Anesthesiology
1996; 85:11–20

Preemptive Analgesia: Intraperitoneal Local Anesthetic in Laparoscopic Cholecystectomy

A Randomized, Double-blind, Placebo-controlled Study

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Background: **A controversy exists over the effectiveness and clinical value of preemptive analgesia. Additional studies are needed to define the optimum intensity, duration, and timing of analgesia relative to incision and surgery.**

Methods: **One hundred twenty patients undergoing laparoscopic cholecystectomy under general anesthesia plus topical peritoneal local anesthetic or saline were studied. Local anesthetic (0.5% bupivacaine with epinephrine) or placebo solutions were given as follows: immediately after the creation of a pneumoperitoneum (blocking before surgery), and at the end of the operation (blocking after surgery). Patients were randomly assigned to one of four groups of 30 patients each. Group A (placebo) received 20 ml 0.9% saline both before and after surgery, group B received 20 ml 0.9% saline before surgery and 20 ml local anesthetic after surgery, group C received 20 ml local anesthetic both before and after surgery, group P received 20 ml local anesthetic before and 20 ml 0.9% saline after surgery. Pain was assessed using a visual analog scale and a verbal rating scale at 0, 4, 8, 12, and 24 h after surgery. Metabolic endocrine responses (blood glucose and cortisol concentrations) and analgesic requirements also were investigated.**

Results: **Pain intensity (visual analog and verbal rating scales) and analgesic requirements were significantly less in the group receiving bupivacaine after surgery compared to placebo. However, in the groups receiving bupivacaine before surgery, both pain intensity and analgesic consumption were less than in the group receiving bupivacaine only after surgery. Blood glucose and cortisol concentrations 3 h after surgery were significantly less in groups receiving bupivacaine before surgery.**

Conclusions: **The results indicate that intraperitoneal local anesthetic blockade administered before or after surgery preempts postoperative pain relative to an untreated placebo-control condition. However, the timing of administration is also important in that postoperative pain intensity and analgesic consumption are both lower among patients treated with local anesthetic before *versus* after surgery. (Key words: Analgesia: preemptive. Anesthetics, intraperitoneal: bupivacaine. Anesthetics, local: bupivacaine. Pain: postoperative. Surgery, laparoscopic: cholecystectomy.)**

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Received from the Department of Anesthesiology, University of Udine, Udine, Italy. Submitted for publication June 19, 1995. Accepted for publication February 29, 1996.

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RECENT advances in the pathophysiology of pain[1–3] have led to the theory that it may be possible to prevent or reduce the central neural hyperexcitability that contributes to enhanced postoperative pain.

Experimental studies have demonstrated postinjury neuroplasticity and windup or expansion of receptive fields of central nervous system neurons, which may lead to pain hypersensitivity.[3–8]

Other studies conducted using animals have demonstrated that an afferent block with local anesthetics performed "before nociceptive stimuli are triggered" can modify the behavioral response and neuronal sensitization of posterior horn neurons.[5,9–10]

Nevertheless, none of these study models can be applied fully or have a concrete clinical application as far as studying postoperative pain in humans is concerned.

Through research conducted on healthy volunteers and on surgery patients, several authors have tended to demonstrate a lower threshold of pain in surgery patients. Moreover, they have found that an afferent block (with local anesthetics) achieved before nociceptive input can reduce or eliminate the onset of hyperexcitability of the posterior horn neurons and can thus significantly reduce both intensity and duration of pain, while also delaying its onset.[11–14]

Other authors, however, fail to show any decrease in threshold of sensitivity to pain in surgery patients[15] or that postoperative pain can be reduced or eliminated through afferent blocks before surgical stimulation,[16–17] or that the implementation of a block *versus* a placebo can reduce postoperative pain or the number of requests for analgesics.[18–21]

The results of these and other studies on preemptive analgesia, as well as those from studies carried out with preventive administration of opioids and nonsteroidal antiinflammatory drugs, were the subject of extensive critical reviews by Dahl and Kehlet,[22] Coderre, *et al.*,[4] Kehlet,[23] and McQuay.[24] These authors agree that conclusive evidence has not yet demonstrated the clinical value of preemptive analgesia. The lack of appropriate methods in most of the published works (lack of control groups, randomization, assessment of postoperative pain intensity, and analgesic requirements) is mainly responsible for the paucity of reliable data.

In short, these authors point out that:

1. Only a few studies that carried out the same nerve blocks before *versus* after surgery, found significant differences in postoperative pain and in the request for analgesia or analgesic consumption.[4,22–24]
2. The studies conducted to compare the effects of anesthetic blockade administered before surgery *versus* a no-treatment control condition show a reduction in central hyperexcitability, but they do not address the issue of whether the timing of administration relative to incision is related to postoperative pain intensity.[22–24]
3. There are differences between the types of nociceptive stimuli caused by well-localized, experimentally induced lesions and the prolonged and mixed extensive input that follows surgery. It was also observed that central sensitization may develop postoperatively as the central effects of the block wane.[4,15–17]
4. Only a complete blockade of the noxious afferent inputs would be expected to prevent central sensitization and thus reduce postoperative pain intensity[4,22–23]; this would account for the negative results obtained in some studies.

The picture is further complicated by the inclusion of patients undergoing major surgery, because complete afferent blockade is highly unlikely to occur.

Further clinical studies are clearly needed to determine not only the implementation, but also the optimum timing and duration of the analgesia necessary to prevent alterations in the posterior horn following more serious tissue lesions than the ones induced in experimental research.

The purpose of this study was to detect any differences in pain intensity, in the request for postoperative analgesia, and in endocrine metabolic response between patients treated with a peritoneal topical anesthesia using local anesthetic and patients who received no treatment. In addition, we have investigated whether changing the timing in which the local anesthesia is administered (before or after surgery) would yield a different response and if prolonging administration of the anesthetic affects this response.

Patients and Methods

We carried out a double-blind, randomized, placebo-controlled prospective study of 120 patients from January 1993 to August 1994.

Patients (ASA physical status 1 or 2) undergoing elective laparoscopic cholecystectomy under general anesthesia plus topical peritoneal local anesthetic or saline were studied after obtaining approval by the ethics committee and informed consent from the participants.

Patients allergic to local anesthetics, as well as those with a history of severe pulmonary and hormonal disease, were excluded from the study.

None of the patients had acute cholecystitis.

All surgeries were carried out by one team of surgeons.

Patients were assigned to four groups by simple randomization (30 patients per group). Group A (placebo) received 20 ml 0.9% saline during both before and after surgery, group B received 20 ml 0.9% saline before surgery and 20 ml 0.5% bupivacaine with epinephrine 1:200,000 after surgery, group C received 20 ml 0.5% bupivacaine with epinephrine 1:200,000 before and after surgery, group P received 20 ml of 0.5% bupivacaine with epinephrine 1:200,000 before surgery and 20 ml 0.9% saline after surgery.

General Anesthesia

All patients received 10 mg o
azepam approximately 1 h befor
the operating room.

All operations started between
Anesthesia was induced with 4
thiopental, 0.1 mg/kg intraven
mide, and 15 mg/kg intravenous
intubation, general anesthesia
0.6–1% isoflurane (end-tidal co
nitrous oxide with oxygen. Ad
ronium bromide were administe
relaxation. Ventilation (tidal vol
adjusted to maintain end-tidal c
34 and 40 mmHg.

Patients were placed in 15–2

During surgery, all patients r
infusion of lactated Ringers so
ml·kg^{-1}·h^{-1} and 1–2 ml·kg
sequent 24-h period.

Peritoneal Topical Anesthes

Local anesthetics or placebo
follows: immediately after the
peritoneum and 10 min befor
gery, the surgeon sprayed the
on the upper surface of the liv
diaphragmatic space to allow
patodiaphragmatic space near
duodenal ligament and above t
done using a catheter inserted
under direct laparoscopic co
operation, before the trocars w
geon sprayed an additional 20
same area as the first solution ar
area.

The surgeon was not informe
solution (placebo or anesthet

Postoperative Managemen

Before induction of anesth
given instructions about the
visual analog scale (VAS; with
pain" and "worst possible pai
"Prince Henry" pain scale (VP
(score = 0); pain on coughing
ing (score = 1); pain on deep
(score = 2); pain at rest, slig
rest, severe (score = 4)[25–26].

General Anesthesia

All patients received 10 mg orally administered diazepam approximately 1 h before being transferred to the operating room.

All operations started between 08:30 and 11:30 AM.

Anesthesia was induced with 4–5 mg/kg intravenous thiopental, 0.1 mg/kg intravenous vecuronium bromide, and 15 mg/kg intravenous fentanyl. After tracheal intubation, general anesthesia was maintained with 0.6–1% isoflurane (end-tidal concentration) and 50% nitrous oxide with oxygen. Additional doses of vecuronium bromide were administered to maintain surgical relaxation. Ventilation (tidal volume, 8–10 ml/kg) was adjusted to maintain end-tidal carbon dioxide between 34 and 40 mmHg.

Patients were placed in 15–20° head-up position.

During surgery, all patients received an intravenous infusion of lactated Ringers solution at a rate of 5–7 $ml \cdot kg^{-1} \cdot h^{-1}$ and 1–2 $ml \cdot kg^{-1} \cdot h^{-1}$ during the subsequent 24-h period.

Peritoneal Topical Anesthesia

Local anesthetics or placebo solutions were given as follows: immediately after the creation of a pneumoperitoneum and 10 min before the beginning of surgery, the surgeon sprayed the first 20 ml of solution on the upper surface of the liver and on the right subdiaphragmatic space to allow it to diffuse into the hepatodiaphragmatic space, near and above the hepatoduodenal ligament and above the gallbladder. This was done using a catheter inserted into the subcostal trocar under direct laparoscopic control. At the end of the operation, before the trocars were withdrawn, the surgeon sprayed an additional 20 ml of solution onto the same area as the first solution and into the deperitonized area.

The surgeon was not informed of the contents of the solution (placebo or anesthetic).

Postoperative Management

Before induction of anesthesia, the patients were given instructions about the use of a 10-cm vertical visual analog scale (VAS; with endpoints labeled "no pain" and "worst possible pain") and the verbal rating "Prince Henry" pain scale (VRS): no pain on coughing (score = 0); pain on coughing but not on deep breathing (score = 1); pain on deep breathing but not at rest (score = 2); pain at rest, slight (score = 3); pain at rest, severe (score = 4)[25–26].

The patients were informed before surgery that they could request an analgesic if pain should set in. For postoperative analgesia, patients received 30 mg intravenous ketorolac when they reported pain, followed by additional doses if requested by the patient. This study envisioned that the patient could be eliminated from the protocol and be administered opioids if he indicated that he was not satisfied with the level of analgesia that was reached.

Patients also were immediately given 20 mg intravenous metoclopramide if they experienced nausea or vomiting.

The degree of postoperative pain was assessed using VAS (spontaneous pain) and VRS (induced pain) scores on arrival at the recovery room (immediately after surgery = 0 h) and at 4-, 8-, 12-, and 24-h intervals after surgery.

Moreover, at the same intervals after surgery, the assessment included consumption of analgesics, monitoring of systolic and diastolic blood pressure, heart rate, respiratory rate, and the presence of nausea, vomiting, and sweating.

Data collection was carried out by a physician who was unaware of the contents of the solution received intraoperatively.

Blood samples were obtained 1 h before and 180 min after surgery to determine plasma glucose and cortisol concentrations.

Plasma glucose concentrations were analyzed with a routine glucose dehydrogenase method (NaDH dependent, Hitachi 717, Germany).

Cortisol concentrations were measured using a commercially available radioimmunoassay method (Coat-a-count Cortisol, Diagnostic Products, Los Angeles, CA). The sensitivity of the assay was 10 $ng \cdot ml^{-1}$ (data are expressed in $\mu M/l$).

Statistical Analysis. Analysis of variance and χ^2 tests were used to check that the four experimental groups were matched in terms of demographic and preoperative clinical variables. The χ^2 test and Fisher's exact test (for variables in which there was low frequency in at least one cell), were used to compare the presence or absence of vomiting, nausea, and sweating, and to compare the use or nonuse of other drugs.

For some of the relevant variables (heart rate, respiratory rate, and analgesic consumption) we performed a repeated-measures analysis of variance to test the time effects, whereas Scheffe's two-tailed t test was conducted to check any significant differences among treatments. For other variables, we performed the

Kruskal-Wallis test followed by the Wilcoxon matched-pairs signed rank test (VAS, VRS). To measure the strength of the linear relationship between the variables, we used Spearman coefficients and relative significance probability of the correlation, under the null hypothesis that the statistic is equivalent to zero. Visual analog scale and VRS are expressed as median and range, whereas all the other parameters are expressed in mean ± SD. All *P* values refer to two-tailed tests (*P* values < 0.05 were considered significant).

Results

Demographic data (age, weight, sex), ASA physical status, duration of surgery, and preoperative heart rate and respiratory rate values, plasma glucose and cortisol concentrations were similar in the four groups (table 1).

Eleven patients (3 in group A, 2 in group B, 2 in group C, and 4 in group P) were excluded from the study: one had been given a 5% glucose solution intravenously after the first hour of surgery, three had received opioid analgesics (the administration of a 5% glucose solution and opioid analgesics occurred through a physician's error in interpreting the protocol), two had intraoperative complications (the laparoscopic cholecystectomy had to be converted to open cholecystectomy), and in five patients the data were not fully investigated (for three of them, there were no data at the 12th h of observation, two did not have the VRS or checks done on nausea, vomiting, and sweating).

None of the patients required opioid analgesics.

No side effects were recorded in our patients.

Postoperative Pain Scores

A comparison among groups showed that the VAS (median and range) pain score value in group B (local anesthetic given after surgery) declined significantly when compared to group A (placebo) at the 8th, 12th, and 24th hours. Group C (local anesthetic before and after surgery) experienced less pain in comparison with group A and group B at all five time points and in comparison with group P (local anesthetic before surgery) on arrival at the recovery room and 4 h after. Group P showed a lower pain intensity compared to group A at 4, 8, 12, and 24 h, and compared to group B at 8, 12, and 24 h (fig. 1 and table 2).

Group C (local anesthetic given before and after surgery), VRS (median and range) was significantly lower than in groups A (placebo) and B (local anesthetic after surgery) at all five points in time and was significantly lower than group P (local anesthetic before surgery) on arrival at the recovery room. Postoperative pain in group P was significantly lower than in group A and group B at 4, 8, 12, and 24 h after surgery. In addition, VRS in group B was lower than in group A at 4, 8, and 24 h (fig. 2 and table 2).

Analgesic Consumption

Patients in groups A, B, C, and P received a mean dose of 110 ± 50 mg, 61 ± 36 mg, 24 ± 24 mg, and 29 ± 18 mg of ketorolac, respectively, during the 24 h after surgery.

Group A (placebo) received a statistically larger dose of analgesics than groups B, C, and P, whereas that requested by group B (local anesthetic after surgery) is significantly higher than that given to groups C and P. There are no significant differences between patients

Table 1. Patient Characteristics and Clinical Variables

	Group A (n = 27)	Group B (n = 28)	Group C (n = 28)	Group P (n = 26)
Sex				
Male	13	11	12	12
Female	14	17	16	14
Age (yr)	46.3 ± 14.6	41.4 ± 10.8	50.6 ± 12.1	48.5 ± 14.3
Weight (kg)	70.3 ± 14.7	74.1 ± 11.5	69.3 ± 11.6	70.3 ± 10.3
Preoperative heart rate (beats/min)	74 ± 4.6	73 ± 6.5	74 ± 4.7	73 ± 5.2
Preoperative respiratory rate (breaths/min)	18 ± 3.2	19 ± 1.6	18 ± 2.7	18 ± 2.8
Duration of surgery (min)	125 ± 36	140 ± 37	142 ± 44	125 ± 27
Preoperative plasma glucose (mg/dl)	91 ± 7.9	94 ± 9.3	90 ± 9.4	94 ± 11.8
Preoperative plasma cortisol (μmol/L)	0.669 ± 0.13	0.633 ± 0.20	0.673 ± 0.12	0.621 ± 0.10

Age, weight, heart rate, respiratory rate, duration of surgery, glucose, and cortisol are expressed as mean ± SD.

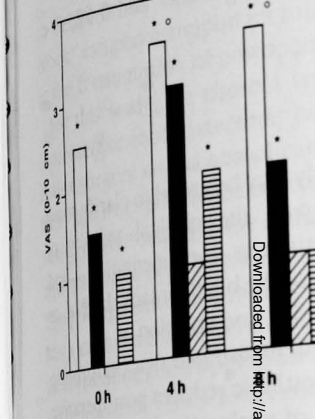

Fig. 1. Visual analog scale (median) was significantly lower in group C (*P < 0.001); no differences were groups. At 4 h, values for group than for groups A, B, and P (*P < 0 P were lower than for group A (* h, values for groups C and P were < 0.001); group A recorded higher Statistical analysis: Kruskal-Wallis test.

with local anesthetic before s anesthetic before and after su

Stress Response Data

Preoperative plasma glucose tions were similar in all groups produced statistically signific glucose and cortisol concentr compared with baseline level

In group C (local anesthetic postoperative glucose (107 cantly lower than in group A dl) and group B (local anesth 29 mg/dl).

The difference between po ative values of glucose was sig C as compared to group A.

Postoperative plasma corti significantly lower in groups P (local anesthetic after surg than in group placebo (1.27 ence between postoperative of plasma cortisol was signi compared to A and B (1.14 significantly different betwee

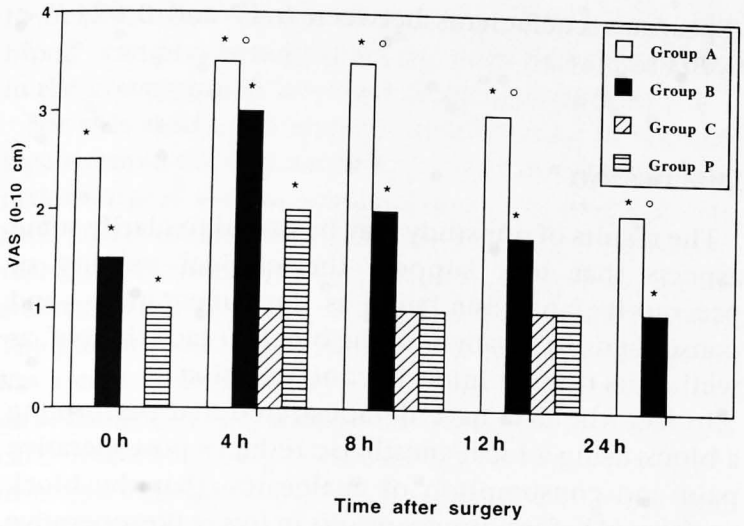

Fig. 1. Visual analog scale (median). At 0 h, visual analog scale was significantly lower in group C than in groups A, B, and P, (*$P < 0.001$); no differences were detected among the other groups. At 4 h, values for group C were significantly lower than for groups A, B, and P (*$P < 0.015$), and values for group P were lower than for group A (°$P < 0.001$). At 8, 12, and 24 h, values for groups C and P were lower than for A and B, (*$P < 0.001$); group A recorded higher values than B (°$P < 0.01$). Statistical analysis: Kruskal-Wallis test and Wilcoxon rank-sum test.

with local anesthetic before surgery (P) *versus* local anesthetic before and after surgery (C; fig. 3).

Stress Response Data

Preoperative plasma glucose and cortisol concentrations were similar in all groups (table 1). All treatments produced statistically significant increases in plasma glucose and cortisol concentrations after surgery when compared with baseline levels.

In group C (local anesthetic before and after surgery), postoperative glucose (107 ± 16 mg/dl) was significantly lower than in group A (placebo; 126 ± 17 mg/dl) and group B (local anesthetic after surgery; 126 ± 29 mg/dl).

The difference between postoperative and preoperative values of glucose was significantly lower in group C as compared to group A.

Postoperative plasma cortisol concentrations were significantly lower in groups C (0.94 ± 0.32 μM/l) and P (local anesthetic after surgery; 0.98 ± 0.24 μM/l) than in group placebo (1.27 ± 0.32 μM/l). The difference between postoperative and preoperative values of plasma cortisol was significantly less in group C compared to A and B (1.14 ± 0.29 μM/l). It also was significantly different between groups P and A.

Arterial Blood Pressure, Heart Rate, and Respiratory Rate

Differences in values of systolic and diastolic arterial pressures both among and within the groups did not correlate with any other variable, nor were they clinically significant. Heart rate in the postoperative period was significantly lower in group P than in group A at 4, 8, 12, and 24 h, and group B at 0, 4, and 12 h after surgery. Heart rate was lower in group C than in group A at 4, 8, and 12 h and in group B at 0 h.

Respiratory rate was significantly higher in group A than in group B at 0, 4, 8, and 24 h. Respiratory rate was higher in group A than in group C at all five time points and was higher in group A than in group P at 4,

Table 2. Median and Range of Visual Analog Scale (VAS) and Verbal Rating "Prince Henry" Pain Scale (VRS) Pain Scores at Each Time Point after Surgery

	Group A (n = 27)	Group B (n = 28)	Group C (n = 28)	Group P (n = 26)
VAS				
0 h				
Median	2.5	1.5	0	1
Range	0–7.5	0–7	0–2	0–7
4 h				
Median	3.5	3	1	2
Range	0.5–7	0–5	0–4	0–6
8 h				
Median	3.5	2	1	1
Range	1–7	0–5	0–3	0–6
12 h				
Median	3	1.75	1	1
Range	0–6	0–6	0–4	0–4
24 h				
Median	2	1	0	0
Range	0–3.4	0–4	0–2	0–5
VRS				
0 h				
Median	2	1.5	0	1
Range	0–4	0–4	0–2	0–4
4 h				
Median	3	2	1	1
Range	1–4	1–4	0–3	0–2
8 h				
Median	3	2	1	1
Range	1–4	1–4	0–3	0–4
12 h				
Median	2	2	0	1
Range	1–4	1–4	0–2	0–2
24 h				
Median	2	1	0	0
Range	0–2	0–3	0–2	0–2

0 h = on arrival in the recovery room; 4, 8, 12, 24 h after surgery.

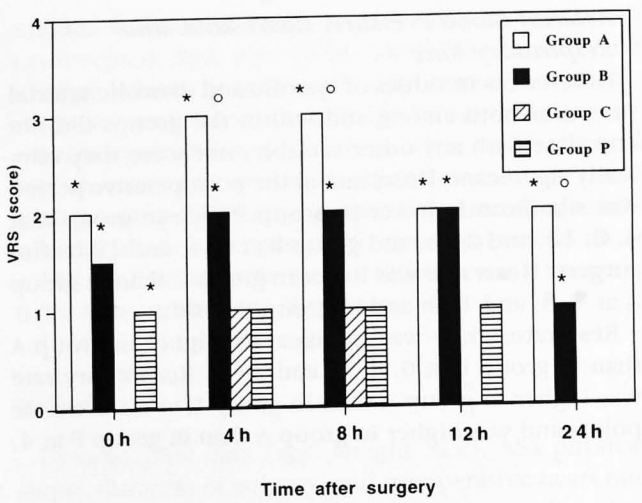

Fig. 2. Verbal rating scale (median). At 0 h, verbal rating scale in group C showed significantly lower values than in groups A, B, and P (*$P < 0.001$). At 4, 8, and 24 h, values for groups C and P were lower than for groups A and B (*$P < 0.01$) and values for group B were lower than for group A (°$P < 0.02$). At 12 h, values for groups C and P were lower than for groups A and B (*$P < 0.05$). Statistical analysis: Kruskal-Wallis test and Wilcoxon rank-sum test.

8, and 12 h. Group B differed significantly from group C at 8 and 12 h.

Nausea, Vomiting, and Sweating

Nausea was experienced by 11 patients in the placebo group (5 with vomiting), 10 in the group with local anesthetic after surgery (6 with vomiting), only 2 in group C (without vomiting), and 5 in group P (2 with vomiting). They all required metoclopramide. Sweating was observed in six patients in group placebo and in four patients in group B. One group C patient and one group P patient experienced sweating.

Parameter Correlations

We found significant positive correlations between specific parameters at each point in time in all groups. In particular, VAS and VRS pain scores were always correlated (Spearman coefficients ranged between 0.56 and 0.99, $P < 0.003$).

Glucose and plasma cortisol (at 180 min, after surgery) are correlated with VAS and VRS at 4 h after surgery (Spearman coefficients between 0.37 and 0.45, $P < 0.0001$).

We also found positive correlations among pain scores (VAS and VRS), heart rate, and respiratory rate (Spearman coefficients between 0.47 and 0.62, $P < 0.001$).

Discussion

The results of our study may be useful to clarify some aspects that may support the clinical validity of preemptive analgesia, such as implementation—and consequently efficacy—of the block or lack thereof, as well as its timing, intensity, and duration.

In fact, the data have demonstrated that performing a block using a local anesthetic reduces postoperative pain and consumption of analgesics, that the block performed before surgery results in lower postoperative pain intensity and reduces postoperative analgesic requirements when compared with a block performed after surgery. Lastly, although neither the clinical nor the statistical data were significant, several signs led us

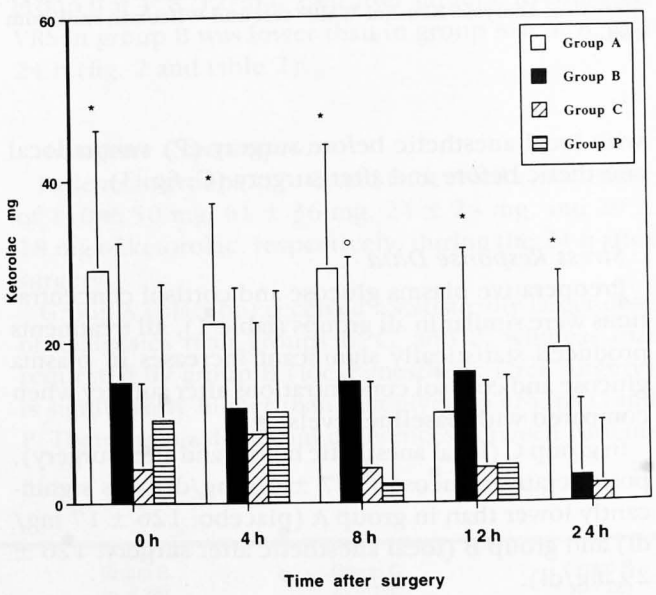

Fig. 3. Mean dose of ketorolac (mean ± SD). At 0 and 24 h, the mean dosage of ketorolac taken by group A was higher than the dosage taken by groups B, C, and P (*$P < 0.05$). There was no difference in dosage among the other groups. At 4 h, the dosage for group A was higher than for group C (*$P < 0.05$). There was no difference in dosage among the other groups. At 8 h, group A took a higher dosage than groups B, C, and P (*$P < 0.05$), consumption in group B was higher than in groups C and P (°$P < 0.05$). There was no difference in consumption between groups C and P. At 12 h, consumption for group B was higher than for groups C and P (*$P < 0.05$). There was no difference in consumption among the other groups. Analysis of variance for each time point was carried out using Sheffe's test.

to believe that "duration or time summation of the block" can play an important role in reducing pain and in the consumption of postoperative analgesics.

For this study, we chose a type of surgery such as laparoscopic cholecystectomy because we thought that major surgery would complicate our study model. In fact, laparoscopic cholecystectomy is not a highly invasive operation and tissue damage, performance time, and technique do not vary significantly among patients. The postoperative pain induced by this type of surgery has a considerable visceral component (owing to surgical handling and diaphragmatic irritation by dissolved carbon dioxide) and a lesser component that is somatic in origin (owing to the holes made in the abdominal wall for the trocars). In addition, at times the visceral component is such that it results in shoulder pain in one third of the patients, similar in location and type to the pain that occurs with biliary colic.[11,27–30] In any case, it can be noted from many studies[11,19,28,31] that this type of surgery provokes a pain that is less intense and shorter in duration and this has led us to use two pain scales (VAS and VRS) that are well-suited to a clinical evaluation of both the spontaneous pain as well as the induced pain typical of the period after this type of surgery.[11,18–19,23]

In our choice of analgesic technique as well, we attempted to simplify the study model as much as possible by using topical peritoneal local anesthesia. Indeed, the experience of many authors[11,30,32–33] has shown that this method of administering local anesthetic is effective in controlling postoperative pain. Furthermore, not only it is a noninvasive technique that presents minimal risks but it is also easy to administer. Instead, the choice of the dose of local anesthetic was made on the basis of several considerations: (1) given the size of the area involved in surgery, a volume of 20 ml was the minimum quantity required for coverage on all levels; this volume does not go against the data listed by other authors, who in some cases have used even larger volumes[11,19,31]; (2) the 0.5% concentration of the local anesthetic was chosen after a comparison of the experience listed in the literature.[11,32] Moreover, while we did not measure the plasma concentrations of the local anesthetic used, we believe our concentrations are not toxic. This consideration is also supported by this and previous clinical experience[11] (no signs of side effects were recorded), as well as by the concentrations recorded by other authors who carried out a direct measurement of local anesthetic or similar (administration in different anatomical areas that nevertheless have comparable absorption characteristics).[31–32,34–35]

This model has shown itself to be effective with regard to the first two points of this work (implementation of the block or lack thereof and its timing). Instead, as far as the third point is concerned (effect of prolonging the block), our model gave us only general indications, probably because of the reduced intensity and duration of postoperative pain. We should point out that within 24 h of the surgery, this pain and analgesic consumption was clinically significant but starting at 24 h they lost both clinical and statistical significance.

A comparison of VAS, VRS, and consumption of analgesics among patients of group A (placebo), group B (local anesthetic given after surgery), group C (local anesthetic given before and after surgery), and group P (local anesthetic given before surgery), shows that performing an anesthetic block, whether before or after surgery, results in a significant reduction in pain and in the need for postoperative analgesics.

This difference also can be detected, although to a lesser extent, in group B, which, according to the initial hypothesis, should be the group farthest from optimum treatment, both in terms of time of implementation and duration of the block.

Unlike other studies based on similar methods,[18,31] we noted a decrease in pain and the consumption of analgesics. This difference may be due to our performing a complete block of afferents using higher concentrations and volumes of local anesthetic than what these authors have done.

VAS, VRS, and consumption of analgesics also differ from the values recorded by other authors.[31,36] This difference may be due to the fact that these authors have invalidated their results by enrolling patients with acute cholecystitis or appendicitis in their studies. In fact, in agreement with some authors,[13,37–38] it is possible that in these cases the presence of an inflammation caused by the acute disease may in itself trigger a neuronal sensitization. Consequently, the antiinflammatory effect of the local anesthetic on the peripheral nociceptors responsible for triggering the primary hyperalgesia, also would be compromised.

The hypothesis that the early block of the nociceptive input performed with local anesthetic is more effective seems to be supported by the comparison of results between group with local anesthetic before surgery (P) and the group with local anesthetic after surgery (B).

In fact, VAS and VRS values and the consumption of analgesics in group P are significantly lower than in group B.

It is interesting to note that VAS and VRS values as well as the consumption of analgesics in group P, which received the local anesthetic about 2¼ h before group B, match the values of the latter only at 0 h after surgery (awakening), whereas 4 h after surgery a difference in the values recorded in the two groups can be detected (significantly lower VRS at 4 h after surgery and lower VAS and analgesic consumption values, which, however, were not significant). A statistically significant difference for all the parameters was recorded starting from the 8th hour up to the end of the control. We may therefore assume that the finding that the data of groups P and B initially match may be caused by the action of the local anesthetic, which in group B would appear to have a simple pain relief effect for 6 or 7 h,[35,39] while in group P it would also appear to cause a reduction in central hyperexcitability on top of the previously mentioned effect, as a function of the administration time of the local anesthetic, with an inhibition or a significant reduction of visceral pain before its onset.

Therefore, these data would appear to confirm that the optimum timing to reduce neuronal sensitization of the posterior horn is before nociceptive stimulation.

The validity of the results obtained may be partly due to the type of antalgic methods used (topical or local anesthesia).[11,13] In fact, it cannot be excluded that the use of these blocks triggers other mechanisms besides the modulation of central hyperexcitability (which pertains to the central blocks), that can relieve postoperative pain. Local anesthetic may well have an antiinflammatory effect on peripheral nociceptors, which would relieve primary hyperalgesia.

Regarding the effectiveness that prolonging the block may have on postoperative pain, an analysis of the data obtained using this study model has allowed us to glean only some general indications. In fact, although the patients in group C (local anesthetic before and after surgery) have referred VAS, VRS and analgesic consumption values that are significantly lower with respect to the values obtained for the group treated after surgery (group B), group C did not demonstrate any statistically significant differences when compared with group P (with the exception of VAS at 0 and 4 h, and VRS at 0 h after surgery) that would allow us to state with any certainty that prolonging the preemptive block is any more effective than the simple preemptive block in itself. This lack of significance, which does not agree with the results of other authors,[14] could nevertheless be due to the type of surgery we used. In fact, the intensity ranges and duration of pain provoked by this type of surgery after preemptive treatment may not be quantitatively sufficient to bring out any significant differences between the two groups (P and C) receiving the antalgic treatments that most closely approach the one that is assumed to be "optimum." Therefore, it is our opinion that there is the need to use a surgical model with a more intense and prolonged major stimulus or to studied a higher number of patients.

All the data reported so far, which also serve to prove the efficacy of a preemptive block, are further supported by the significant differences detected in the postoperative glucose and cortisol concentrations among the four groups.

Given the numerous variables that may affect them, plasma cortisol and, to a greater extent, glucose concentrations cannot be considered two highly specific parameters in determining surgical stress. However, the correlations that emerged between glucose and plasma cortisol concentrations and between both of these values and the pain scales, would suggest that the surgical stress response was less in groups with local anesthetic before (group P) and before and after surgery (group C) than in the other groups. Our conclusions agree with the results of other authors.[11,14,40]

Other parameters such as heart rate and respiratory rate, which represent important indicators of patient discomfort (these values are often correlated with the VAS and VRS values), show a slight but significant decrease in groups undergoing block (B, C, and P), as compared to the placebo group. This also is found in patients who underwent a preemptive treatment (C and P) as compared to patients who underwent a "late" block (B), although to a lesser extent. Moreover, the marked reduction in the onset of nausea, vomiting, and sweating in groups C and P would lead us to assume that a lower autonomic system response to surgery occurred in these groups.

We must further add that the preoperative administration of fentanyl (as one component of the general anesthetic technique) may have reduced the response to pain in all patients. In fact, although the per-kilogram dose of fentanyl and its administration time were the same for all patients and thus cannot represent a variable in drawing a comparison among groups, it is also true that the preoperative administration of opioids

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The authors thank Vittorio Pasqualu
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References

1. Woolf CJ: Evidence for a central
hypersensitivity. Nature 198[illegible]306:6
2. Wall PD: The prevention of post
289–90
3. Woolf CJ and Wall PD: Morph
sensitive actions of C-fibre input on th
1986; 64:221–5
4. Coderre TJ, Katz J, Vaccarino
central neuroplasticity to pathologic
experimental evidence. Pain 1993;
5. Woolf CJ: Recent advances in
pain. Br J Anaesth 1989; 63:39–46
6. Woolf CJ: Central mechanisms
the VIth World Congress on Pain. E
Woolf CJ. Amsterdam, Elsevier, 199
7. Dubner R: Neuronal plasticity
tissue inflammation or nerve injury
Congress on Pain. Edited by Bond
sterdam, Elsevier, 1991, pp 263–7
8. Katz J, Kavanagh BP, Sandler
Friedlander M, Shaw BF: Preemptive
neuroplasticity contributing to pos
1992; 77:439–46
9. Coderre TJ, Vaccarino AL, Me
plasticity in the tonic pain response
tion. Brain Res 1990; 535:155–8
10. Vaccarino AL and Melzack R
pain: Differential role of the cingu
medial bulboreticular formation. P
11. Pasqualucci A, Contardo R,
Donini A, Sorrentino M, Pasetto A,
peritoneal local anesthetic on analg
response after laparoscopic cholec
blind controlled study. J Laparoen
12. Dahl JB, Erichsen CJ, Fugls
Pain sensation and nociceptive ref
surgical patients. Br J Anaesth 199

plays a very important role in the preemption of postoperative pain. Therefore, we believe that all the differences obtained among the groups have been underestimated owing to the preoperative administration of fentanyl.[4,23–24,37,41]

In conclusion, we believe the results indicate that intraperitoneal local anesthetic blockade administered before or after surgery relieves postoperative pain and analgesic consumption when compared to an untreated placebo-control condition. However, the timing of the administration of the local anesthetic is of fundamental importance to preempt postoperative pain.

The authors thank Vittorio Pasqualucci, Full Professor of Anesthesiology and Intensive Care, University of Perugia, for his help in planning this study.

References

1. Woolf CJ: Evidence for a central component of postinjury pain hypersensitivity. Nature 1983; 306:686–8

2. Wall PD: The prevention of postoperative pain. Pain 1988; 33: 289–90

3. Woolf CJ and Wall PD: Morphine-sensitive and morphine-insensitive actions of C-fibre input on the rat spinal cord. Neurosci Lett 1986; 64:221–5

4. Coderre TJ, Katz J, Vaccarino AL, Melzack R: Contribution of central neuroplasticity to pathological pain: Review of clinical and experimental evidence. Pain 1993; 52:259–85

5. Woolf CJ: Recent advances in the pathophysiology of acute pain. Br J Anaesth 1989; 63:139–46

6. Woolf CJ: Central mechanisms of acute pain. Proceedings of the VIth World Congress on Pain. Edited by Bond MR, Charlton JE, Woolf CJ. Amsterdam, Elsevier, 1991, pp 25–34

7. Dubner R: Neuronal plasticity and pain following peripheral tissue inflammation or nerve injury. Proceedings of the VIth World Congress on Pain. Edited by Bond MR, Charlton JE, Woolf CJ. Amsterdam, Elsevier, 1991, pp 263–76

8. Katz J, Kavanagh BP, Sandler AN, Nierenberg H, Boylan JF, Friedlander M, Shaw BF: Preemptive Analgesia: Clinical evidence of neuroplasticity contributing to postoperative pain. ANESTHESIOLOGY 1992; 77:439–46

9. Coderre TJ, Vaccarino AL, Melzack R: Central nervous system plasticity in the tonic pain response to subcutaneous formalin injection. Brain Res 1990; 535:155–8

10. Vaccarino AL and Melzack R: Temporal processes of formalin pain: Differential role of the cingulum bundle, fornix pathway and medial bulboreticular formation. Pain 1992; 44:257–71

11. Pasqualucci A, Contardo R, Da Broi U, Colo' F, Terrosu G, Donini A, Sorrentino M, Pasetto A, Bresadola F: The effects of intraperitoneal local anesthetic on analgesic requirements and endocrine response after laparoscopic cholecystectomy: A randomized double-blind controlled study. J Laparoendosc Surg 1994; 4:405–12

12. Dahl JB, Erichsen CJ, Fuglsang-Frederiksen A and Kehlet H: Pain sensation and nociceptive reflex excitability in volunteers and surgical patients. Br J Anaesth 1992; 69:117–21

13. Ejlersen E, Andersen HB, Eliasen K, Mogensen T: A comparison between preincisional and postincisional lidocaine infiltration and postoperative pain. Anesth Analg 1992; 74:495–8

14. Katz J, Clairoux M, Kavanagh BP, Roger S, Nierenberg H, Redahan C and Sandler AN: Pre-emptive lumbar epidural anaesthesia reduces postoperative pain and patient-controlled morphine consumption after lower abdominal surgery. Pain 1994; 59:395–403

15. Lund C, Hansen OB, Kehlet H: Effect of surgery on sensory threshold and somatosensory evoked potentials after skin stimulation. Br J Anaesth 1990; 65:173–6

16. Dierking GW, Dahl JB, Kanstrup J, Dahl A, Kehlet H: Effect of pre- vs postoperative inguinal field block on postoperative pain after herniorrhaphy. Br J Anaesth 1992; 68:344–8

17. Dahl JB, Hansen BL, Hjortsø NC, Erichsen CJ, Møiniche S, Kehlet H: Influence of timing on the effect of continuous extradural analgesia with bupivacaine and morphine after major abdominal surgery. Br J Anaesth 1992; 69:4–12

18. Rademarker BMP, Kalkman CJ, Odoom JA, de Wit L and Ringers J: Intraperitoneal local anaesthetics after laparoscopic cholecystectomy: Effects on postoperative pain, metabolic responses and lung function. Br J Anaesth 1994; 72:263–6

19. Joris J, Thiry E, Paris P, Weerts J, Lamy M: Pain after laparoscopic cholecystectomy: Characteristics and effect of intraperitoneal bupivacaine. Anesth Analg 1995; 81:379–84

20. Gibbs P, Purushotham A, Auld C, Cuschieri RJ: Continuous wound perfusion with bupivacaine for postoperative wound pain. Br J Surg 1988; 75:923–4

21. van Raay JJAM, Roukema JA, Lenderink BW: Intraoperative wound infiltration with bupivacaine in patients undergoing elective cholecystectomy. Arch Surg 1992; 127:457–9

22. Dahl JB, Kehlet H: The value of pre-emptive analgesia in the treatment of postoperative pain. Br J Anaesth 1993; 70:434–9

23. Kehlet H: Postoperative pain relief—What is the issue? Br J Anaesth 1994; 72:375–8

24. McQuay HJ: Do preemptive treatments provide better pain control? Proceedings of the 7th World Congress on Pain, Progress in Pain Research and Management, Vol. 2. Edited by GF Gebhart, DL Hammond, TS Jensen, Seattle, IASP, 1994, pp 709–23

25. Huskisson EC: Measurement of pain. Lancet 1974; 2:1127–31

26. Pybus DA, Torda TA: Dose-effect relationships of extradural morphine. Br J Anaesth 1982; 54:1259–62

27. Joris J, Cigarini I, Legrand M, Jacquet N, De Groote D, Franchimont P, Lamy M: Metabolic and respiratory changes after cholecystectomy performed via laparotomy or laparoscopy. Br J Anaesth 1992; 69:341–5

28. Barkun JS, Barkun AN, Sampalis JS, Fried G, Taylor B, Wexler MJ, Goresky CA, Meakins JL: Randomized controlled trial of laparoscopic versus mini cholecystectomy. Lancet 1992; 340: 1116–9

29. Dobbs FF, Kumar V, Alexander JI, Hull MGR: Pain after laparoscopy related to posture and ring versus clip sterilization. Br J Obstet Gynaecol 1987; 94:262–6

30. Narchi P, Benhamou D, Fernandez H: Intraperitoneal local anaesthetic for shoulder pain after day-case laparoscopy. Lancet 1991; 338:1569–70

31. Scheinin B, Kellokumpu I, Lindgren L, Haglund C, Rosenberg PH: Effect of intraperitoneal bupivacaine on pain after laparoscopic cholecystectomy. Acta Anaesthesiol Scand 1995; 39:195–8.

32. Spielman FJ, Hulka JF, Ostheimer GW, Mueller RA: Pharmacokinetics and pharmacodynamics of local analgesia for laparoscopic tubal ligations. Am J Obstet Gynecol 1983; 146:821–4

33. Goegler S, Blobner M, Busley R: Subphrenic catheter for postoperative analgesia after laparoscopic cholecystectomy. (abstract) ANESTHESIOLOGY 1993; 79:A26

34. Moore DC, Mather LE, Bridenbaugh PO, Bridenbaugh LD, Balfour RI, Lysons DF, Horton WG: Arterial and venous plasma levels of bupivacaine following epidural and intercostal nerve blocks. ANESTHESIOLOGY 1976; 45:39–45

35. Stromskag KE, Reiestad F, Holmqvist ELO, Ogenstad S: Intrapleural administration of 0,25%, 0,375%, and 0,5% bupivacaine with epinephrine after cholecystectomy. Anesth Analg 1988; 67:430–4

36. Turner GA, Chalkiadis G: Comparison of preoperative with postoperative lignocaine infiltration on postoperative analgesic requirements. Br J Anaesth 1994; 72:541–3

37. Richmond CE, Bromley LM, Woolf CJ: Preoperative morphine pre-empts postoperative pain. Lancet 1993; 342:73–5

38. Dahl JB, Møiniche S, Kehlet H: Wound infiltration with local anaesthetics for postoperative pain relief. Acta Anaesthesiol Scand 1994; 38:7–14

39. Stromskag KE, Minor BG, Lindeberg A: Comparison of 40 milliliters of 0,25% intrapleural bupivacaine with epinephrine with 20 milliliters of 0,5% intrapleural bupivacaine with epinephrine after cholecystectomy. Anesth Analg 1991; 73:397–400

40. Rademaker BMP, Ringers J, Odoom JA, de Wit L, Kalkman CJ, Oosting J: Pulmonary function and stress response after laparoscopic cholecystectomy: Comparison with subcostal incision and influence of thoracic epidural analgesia. Anesth Analg 1992; 75:381–5

41. Kiss IE, Kilian M: Does opiate premedication influence postoperative analgesia? A prospective study. Pain 1992; 48:157–8

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References

1. Cucchiara RF: Differentia
2. Miller RA, Crosby G, Sur
deficit during sedation a pati
SIOLOGY 1987; 67:844–6