a complex but does not necessarily reduce the number of optimization steps required to reach the final solution. In fact, with few patients testing each combination and few combinations in the complex, the correct search direction may be deviated by measurements coming from outlying pa-

Table 6. Incidence of Side Effects and Pain Requiring an Early Discontinuation of the Patient-controlled Analgesia Combination

Combination	n	Mo-Ke-Lo	Sedation	Nausea	Pruritus	Unpleasant Dreams or Hallucinations	Pain
A	6	0.9–0.7–8	0	0	0	0	1 (6)
B	6	1.0–0.6–9	0	0	1 (35)	0	1 (11)
C	6	0.7–0.4–8	0	0	0	1 (20)	2 (2, 22)
D	6	0.5–0.6–6	0	0	0	0	1 (26)
E	6	0.7–0.7–7	0	0	0	1 (25)	0
F	6	0.7–1.0–9	0	0	0	0	0
G	6	0.4–0.8–9	0	1 (6)	0	0	0
H	6	0.4–1.0–7	0	0	0	0	3 (2, 3, 11)
I	6	1.0–1.0–8	1 (46)	0	0	0	0
K	6	1.1–1.2–8	0	0	1 (38)	0	0
L	6	1.3–1.3–8	0	0	0	0	1 (16)
M	6	1.4–1.4–11	0	0	0	1 (21)	1 (30)
E-retest	6	0.7–0.7–7	0	0	0	0	0
K-retest	6	1.1–1.2–8	0	0	0	0	0

In no patient the combination was discontinued because of respiratory depression. Combinations E and K were re-analyzed in 6 patients because of retesting (see Methods, Optimization Procedure). 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 patient-controlled analgesia combination because of side effects or pain is reported (h). See table 2 for a description of the criteria for discontinuing the therapy.

Ke = concentration of ketamine in the patient-controlled analgesia solution (mg/ml); Lo = lockout interval (min); Mo = concentration of Morphine in the patient-controlled analgesia solution (mg/ml).

tients. As a result, more steps would be required to head back to the optimal point. On the other hand, high values for m and n may provide correct search direction but at the cost of an expensive or even unfeasible study. We addressed this point by defining the optimal values for m and n (see Appendix).

Second, to calculate the new combination at each optimization step, the complexes were partitioned into "good" and "bad" combinations at half in the previous study.[15] This means that in a complex of, for example, eight combinations, four would be "good" and four would be "bad." Partitioning the complexes into the categories "good" and "bad" to compute the next combination makes sense if we believe that combinations can be naturally clustered into two groups. However, given that the assumption is true, defining the clusters by 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 very 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. We needed a more rational algorithm to define clusters (see Appendix).

Third, taking decisions about future combinations exclusively by considering the average pain score across the patient may be too restrictive. Let us consider, as an example, two combinations whose average pain scores differ from each other markedly. We tend to consider these combination as if they belong to two separate clusters. However, if the distributions of pain scores among the patients are such that they significantly overlap, only considering the mean value would give us very limited information. In the current model, we considered the distribution of pain scores rather than just the average pain score among patients for cluster definition.

The coefficient α (Appendix, equation 5) defines the incremental changes toward the final combination, *i.e.*, away from the "bad" combinations. Lower values of α cause small changes, requiring more steps to reach the end point. On the other hand, large values of α may result in missing the optimum and possibly end up in toxic range. The optimal value of α remains undetermined, and the exact choice of α is inevitably somewhat arbitrary. The optimal α value is likely to depend on the type of experiment. For example, whenever severe toxicity is anticipated, low α values should be chosen, which was not the case of our investigation. The actual value chosen for α can be defended if the procedure converges to the end point in a limited number of iterations, without overshooting its target too often. Based on experience from previous studies,[15,16] we chose a value of α of 1.3 for the current study.

The low number of patients analyzed for each combination increases the influence of a single outlier on the results. One or more good outliers could shift the pain score of an otherwise "bad" combination into the "good" subgroup of combinations. This could influence the subsequent optimization steps. Although the potential effects of such an event on the results are unclear, it is possible that it could delay the identification of a satisfactory group of good combinations. However, it is important to recognize that using our methodology, no excessive weight on single combinations should be given. Rather, the trend of the sequential procedure is considered and the conclusions are based on the analysis of the final group of "good" combinations.

Theoretically, it is possible that the response surface has more than one minimum, so that the procedure could lead to a local optimum (statistical term that indicates particular set of parameters that produces good results but not the optimal set) instead of leading to the global one. A possible way of minimizing this problem is to start the search from two or more differently located starting complexes and test whether the procedure leads to different end points. However, this would require more resources, thereby reducing the main advantage of the direct search procedure: reaching the desired result by investigating few combinations. According to Berenbaum,[19] adequately characterized biologic response surfaces show almost always one single optimum. In this study, we assumed that that was the case. In spite of aforementioned improvements in the model, the study does not provide guarantee that the best combinations are really the best ones among all possible combinations. In this sense, the term *optimization* must be taken with caution. It indicates the process of sequentially improving the end point, rather than the assumption that the best combination has been identified with certainty.

By nature, this study cannot provide strong evidence that combinations of morphine with ketamine are superior to morphine alone. The usefulness of the combination is supported by strong pathophysiological and pharmacological data (see introduction), as well as by randomized clinical trials.[10,11] On the other hand, the recent publication of negative studies[12–14] questions the usefulness of adding ketamine to morphine for PCA. However, none of these studies used one of the combinations that were included in the final set of the current study. Because of the contradictory results of clinical research, there is still a place for additional randomized controlled trials comparing the combination with morphine alone. In this case, the current study provides indication on the combination that should be used as a comparison with morphine alone. In our opinion, the scientific based approach presented here should be preferred to the purely empiric criteria usually employed to select the combinations analyzed in randomized controlled trials.

As for all investigations conducted on a low number of patients, optimization studies cannot demonstrate the safety of a therapeutic regimen. Prospective observational

studies analyzing the morphine–ketamine combination on a large patient population are necessary to detect the incidence and severity of uncommon side effects.

The study supports combinations of morphine with ketamine in a ratio of 1:1 and a lockout interval of 8 min for postoperative PCA following spine and hip surgery. This second experience with a direct search method in clinical research confirmed its usefulness for improving therapeutic regimens. The method still needs further validation and can probably be improved.

The authors thank the staff of the Pharmacy, University Hospital of Bern, Bern, Switzerland, for their cooperation.

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 morphine concentration in the PCA solution, ketamine concentration, and lockout interval were optimized. In a previous study,[15] we utilized the direct search method by Berenbaum[16] 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, we developed and tested an improved direct search method, to which we will refer as method 2. This method does address the three major drawbacks of method 1 mentioned in the section "Discussion."

First, we recall the main steps of the algorithm of method 1. Second, we discuss the modifications that 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 in which method 1 was applied.[15] Method 2 was designed to improve the efficiency of the clinical investigation, since it aims at using the minimum number of patients that is required to reach the end point. For the sake of simplicity, we assume that morphine concentration in the PCA solution, ketamine concentration in the PCA solution, and lockout interval are the independent variables in both methods.

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 lockout time and morphine and ketamine concentrations in the PCA solution. Precisely, $ci = (m_i, k_i, l_i)$, where m_i, k_i, and l_i are, respectively, the morphine concentration, the ketamine concentration, and the lockout time investigated in that particular combination ($i = 1, \ldots, m$). Each combination is tested on n subjects. Let us denote as PS_{ij} 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:

$$PS_i = \sum_{j=1}^{n} \frac{PS_{ij}}{n} \tag{1}$$

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

$$PS_1 < PS_2 < \ldots < PS_m . \tag{2}$$

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

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

$$B = \sum_{m/2+1}^{m} \frac{c_i}{m/2} \tag{4}$$

For example, if the ketamine concentrations in the 4 "good" combinations are 0.7, 0.7, 1.0, and 0.8, G_k would be $(0.7 + 0.7 + 1.0 + 0.8)/4 = 0.8$. B_k is calculated for ketamine in the same fashion, by considering the ketamine concentrations of the 4 "bad" combinations. The same procedure is applied to morphine concentration and lockout interval.

The new combination N to be tested is obtained as

$$N = G + \alpha(G - B) \tag{5}$$

where α is constrained to be a positive number (see Discussion).

Equation 5 shows the basic principle of the direct search method. If the average ketamine concentration of the 4 "good" combinations is higher than the average ketamine concentration of the 4 "bad" combinations, the new combination of the optimization procedure will contain a higher ketamine concentration.

Method 2

Choosing m and n. By analyzing the data published in the previous study retrospectively,[15] we could conclude 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, clonidine, and infusion rate to minimize the pain score and the side effects. By using the data of the previous study to modify the search procedure of the current one, we implicitly assume that the interindividual variability among the subjects with regard to the drugs used in the two studies is 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 of 6–11. For every m, we assumed that n patients tried each combination with n in the range of 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 Partitioning the Complexes) and computed the new combination according to equation 5. The higher m and n, 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 end point. 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 4 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 improvements.

Based on these data, we included 6 patients per combination and 8 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, then also the ranking in equation 2 is random. We chose to partition the complexes

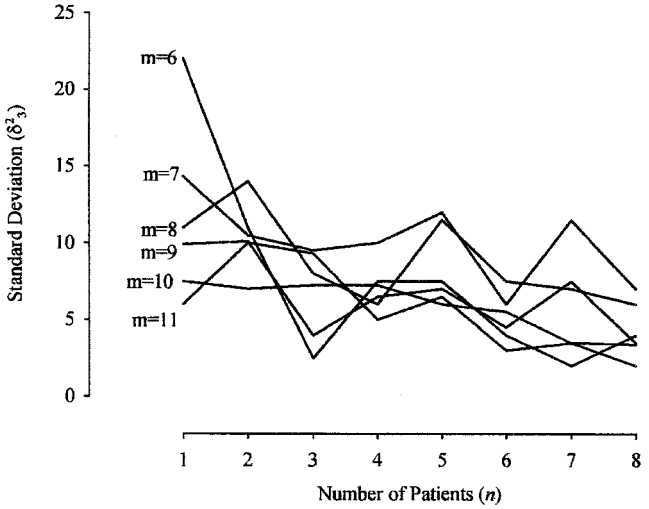

Fig. 4. Simulation procedure conducted on the data of the previous study[15] to find the optimal number of combinations per complex (m) and the optimal number of patients per combination (n) for the current study. Variability of the clonidine concentration in the new combination to be tested is shown. 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 number of combinations in the complex.

with the maximum likelihood that the highest pain score in group G was less than the lowest in group B.

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

$$PS_i = \sum_{h=0}^{k} \frac{h\, N_{ih}}{n} \tag{6}$$

where N_{ih} is the number of individuals with average pain score h receiving combination i. Note that PS_i as defined in equation 6 does coincide with PS_i defined in equation 1. We normalized the pain scores by constructing class intervals (table 7). Despite the scaling of the pain scores, we did not modify the indices in all equations of this appendix. Indeed, neither the mathematical treatise nor the decision process about optimization steps depends on the scale adopted for the pain scores.

Example: Average pain score of combination A (see table 7):

$$PS_A = (2 \times 0.2 + 1 \times 0.6 + 2 \times 1.0 + 0 \times 1.4 + 1 \times 1.8)/6 = 0.8$$

If N_{ih} is a random variable, then PS_i is also random. If the number of subjects investigated per combination n is constant, we could consider equivalently:

$$PS_{i,t} \triangleq nPS_i = \sum_{h=0}^{k} h\, N_{ih} \tag{7}$$

The distribution properties of $PS_{i,t}$ have not been published.[18] However, by defining as n_i the number of patients reporting an average pain score in the class i, the density of $PS_{i,t}$ can be given as

$$f(r) = P(PS_{i,t} = r) \sum_{(n_0, \ldots, n_k) \in S_h} = P(N_0 = n_0, \ldots, N_k = n_k)$$

$$\forall\ r = 1, \ldots, kn \tag{8}$$

where $P(N_0 = n_0, \ldots, N_k = n_k)$ denotes the probability that the number of patients falling into the first pain class N_0 is n_0, the number of patients falling into pain class N_1 is n_1, and so on.

The above formula allows us to calculate how probable it is that the total pain score $PS_{i,t}$ assumes the value h for every possible h. Since $PS_{i,t}$ is a discrete variable, this probability can be calculated by summing the probability of all possible distribution of patients across the pain score, such that $PS_{i,t}$ is equal to h. Mathematically, the set of such combinations can be expressed as

$$S_h = \left\{ (n_0, \ldots, n_k) s.t \sum_{j=0}^{k} j\, n_j = h \right\}. \tag{9}$$

To compute the probability in equation 8, we must know the probability π_j that a patient testing the combination will rate pain with a score j. To do this, we can use the maximum likelihood estimates:

$$\hat{\pi}_j = \frac{n_j}{n} \tag{10}$$

With the proposed approach, we can estimate the density directly from a given realization $\{n_0, \ldots, n_k\}$. Two examples are represented in figure 5.

After having ranked the combinations $\{c_1, c_2, \ldots, c_m\}$ according to their average pain score as in equation 2, let us define the two groups

$$G = \{c_1, c_2, \ldots, c_q\} \tag{11}$$

$$B = \{c_{q+1}, c_{q+2}, \ldots, c_m\} \tag{12}$$

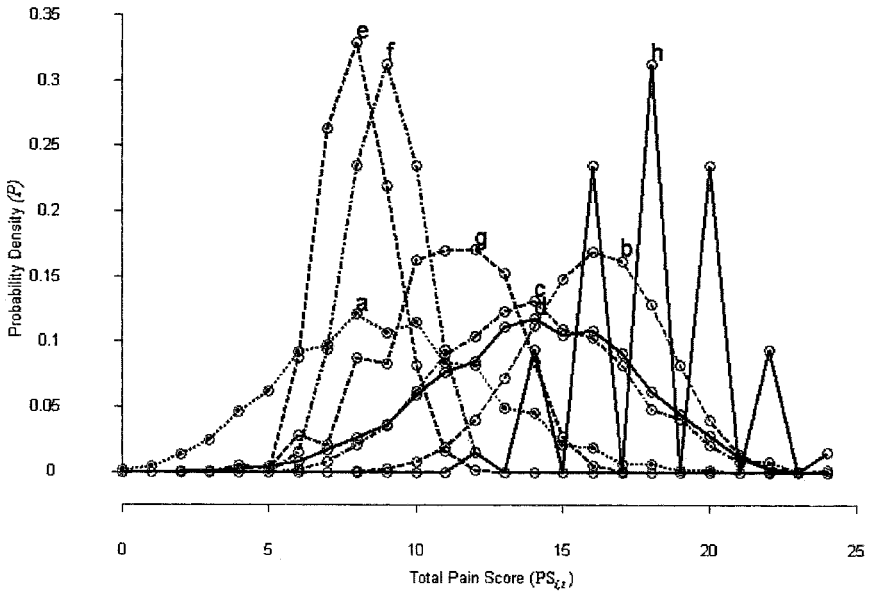

Fig. 5. Probability densities of $PS_{i,t}$ for the observation vectors of the initial complex. Vectors are defined with table 7, PS_A = (2,1,2,0,1), PS_B = (0,1,1,3,1), *etc.* The first place in the observation vector PS_i i represents the number of patients who rated the combination i with the first score, the second place represents the number of patients who rated the combination i with the second score, and so on. The cutting point for the partitioning of the complexes occurs at the point of the highest probability, between the combination F and G with *P* ($PS_F < PS_G = 0.73$).

Table 7. Distribution in Pain Classes, Average Pain Score, and Ranking of Initial Complex

	Distribution in Pain Classes, No. of Patients in Each Category						
Combination	I (0.2)	II (0.6)	III (1.0)	IV (1.4)	V (1.8)	Average Pain Score	Rank
A	2	1	2	0	1	0.80	2
B	0	1	1	3	1	1.27	7
C	0	2	2	0	2	1.13	6
D	1	1	0	3	1	1.13	5
E	0	4	2	0	0	0.73	1
F	0	3	3	0	0	0.80	3
G	1	0	4	1	0	0.93	4
H	6	0	0	3	0	1.40	8

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 0–0.4, 0.4–0.8, 0.8–1.2, 1.2–1.6, and 1.6–2.0. The new pain scores of the normalized classes are chosen as the midpoints of the new classes (values in brackets).

with the index q such that

$$P(PS_{q+1} > PS_q) = P(PS_{t,q+1} > PS_{t,q}) \quad (13)$$

is maximized. The above probability can be calculated as

$$P(PS_{t,q} - PS_{t,q+1} < 0) = \sum_{s=-(k-1)n}^{-1} \sum_{r=0}^{(k-1)n} f_q(s + r)\, f_{q+1}(r)\,. \quad (14)$$

Let us calculate, as an example, the partitioning resulting from the first set of initial combinations. Table 7 reports the number of patients falling into the pain classes I–V for the combinations A, . . . , H, the average pain score, and the ranking for each combination. The following ranking holds for the combinations A–H:

$$PS_E < PS_A < PS_F < PS_G < PS_D < PS_C < PS_B < PS_H \quad (15)$$

We computed the probability of each pair of subsequent inequalities ($PS_E < PS_A$, $PS_A < PS_F$, $PS_F < PS_G$, $PS_G < PS_D$, $PS_D < PS_C$, $PS_C < PS_B$, $PS_B < PS_H$) in equation 15 according to equation 14, and we chose the highest probability as the cutting point for the partitioning of the complexes. The highest probability occurs between the combination F and G with P ($PS_F < PS_G = 0.73$; fig. 5).

Computing the New Combination. Given the two clusters, the centroids G and B are computed separately for every variable with equations 11 and 12.

Example for calculating the centroids for ketamine:

$$G_{Ke} = (Ke_E + Ke_A + Ke_F)/3 = (0.7 + 0.7 + 1.0)/3 = 0.8$$

$$B_{Ke} = (Ke_G + Ke_D + Ke_C + Ke_B + Ke_H)/5 = (0.8 + 0.6 + 0.4 + 0.6 + 1.0)/5 = 0.68$$

We computed the new combination N with equation 5.

Example for calculating the new ketamine concentration:

$$N_{Ke} = G_{Ke} + \alpha(G_{Ke} - B_{Ke}) = 0.8 + 1.3(0.8 - 0.68) = 0.96$$

The rules presented in table 3 were followed. No combination violated the toxicity constraint (*i.e.*, unacceptable incidence of side effects). Therefore, it was not necessary to apply the regression model proposed by Berenbaum[16] to perform a step back from the toxicity into the therapeutic response surface.

References

1. Tsui SL, Irwin MG, Wong CM, Fung SK, Hui TW, Ng KF, Chan WS, O'Reagan AM: An audit of the safety of an acute pain service. Anaesthesia 1997; 52:1042–7
2. Vinik HR, Kissin I: Rapid development of tolerance to analgesia during remifentanil infusion in humans. Anesth Analg 1998; 86:1307–11
3. Dickenson AH, Sullivan AF: Evidence for a role of the NMDA receptor in the frequency dependent potentiation of deep rat dorsal horn nociceptive neurones following C fibre stimulation. Neuropharmacology 1987; 26:1235–8
4. Mao J: NMDA and opioid receptors: Their interactions in antinociception, tolerance and neuroplasticity. Brain Res Brain Res Rev 1999; 30:289–304
5. Price DD, Mayer DJ, Mao J, Caruso FS: NMDA-receptor antagonists and opioid receptor interactions as related to analgesia and tolerance. J Pain Symptom Manage 2000; 19:S7–11
6. Dickenson AH: Central acute pain mechanisms. Ann Med 1995; 27:223–7
7. Celerier E, Rivat C, Jun Y, Laulin JP, Larcher A, Reynier P, Simonnet G: Long-lasting hyperalgesia induced by fentanyl in rats: Preventive effect of ketamine. ANESTHESIOLOGY 2000; 92:465–72
8. Houghton AK, Parsons CG, Headley PM: Mrz 2/579, a fast kinetic NMDA channel blocker, reduces the development of morphine tolerance in awake rats. Pain 2001; 91:201–7
9. Shimoyama N, Shimoyama M, Inturrisi CE, Elliott KJ: Ketamine attenuates and reverses morphine tolerance in rodents. ANESTHESIOLOGY 1996; 85:1357–66
10. Adriaenssens G, Vermeyen KM, Hoffmann VL, Mertens E, Adriaensen HF: Postoperative analgesia with i.v. patient-controlled morphine: Effect of adding ketamine. Br J Anaesth 1999; 83:393–6
11. Javery KB, Ussery TW, Steger HG, Colclough GW: Comparison of morphine and morphine with ketamine for postoperative analgesia. Can J Anaesth 1996; 43:212–5
12. Burstal R, Danjoux G, Hayes C, Lantry G: PCA ketamine and morphine after abdominal hysterectomy. Anaesth Intensive Care 2001; 29:246–51
13. Reeves M, Lindholm DE, Myles PS, Fletcher H, Hunt JO: Adding ketamine to morphine for patient-controlled analgesia after major abdominal surgery: A double-blinded, randomized controlled trial. Anesth Analg 2001; 93:116–20
14. Murdoch CJ, Crooks BA, Miller CD: Effect of the addition of ketamine to morphine in patient-controlled analgesia. Anaesthesia 2002; 57:484–8
15. Curatolo M, Schnider T, Petersen-Felix S, Weiss S, Signer C, Scaramozzino P, Zbinden A: A direct search procedure to optimize combinations of epidural bupivacaine, fentanyl, and clonidine for postoperative analgesia. ANESTHESIOLOGY 2000; 92:325–37
16. Berenbaum MC: Direct search methods in the optimisation of cancer chemotherapy regimens. Br J Cancer 1990; 61:101–9
17. Fisher DM: The direct search procedure: A new approach to evaluating clinical regimens. ANESTHESIOLOGY 2000; 92:301–3
18. Johnson N, Kotz S, Balakrishnan N: Discrete Multivariate Distributions, 1997 edition. New York, Wiley Interscience, 1997
19. Berenbaum MC: What is synergy? Pharmacol Rev 1989; 41:93–141