

Epidural Clonidine or Bupivacaine as the Sole Analgesic Agent during and after Abdominal Surgery

A Comparative Study

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Background: The rationale of this study was to compare high-dose epidural clonidine with a more commonly used agent, such as bupivacaine. This was performed to give a more objective idea of the relative analgesic potency of epidural clonidine.

Methods: Sixty patients undergoing intestinal surgery during propofol anesthesia were studied. At induction, the patients received epidurally a dose of 10 mg/kg clonidine in 7 ml saline followed by an infusion of 6 mg · kg⁻¹ · h⁻¹ (7 ml/h) (group 1, n = 20), a dose of 7 ml bupivacaine, 0.5%, followed by 7 ml/h bupivacaine, 0.25% (group 2, n = 20), or a dose of 7 ml bupivacaine, 0.25%, followed by 7 ml/h bupivacaine, 0.125% (group 3, n = 20). Intraoperatively, increases in arterial blood pressure or heart rate not responding to propofol (0.5 mg/kg) were treated with intravenous alfentanil (0.05 mg/kg). Additional doses of propofol were given to maintain an adequate bispectral index. The epidural infusions were maintained for 12 h. In cases of subjective visual analogue pain scores up to 5 cm at rest or up to 8 cm during coughing, the patients were given access to a patient-controlled analgesia device.

Results: During anesthesia, patients in group 1 required less propofol than those in groups 2 and 3 (78 [36-142] mg vs. 229 [184-252] mg and 362 [295-458] mg; $P < 0.05$) and less alfentanil than patients in group 3 (0 [0-0] mg vs. 11 [6-20] mg; $P < 0.05$). Analgesia lasted 380 min (range, 180-645 min) in group 1 versus 30 min (range, 25-40 min) in group 2 and 22 min (range, 12.5-42 min) in group 3 ($P < 0.05$). There was no suggestion of a hemodynamic difference among the three groups except for heart rates that were significantly reduced in patients in group 1. Sedation scores were significantly higher in this group during the first 2 h postoperatively.

Conclusion: Our results show that high doses of epidural

clonidine potentiate general anesthetics and provide more efficient postoperative analgesia than the two bupivacaine dosage regimens investigated. (Key words: α_2 -Adrenergic agonist; local anesthetic; pain management.)

THE α_2 -adrenergic agonist clonidine has demonstrable specific analgesic properties in animal models and humans when administered by spinal or epidural routes.¹ In clinical situations such as postoperative pain, the exact potency of this analgesic effect remains unclear. This occurred mainly because of the potentiating properties of the α_2 -adrenergic agonists and the concomitant administration of opioids or local anesthetics.² In a previous dosage-finding investigation we demonstrated that epidural clonidine, used as the sole analgesic agent, provided dosage-dependent control of the hemodynamic changes associated with surgical stimulation.³ It also produced dosage-dependent postoperative analgesia in young adult patients undergoing intestinal resection and reanastomosis. The rationale of the current study was to compare high-dose epidural clonidine with a more commonly used agent, such as bupivacaine. This was performed to give a more objective idea of the relative analgesic potency of epidural clonidine.

Methods

The current double-blind study was approved by the institutional ethics committee, and all patients gave their informed consent. Sixty adult patients between 18 and 45 yr of age scheduled for extensive intestinal resection for inflammatory bowel disease or second-stage reanastomosis were enrolled. They were studied according to the same protocol used in the previous experimentation.³ In the current study, however, no premedication was given the night before surgery and before the procedure.

In the operating room, an epidural catheter was in-

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serted in all patients at the T7-8 vertebral interspace. At that time, patients were randomly assigned to receive one of the three epidural solutions: Patients in group 1 ($n = 20$) received an initial dose of clonidine of 10 mg/kg in 7 ml saline given in 15 min, followed immediately by an infusion of $6 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ (7 ml/h). Patients in group 2 ($n = 20$) received an initial dose of bupivacaine, 0.5% (7 ml = 35 mg), given in 15 min, followed immediately by an infusion of bupivacaine, 0.25% (7 ml/h = 17.5 mg/h). Patients in group 3 ($n = 20$) received an initial dose of bupivacaine, 0.25% (7 ml = 17.5 mg), given in 15 min, followed immediately by an infusion of bupivacaine, 0.125% (7 ml/h = 8.75 mg/h).

The study solutions were prepared by an anesthesiologist not involved in the patients' care, and the patient and the anesthesiologist who delivered spinal analgesia were blinded to the study solutions. The maintenance epidural infusion was maintained in all three groups during the first 12 h postoperatively.

In addition to routine monitoring and an intraarterial catheter for systemic blood pressure monitoring, patients also were connected to an electroencephalogram bispectrum analyzer (Aspect A-1000, Aspect Medical System, Framingham, MA).

General anesthesia was induced concomitantly with the epidural infusion. Induction of anesthesia consisted of propofol (approximately 2 mg/kg) and atracurium (0.5 mg/kg). An intravenous bolus of lidocaine (1 mg/kg) was given before tracheal intubation. Anesthesia was maintained with a propofol infusion of $3 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ in the clonidine group and $5 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ in both bupivacaine groups (the propofol infusions were initiated by the anesthesiologist who prepared the epidural solutions and were blinded to the anesthesiologist in charge of the patient). This was performed because of the well-demonstrated anesthetic-sparing properties of the α_2 -adrenoceptor agonists.^{4,5}

Additional bolus doses of propofol (0.5 mg/kg in bolus) were given independently of the propofol infusions in the presence of a 20% increase of the mean arterial pressure or heart rate compared with the baseline values recorded after the initial dose of the epidural drugs and before skin incision (*epidural baseline*). If heart rate or mean arterial blood pressure did not return to this epidural baseline 3 min after an additional dose of propofol, an intravenous bolus of alfentanil, 0.05 mg/kg, was injected. Additional doses of propofol also were given to maintain a bispectral index between 55 and 65 or in response to signs (sweating, tears, or movements) of inadequate anesthesia depth.

After recovery, the following observations were made every 30 min during the first 12 h postoperatively:

1. Patient sedation scores were assessed using a four-point scale (see De Kock *et al.*³).
2. The sensory block provided by epidural solutions was evaluated using an ether swab.
3. Pain at rest and when coughing was assessed using a 10-cm visual analog scale of pain intensity (left end: no pain; right end: the worst pain imaginable). In cases of subjective scores 5 cm or more at rest or 8 cm or more after imposed cough stress, the patients were given the analgesic-demand button of a patient-controlled analgesia device programmed to deliver boluses of 1.5 mg intravenous morphine (lockout time of 7 min, 4-h limit, 40 mg). The analgesic-demand button also was given when patients spontaneously complained of unbearable pain. After the first analgesic request, the patients were instructed to press the button as soon as spontaneous pain occurred.

The correct placement of the epidural catheter in the 20 patients receiving clonidine was confirmed *a posteriori* at the end of the study period (after 36 h) by the effective sensory block afforded by a bolus of 5 ml bupivacaine, 0.5%. Intraoperative hemodynamics were continuously monitored throughout the study period and for the first 48 h postoperatively.

Perioperative complications were recorded (*e.g.*, heart block, intraoperative hypotension defined as a 30% decrease in systolic arterial blood pressure, orthostatic hypotension, rebound hypertension, nausea and vomiting) during the first 48 h. Patients were systematically questioned for intraoperative recall.

Statistical analysis was performed using Statistica for Windows (version 5; Statsoft, Tulsa, OK). Statistical power calculations ($\alpha = 5\%$, $\beta = 10\%$) based on previous studies^{3,6,7} suggested that a group size of 20 should detect a difference of at least two in the number of intraoperative additional anesthetic analgesic supplementations necessary and of 60 min in the duration of postoperative analgesia. Demographic data and hemodynamic data were based on analysis of variance and analysis of variance for repeated measures. Intergroup *post hoc* comparisons were made using the Tukey test. Data not normally distributed were analyzed using Kruskal-Wallis one-way analysis of variance on ranks. Comparisons of the duration of complete postoperative analgesia provided by the different epidural solution (before the first analgesia request) among the three groups were

Table 1. Demographic Data

	Group 1 (n = 20)	Group 2 (n = 20)	Group 3 (n = 20)
Age (yr)	34.6 ± 6.	35.9 ± 7	32.7 ± 7
Weight (kg)	66.7 ± 10	66.3 ± 8	60.9 ± 10
Male/female	14/6	14/6	16/4
Previous abdominal procedure (n)	1.6 ± 0.7	1.4 ± 0.6	1.5 ± 0.4
Duration of anesthesia (min)	220 ± 54	198 ± 46	203 ± 30

Values are means ± SD. No statistically significant differences were noted between the three groups.

made by survival analysis using the Kaplan-Meier product-limit method. Intergroup comparison for this parameter was performed using the Cox *F* test. Comparison of the observed proportions were performed using chi-squared analysis and the Fisher exact test with Yates correction if appropriate. Results are expressed as the mean ± SD or median + range for data not normally distributed. A probability (*P*) value of less than 0.05 was considered to be statistically significant.

Results

The demographic data of the patients enrolled in the study are summarized in table 1. There was no significant difference among the groups with respect to age, weight, gender, or duration of surgery. The placement of the epidural catheter was easy and successful at the first attempt in all the patients.

Anesthetic/Analgesic Effectiveness

Significantly fewer patients in group 1 than in groups 2 or 3 required supplemental propofol injections (*P* < 0.05). The numbers of propofol/alfentanil injections per patient are presented in table 2. Bispectral index during the first 2 h postoperatively is summarized in figure 1.

As determined by the spontaneous complaint of unbearable abdominal pain or visual analog scale scores at rest and when coughing, the time to first intravenous morphine administration in group 1 (380 min; range, 180–645 min) significantly differed from those observed in group 2 (30 min; range 25–40 min) and in group 3 (22 min; range, 12.5–42 min) (*P* < 0.05) (fig. 2). Differences in other measurements of postoperative analgesia were consistent with this primary observation (table 3). Pain visual analog scale scores during the first 12 h postoperatively are presented on figure 3. Segments reached by the sensory block provided by the study solutions at

recovery and at the time of the first analgesia demand are presented in figure 4.

Side Effects

During the first 2 h postoperatively, sedation scores were significantly higher (*P* < 0.05) in the clonidine group compared with the two bupivacaine groups. Nevertheless, no patient in this group received a score of 3. Time spent to reach scores of 1 and 0 is presented in figure 5.

During anesthesia, there was no suggestion of a hemodynamic difference among the three groups except for heart rate, which was significantly reduced in patients receiving epidural clonidine (*P* < 0.05) (table 4, fig. 6). In none of the patients considered was bradycardia (heart rate < 40 beats/min) or hypotension sufficient to necessitate a specific intervention during the operating period. The nature and incidence of the other postoperative side effects are summarized in table 5. The postoperative course was uneventful for all the patients.

Discussion

In the clinical setting studied, very-high-dose thoracic epidural clonidine provided adequate control of the hemodynamic changes associated with surgical stimulation. It also produced reliable postoperative analgesia. These results are in accordance with the data obtained in animals and human volunteers that established the α_2 -adrenergic system as an important element in the modulation of pain perception at the spinal level.^{1,8} It confirms the results that we obtained in a previous dose-response study.³ In the current study, however, we administered a higher dose than before. This was given to verify whether the analgesic effects showed using large doses (8 mg/kg followed by 2 mg · kg⁻¹ · h⁻¹) would be maintained using larger single doses of epidural clonidine. Studies on Wistar male rats have shown a biphasic effect of clonidine, the largest dose being associated with a reduction of analgesic benefits measured, in this model, as potentiation of opiate analgesia.^{9,10} Our results do not support this U-shaped concentration-effect relation. During anesthesia, large doses of epidural clonidine were particularly efficient to blunt the episode of hypertension or tachycardia related to surgery. A purely hemodynamic effect is ruled out by the data obtained using the electroencephalographic bispectral index. Patients in the clonidine group required significantly fewer propofol supplementations than pa-

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Table 2. Intraoperative Anesthetic and Analgesic Requirements

	Group 1 (n = 20)	Group 2 (n = 20)	Group 3 (n = 20)
Propofol			
Dose at induction (mg)	182 ± 18	192 ± 24	187 ± 26
Bolus supplementations			
n	2 (1-4)*†	7 (5.5-7)†	12 (10-17)
mg	78 (36-142)*†	229 (184-252)†	362 (295-458)
Alfentanil			
Bolus supplementations			
n	0 (0-0)†	0 (0-1)†	3.5 (2-6)
mg	0 (0-0)†	0 (0-3)†	11 (6-20)
Latency to spontaneous breathing (min)	6 ± 5	6 ± 4	8 ± 6

Values are mean ± SD except for bolus supplementations [median (range)].

* $P < 0.05$, group 1 versus group 2.

† $P < 0.05$, group 1 or 2 versus group 3.

tients in both bupivacaine groups to maintain this index in a range compatible with adequate anesthesia. Because systemic absorption of spinal clonidine is fast and significant,^{8,11} this anesthetic-sparing effect is probably the result of a central hypnotic action consecutive to systemic resorption.¹² Nevertheless, a specific spinal anes-

thetic-sparing effect is not ruled out. It was shown that an important reduction of the noxious afferent inputs to the central site consecutive to a spinal regional effect can influence the state of general anesthesia.¹³ In anesthetized patients, large-dose epidural clonidine (8 µg/kg) was shown to afford a greater depression of the electro-

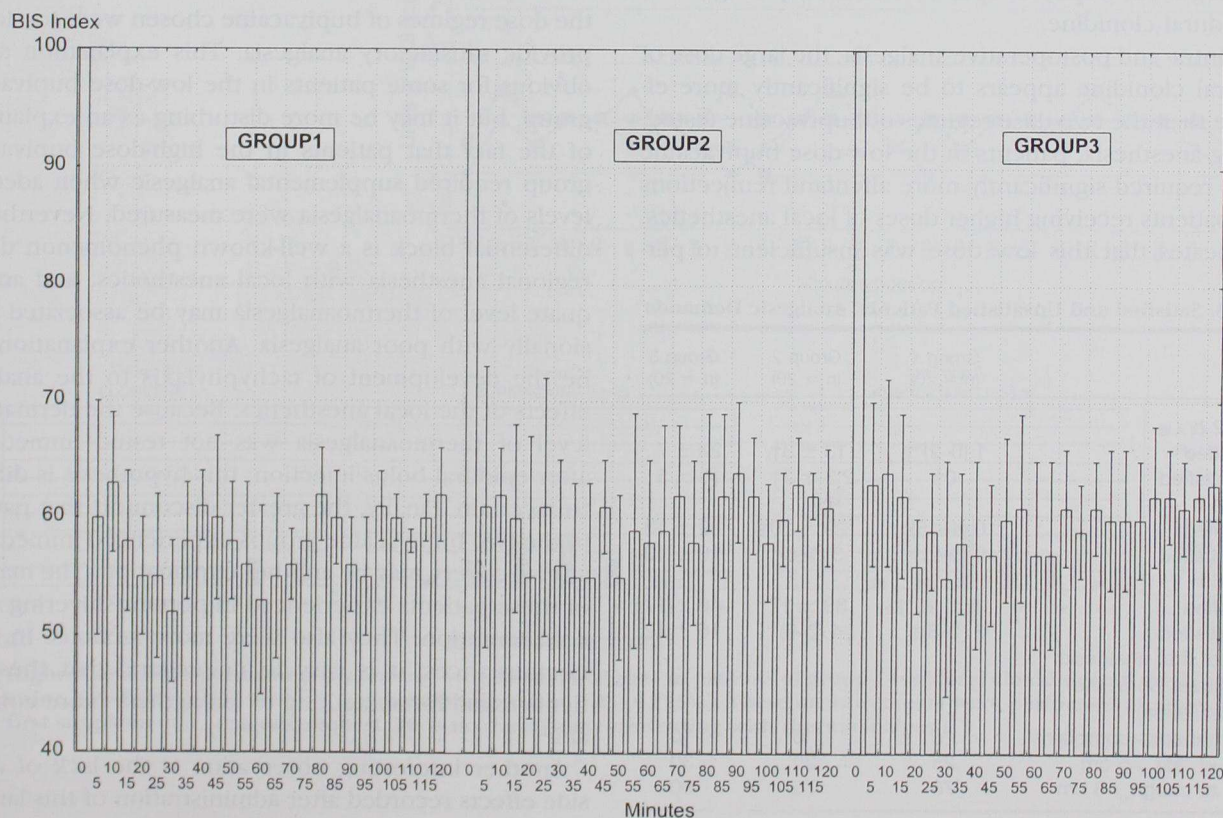


Fig. 1. Bispectral index during the first 2 h of surgery. Group 1 = epidural clonidine; group 2 = epidural bupivacaine, 0.5–0.25%; group 3 = epidural bupivacaine, 0.25–0.125%. The data are expressed as the mean ± SD.

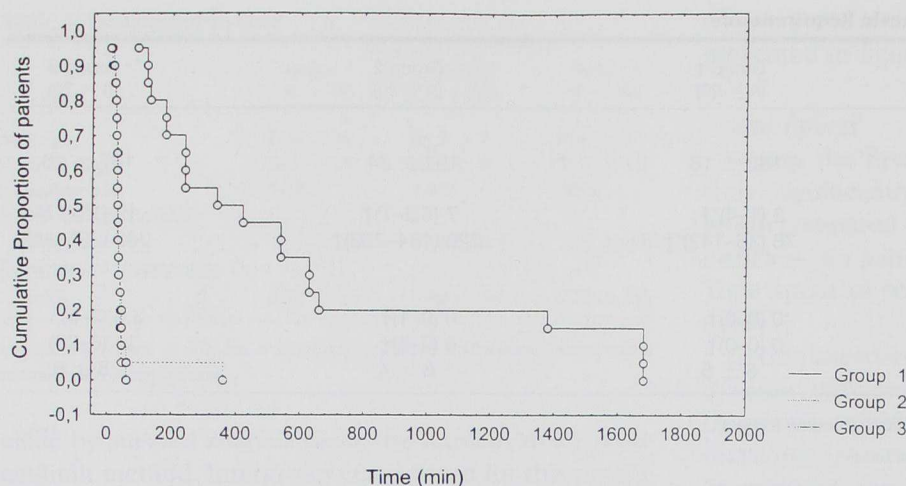


Fig. 2. Duration of postoperative analgesia provided by the different epidural solutions. Group 1 = epidural clonidine; group 2 = epidural bupivacaine, 0.5–0.25%; group 3 = epidural bupivacaine, 0.25–0.125%. The data are presented as survival proportions. Time 0 represents the extubation. The duration of analgesia among the three groups is significantly different ($P < 0.05$, Kaplan-Meier product-limit method). The duration of analgesia observed in group 1 was significantly different from groups 2 and 3 ($P < 0.05$, Cox F test).

encephalogram than the same dose injected by the systemic route.¹⁴ In another clinical work, epidural clonidine (4 mg/kg followed by 2 mg · kg⁻¹ · h⁻¹) was clearly associated with a greater reduction of the intraoperative anesthetic/analgesic supplementations⁵ compared with systemic administration. These two observations argue for a specific spinal anesthetic-sparing effect of epidural clonidine.

For intra- and postoperative analgesia, the large dose of epidural clonidine appears to be significantly more effective than the two-dose regimes of bupivacaine tested. During anesthesia, patients in the low-dose bupivacaine group required significantly more alfentanil reinjections than patients receiving higher doses of local anesthetics. It indicates that this low dose was insufficient to per-

fectly control the nociceptive inputs arising from the surgical field. In the postoperative period, it is quite surprising to observe the short delay that elapsed before patients in both bupivacaine groups required supplemental morphine analgesics and the amount of rescue analgesics necessary during the epidural infusions. Several explanations can be given for this observation. First, the dose regimes of bupivacaine chosen were too low to provide satisfactory analgesia. This explanation seems obvious for some patients in the low-dose bupivacaine group, but it may be more disturbing as an explanation of the fact that patients in the high-dose bupivacaine group required supplemental analgesic when adequate levels of thermoanalgesia were measured. Nevertheless, differential block is a well-known phenomenon during regional anesthesia with local anesthetics, and an adequate level of thermoanalgesia may be associated occasionally with poor analgesia. Another explanation may be the development of tachyphylaxis to the analgesic effects of the local anesthetics. Because the dermatomal level of thermoanalgesia was not tested immediately after epidural bolus injection, this hypothesis is difficult to ascertain. Finally, the greater discomfort that patients in the two bupivacaine groups experienced immediately after recovery may be another explanation. The majority of these patients experienced important shivering and a cold sensation. They also were more anxious. In these circumstances, it is easy to understand that these patients asked for something to make them more comfortable.

Another interesting observation is the lack of major side effects recorded after administration of this large of a dose of clonidine; particularly, no major hypotensive event was noted. This can be explained by the actions of

Table 3. Satisfied and Unsatisfied Patients' Analgesic Demands

	Group 1 (n = 20)	Group 2 (n = 20)	Group 3 (n = 20)
After 12 h			
Satisfied	1 (0–2)*†	13 ± 3†	23 ± 7
Unsatisfied	0†	2.3 ± 2†	10 ± 5
After 24 h			
Satisfied	10 (4–15)*†	29 ± 10†	39 ± 13
Unsatisfied	0 (0–2)†	3 (1–8)†	16 ± 10
After 36 h			
Satisfied	18 ± 13*†	39 ± 17†	48 ± 17
Unsatisfied	3 (1–8)†	4 (2–9)†	16 ± 12
Cause of first analgesic request (% of the population)			
Spontaneous complaint	5	5	10
VAS at rest >5 cm	25	20	30
VAS at cough >8 cm	70	75	60

* $P < 0.05$, group 1 versus group 2.

† $P < 0.05$, group 1 or 2 versus group 3.

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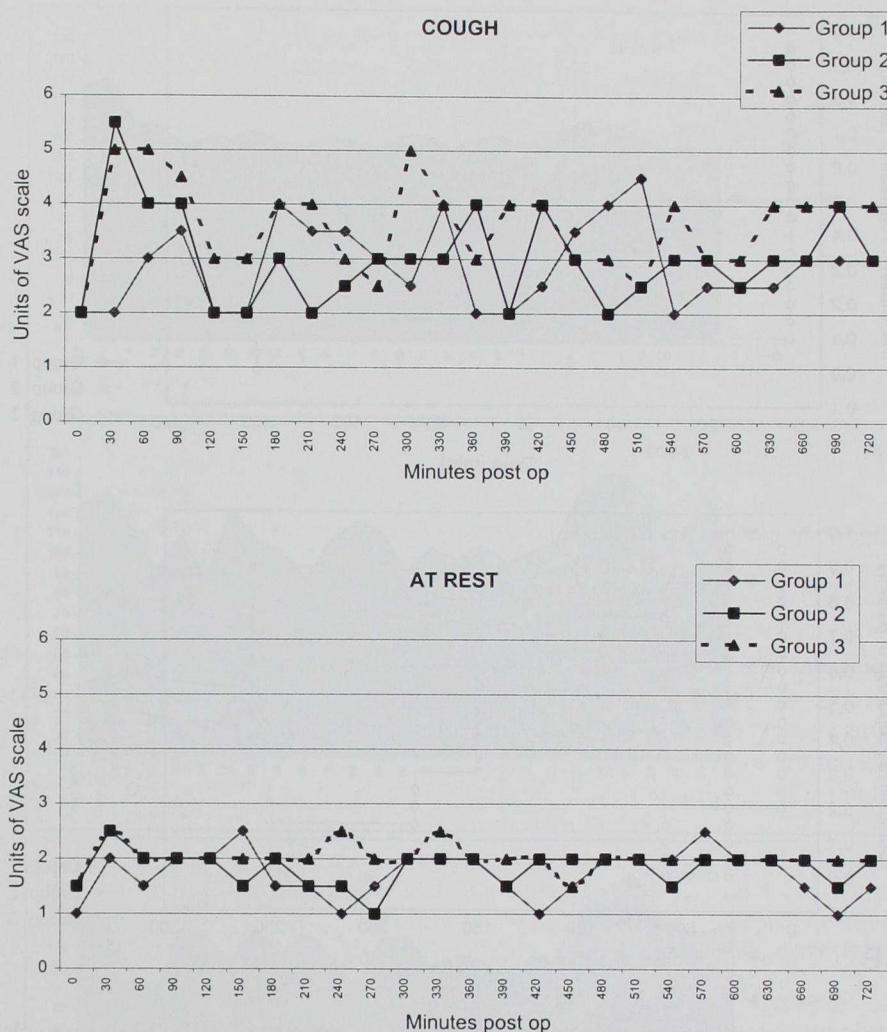


Fig. 3. Pain visual analog scale scores at rest and when coughing during the first 12 h postoperatively. Group 1 = epidural clonidine; group 2 = epidural bupivacaine, 0.5–0.25%; group 3 = epidural bupivacaine, 0.25–0.125%. The data are expressed as the mean.

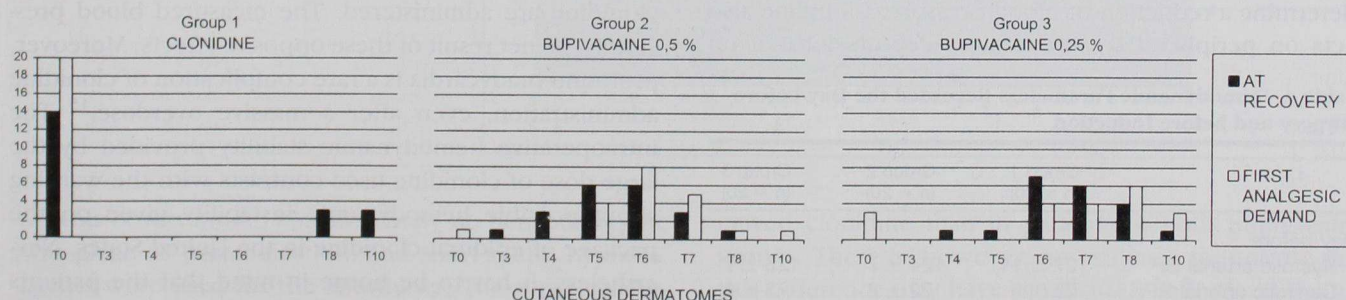


Fig. 4. Highest cutaneous dermatome presenting with thermoanalgesia in patients of group 1 (epidural clonidine), group 2 (epidural bupivacaine, 0.5–0.25%), and group 3 (epidural bupivacaine, 0.25–0.125%). These measurements were performed at recovery and at the first supplemental analgesic request. T0 = no dermatome presenting with thermoanalgesia.

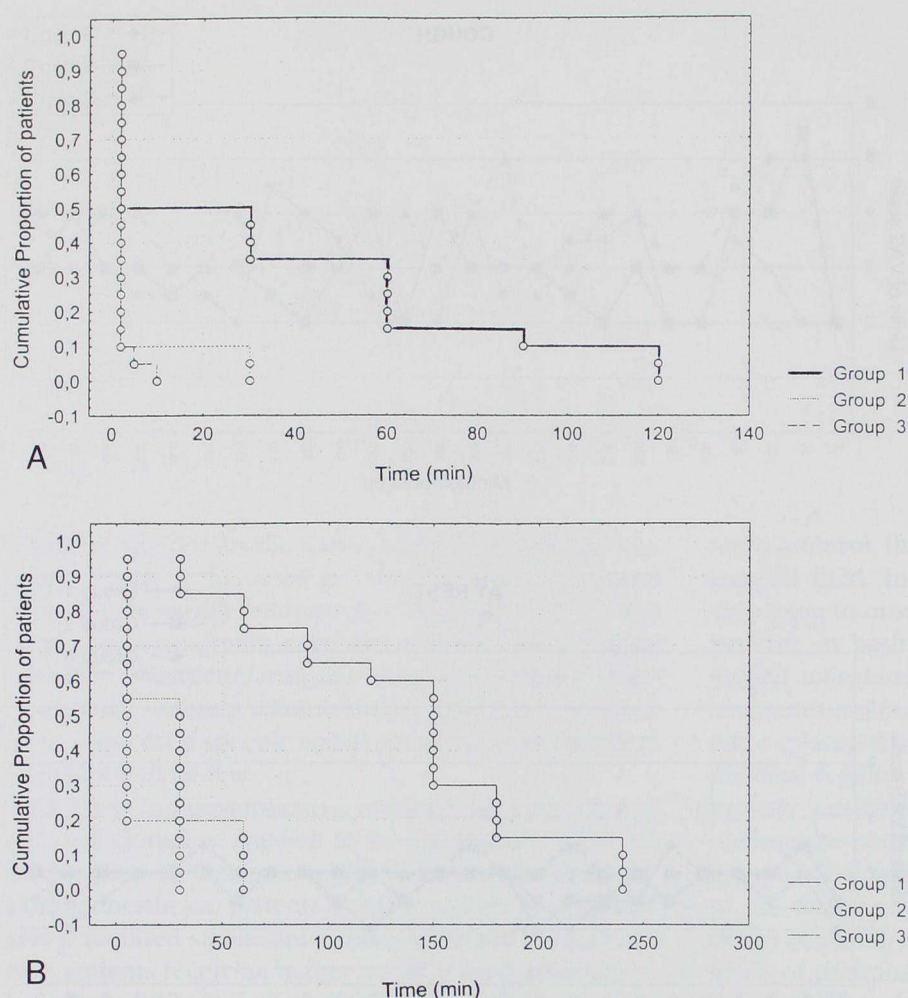


Fig. 5. (A) Time spent before patients became arousable by verbal command (sedation score 2 to sedation score 1) in patients of group 1 (epidural clonidine), group 2 (epidural bupivacaine, 0.5–0.25%), and group 3 (epidural bupivacaine, 0.25–0.125%). (B) Time spent before patients became alert or drowsy but easily arousable (sedation score 1 to sedation score 0) in patients of group 1, group 2, and group 3. The data are presented as survival proportions. Time 0 = extubation time. The durations of sedation among the three groups are significantly different ($P < 0.05$, Kaplan–Meier product-limit method). The duration of sedation observed in group 1 is significantly different from groups 2 and 3 ($P < 0.05$, Cox F test).

clonidine at different sites involved in blood pressure control. Clonidine acts at central and medullary sites that determine a reduction of blood pressure. Clonidine also acts on peripheral α_2 -adrenergic receptors located on

Table 4. Hemodynamic Parameters Recorded the Day before Surgery and before Induction

	Group 1 (n = 20)	Group 2 (n = 20)	Group 3 (n = 20)
Day before			
Systolic arterial BP	127 ± 11	124 ± 7	125 ± 7
Diastolic arterial BP	75 ± 5	72 ± 8	73 ± 6
Heart rate	80 ± 8	77 ± 9	78 ± 10
Preinduction			
Systolic arterial BP	132 ± 11	131 ± 15	128 ± 13
Diastolic arterial BP	79 ± 7	82 ± 14	78 ± 8
Heart rate	85 ± 6	86 ± 9	86 ± 10

Values are mean ± SD. No statistically significant differences were noted between the three groups.

BP = blood pressure.

the blood vessels that determine vasoconstriction.¹ This effect is important particularly when large doses of clonidine are administered. The measured blood pressure is the net result of these opposite effects. Moreover, profound bradycardia is a rare complication of clonidine administration, even after a massive overdose.¹⁵ The intraoperative hemodynamic stability provided by the large dose of clonidine used contrasts with the warning about possible hemodynamic instability given on the package of epidural clonidine in the United States. Nevertheless, it has to be borne in mind that the patients involved were young and were American Society of Anesthesiologist physical status II, and the surgical procedures considered were simple, with no major fluid shift or blood loss.

Another surprise from this study is the absence of major and long-lasting postoperative sedation after these huge doses of clonidine. Two explanations can be given

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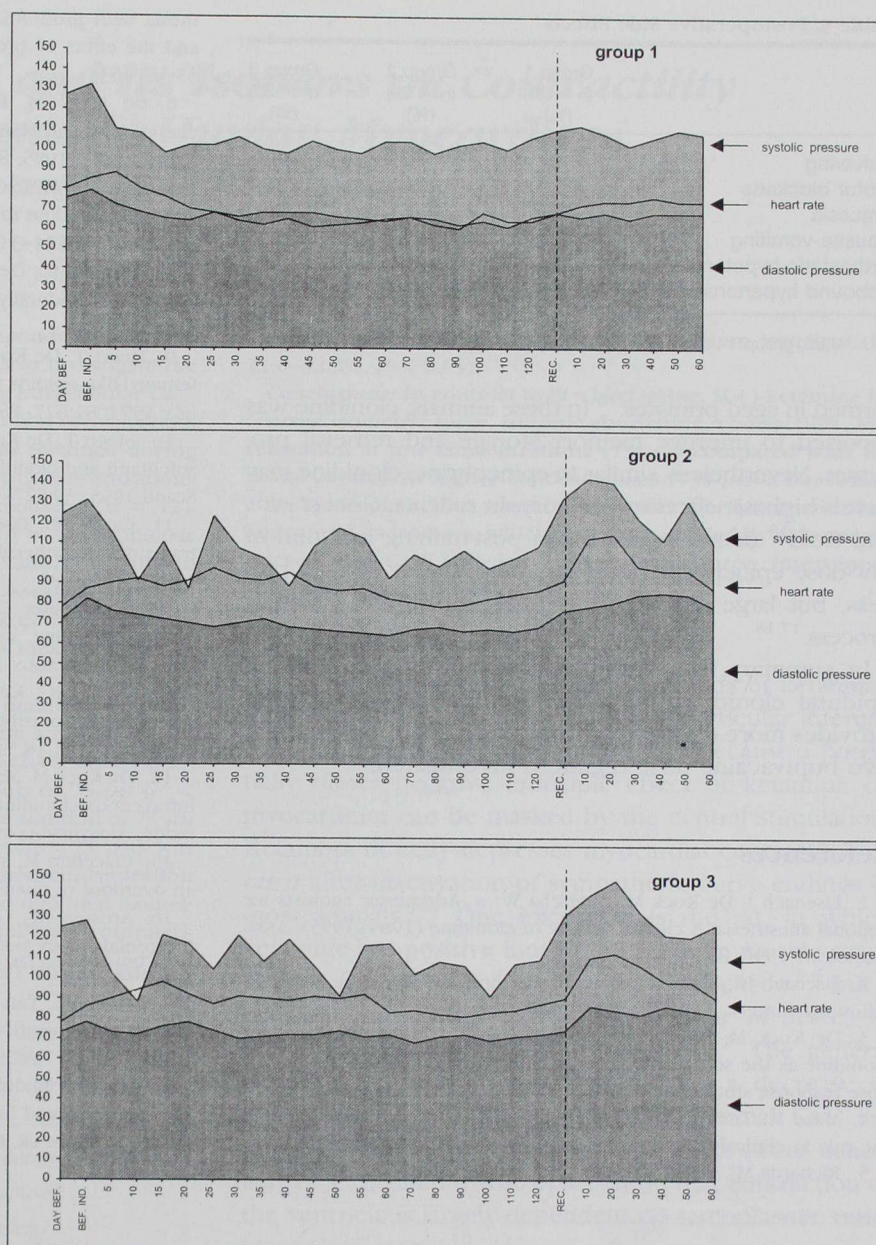


Fig. 6. Arterial blood pressure and heart rate during anesthesia (the first 2 h) and recovery (first hour) in patients of group 1 (epidural clonidine), group 2 (epidural bupivacaine, 0.5–0.25%), and group 3 (epidural bupivacaine, 0.25–0.125%). During anesthesia, preinduction hemodynamic values were significantly reduced to the same extent in any group considered ($P < 0.001$). Heart rate was significantly lower in patients of group 1 ($P < 0.05$). After recovery, a significant increase in heart rate and systolic arterial blood pressure was noted in groups 2 and 3 versus group 1 ($P < 0.001$).

for this observation. First, absolutely no benzodiazepine was given as premedication, and short-acting hypnotic agents were used for the anesthesia. These precautionary measures avoided oversedation consecutive to the potentiation by clonidine of the other sedative drugs and particularly the benzodiazepines.⁶ Another explanation could be the development of tachyphylaxis to the sedative effects of the α_2 -adrenergic agonists, but there exist no arguments to prove this in the current work. Moderate sedation was more frequent in patients having re-

ceived clonidine than in patients of both bupivacaine groups. There is, however, no evidence to indicate that this difference may have significantly influenced the analgesic requirements. In a previous study we were unable to show a correlation between duration of analgesia and duration of sedation in patients having received epidural clonidine as the sole analgesic agent.³

More disturbing is the profound amnesia that occurred in 30% of the patients treated with these high doses of clonidine. This observation contrasts with studies per-

Table 5. Postoperative Side Effects

	Group 1 (n = 20) (%)	Group 2 (n = 20) (%)	Group 3 (n = 20) (%)
Shivering	0*	65	60
Motor blockade	0	10	0
Amnesia	30*	0	0
Nausea-vomiting	10*	45	50
Orthostatic hypotension	10	5	5
Rebound hypertension	0	0	0

* $P < 0.05$, group 1 versus groups 2 and 3.

formed in aged primates.¹⁶ In these animals, clonidine was reported to improve memory storage and retrieval processes. Nevertheless, similar to epinephrine, clonidine may have a biphasic effect on memory. In rodents, Gold *et al.*¹⁷ and Gold¹⁸ demonstrated that a post-training injection of low-dose epinephrine facilitates the memory storage process, but large doses of this drug impair the retention process.^{17,18}

In summary, our results show that a high dose of epidural clonidine potentiates general anesthetics and provides more efficient postoperative analgesia than the two bupivacaine dose regimens investigated.

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