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Addition of Clonidine Enhances Postoperative Analgesia from Epidural Morphine: A Double-blind Study

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This study was undertaken to evaluate the analgesic effect of the combination of epidural morphine and clonidine *versus* epidural morphine alone in patients with postoperative pain. A randomized double-blind design was used, and 91 patients scheduled for postoperative pain relief by epidural morphine were studied. Patients received either a continuous epidural infusion of morphine and clonidine (group 1; n = 45) or morphine alone (group 2; n = 46) over the 72 h after major abdominal surgery. In the first 24 h, the dose of morphine was 6 mg per 24 h; during the second 24 h, it was decreased to 4 mg per 24 h; and in the final 24 h, it was decreased to 2 mg per 24 h in both groups. Group 1 patients received clonidine (450 μg) during each 24-h period. Additional epidural bolus injections of 2 mg morphine and intravenous meperidine were given on demand. The pain score, blood pressure, heart rate, respiratory rate, and relative forced vital capacity were measured at fixed times during the first 72 h after operation. Total consumption of analgesics and side effects were recorded. Although the total consumption of analgesics was significantly higher in group 2 ($P < 0.05$), pain scores were lower in group 1 than group 2 during the entire observation period ($P < 0.05$). Epidural clonidine produced a significant decrease ($P < 0.05$) in heart rate and blood pressure, whereas the respiratory rate was not affected. Due to the better pain relief in group 1, the forced vital capacity was increased ($P < 0.05$). The incidence of side effects was similar in both groups. The authors concluded that epidural clonidine enhances the analgesic effect of epidural morphine after major abdominal surgery without causing more side effects. Circulatory effects resulting from combined administration of epidural clonidine and morphine should be considered when using this combined therapy. (Key words: Analgesia: postoperative. Analgesics, opioid: morphine. Anesthetic technique: epidural. Interactions, epidural: morphine–clonidine. Pain: postoperative. Sympathetic nervous system, α_2-adrenoceptor agonist: clonidine.)

SYSTEMIC OR SPINAL administration of clonidine produces profound antinociception in animals[1,2] which is antagonized by α-blocking agents but not by naloxone, suggesting that it is due to an α_2-adrenergic action in the spinal dorsal horn.[3] Early reports in humans have shown that intravenous injection of clonidine relieves postoperative pain.[4] Profound analgesia is produced by intrathecal clonidine in cancer-related pain that was resistant to intrathecal administration of morphine.[5,6] Occasional tourniquet pain persisting after spinal anesthesia with bupivacaine may successfully be depressed by an additional administration of intrathecal clonidine.[7] Epidural clonidine has been found to be effective in neurogenic[8,9] and postoperative pain[10]; however, in a double-blind, placebo-controlled study, epidural clonidine (3 μg/kg) failed to show any analgesic effects in postthoracotomy pain.[11]

Epidural opioid analgesia is an effective and common method to control postoperative pain.[12] In animals, antinociceptive interactions between clonidine and morphine were found at the spinal level.[13–15] Likewise, an enhancement of epidural morphine analgesia by epidural clonidine was reported in patients suffering from postoperative pain.‡ With intractable cancer pain, the combined spinal administration of morphine and clonidine produced better pain relief than morphine alone. Unfortunately, these previous studies consisted of small series dealing with postoperative pain relief‡,[16,17] or of isolated case reports involving cancer-related pain.[5,6] In this study, using a double-blind design, the analgesic, hemodynamic, respiratory, and side effects of continuous epidural infusion of morphine and clonidine in combination or of morphine alone were compared in patients after major abdominal surgery.

Patients and Methods

The study was approved by the Ethics Committee of the University of the Saarland. Ninety-one patients undergoing major abdominal surgery and scheduled for postoperative pain control by epidural drug administration were studied. Exclusion criteria were a history of drug abuse or a neuroticism score of 13 or more according to the Eysenck personality inventory[18] because of the positive correlation between level of anxiety before surgery and severity of postoperative pain.[19] Patients unable to understand the study protocol and assist in the measurements were also excluded. All patients were informed about the study protocol and gave written consent before the operation. Patients were instructed how to use the

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visual linear analogue scale for pain measurement and the spirometer to determine pulmonary function. They were informed that they would receive a continuous infusion of an analgesic for postoperative pain relief through the epidural catheter. They were guaranteed additional epidural bolus injections and supplementary intravenous (iv) analgesia when required. The patients were randomly assigned either to group 1 (n = 45), which received epidural morphine and clonidine, or group 2 (n = 46), which received epidural morphine alone. The study was double-blind, and the code was broken after all data had been collected.

Preanesthetic medication consisted of 0.75 mg/kg meperidine and 0.5 mg im atropine given 45 min before surgery. After insertion of iv catheters, an epidural catheter was introduced into the lumbar epidural space at the level of L1–2 or L2–3 using the "loss of resistance" technique. A test dose of 4 ml plain bupivacaine 0.5% was given by the epidural catheter. Twenty minutes later, the distribution of analgesia was determined, using the sensation of cold elicited by swabs soaked with ether. A segmental blockade ascertained the proper position of the epidural catheter in all cases.

General anesthesia was induced with 4–6 mg/kg thiopental or 0.2 mg/kg etomidate and 0.1 mg fentanyl. Muscle relaxation was produced by 0.1 mg/kg vecuronium, which also facilitated tracheal intubation. Normocapnia was achieved with controlled ventilation using a Draeger (Lubeck, FRG) AV I. Anesthesia was maintained with 66% N_2O in oxygen and supplemented with isoflurane. Additional doses of fentanyl and vecuronium were given when necessary. Residual neuromuscular blockade was antagonized by 10 mg pyridostigmine (adding 0.5 mg atropine) at the end of the surgical procedure. After tracheal extubation, the patients were transferred to the recovery room and then to an intensive care unit (ICU). Opiate antagonists were not used.

Immediately after completion of surgery, all patients received an epidural bolus injection of 2 mg morphine hydrochloride (dissolved in 2 ml sodium chloride 0.9%). The epidural catheter then was connected to an infusion device (Travenol® infusor, Baxter, Deerfield, IL) that has a constant flow rate of 2.2 ml/h when 0.9% sodium chloride is used as carrying solution. It was prepared with the coded test drug dissolved in 52.8 ml 0.9% sodium chloride. Patients continuously received either epidural morphine and clonidine (group 1) or morphine alone (group 2) over the 72 h after surgery. In the first 24 h, the dosage of morphine was 6 mg per 24 h; during the second 24 h, it was decreased to 4 mg per 24 h; and in the final 24 h, it was decreased to 2 mg per 24 h in both groups. Group 1 patients received clonidine (450 μg) during each 24-h period. In pilot studies, the lowest effective dose of continuous epidural morphine per 24-h period was determined. Preliminary studies at our institution also showed that continuous epidural infusion of clonidine and morphine provided better pain relief than epidural bolus injections. The addition of clonidine (450 μg per 24 h) to the continuous epidural morphine infusion proved to be the most effective dose for pain control after major abdominal surgery.

The patients received additional analgesics when needed for supplementary pain relief. Initially, they were given additional epidural bolus injections of 2 mg morphine hydrochloride (dissolved in 2 ml 0.9% sodium chloride). If a second epidural bolus injection failed to relieve pain within 30 min or patients complained about such severe pain that further waiting would have been distressing, then they received 50 mg meperidine iv. The additional consumption of epidural morphine and meperidine during every 24-h infusion period was recorded. The pain scores were taken as an amount of the analgesic effect and the mutual interaction of the test drugs given epidurally. The difference in consumption of drugs between group 1 and group 2 is an indicator of the quality of analgesia.

The intensity of postoperative pain was assessed 4 h (on the day of operation), 16, 20, 24, 28 h (first postoperative day), 40, 44, 48, 52 h (second postoperative day), and 64, 68, and 72 h (third postoperative day) after termination of surgery with the visual analogue scale according to Scott and Huskisson.[20] For each measurement, a 100-mm long vertical line divided from zero ("no pain") to ten ("intractable pain") was used. In all patients, the pain assessment was carried out by one of the authors (K.L.) at the above times independent of whether additional analgesics were administered before or after. Respiratory rate and the degree of sedation were determined simultaneously. A four-point sedation score was used: awake patients were classified as 1; drowsy patients who immediately responded when spoken to were classified as 2; sleeping patients who responded to stronger stimuli were classified as 3; and patients difficult to awaken were classified as 4.

Pulmonary function was measured 16, 24 h (first postoperative day), 40, 48 h (second postoperative day), 64, and 72 h (third postoperative day) after termination of surgery using a digital spirometer with automated BTPS correction. From the flow–volume curves, the forced vital capacity (FVC) was calculated and compared to preoperative values.

Postoperative monitoring of blood pressure (either noninvasive oscillometric or intraarterial measurement) and heart rate (ECG) followed the routine of the ICU and was additionally recorded every 4 h for this study. A decrease in mean arterial pressure >30% was treated with 250 ml iv colloid fluid (5% serum albumin solution) administration. If there was an inadequate response to this

TABLE 1. Patients' Characteristics

Characteristic	Group 1 (n = 45)	Group 2 (n = 46)
Age (yr)	56.7 ± 11.3	55.9 ± 11.5
Sex (m/f)	37/8	36/10
Weight (kg)	74.6 ± 12.4	73.4 ± 12.2
Height (cm)	171.9 ± 11.3	173.3 ± 11.5
Preoperative systolic blood pressure (mmHg)	140 ± 16.6	133 ± 15.2
Preoperative diastolic blood pressure (mmHg)	82 ± 8.4	81 ± 7.6
Preoperative heart rate (beats per min)	78 ± 9.9	77 ± 8.7
Preoperative forced vital capacity (l)	3.2 ± 0.7	3.4 ± 0.8

Mean ± SD.

TABLE 2. Intraoperative Characteristics

Characteristic	Group 1 (n = 45)	Group 2 (n = 46)
Procedure (number of patients)		
Gastrectomy	8	8
Colectomy	6	8
Rectum resection	6	5
Radical cystectomy	12	12
Radical prostatectomy	13	13
Duration of operation (min, mean ± SD)	269 ± 103	255 ± 101
Intraoperative fentanyl consumption (mg, mean ± SD)	0.34 ± 0.22	0.32 ± 0.19

treatment, a vasopressor was administered. Side effects were registered during the study at each point of measurement and graded as severe or moderate.

Data are presented as mean ± SD. Visual analogue scale (VAS) scores, total analgesic drug consumption, and hemodynamic data were compared among groups using one-way analysis of variance (ANOVA) for repeated measures. Homogeneity of variances for the variables was checked by the BOX-M-test. Noncontinuous variables and additional epidural morphine and meperidine injections were compared using the chi-squared test. All tests used were performed by the Statistical Package for Social Sciences (SPSS-X Release 3.0).[21]§ P of 0.05 was considered significant.

Results

The patients in both groups were similar in age, sex, weight, height, preoperative hemodynamic and respiratory status, duration of operation, and type of surgery (table 1). The groups did not differ in the amount of intraoperative opioid analgesics received. Group 1 was given 0.34 ± 0.21 mg fentanyl (mean ± SD), and group 2 was given 0.32 ± 0.18 mg fentanyl (mean ± SD; table 2). In all patients, the clinical course was uncomplicated.

The combined administration of epidural morphine and clonidine produced significantly better postoperative pain relief than that produced by epidural morphine alone. This was confirmed both by the pain scores and by a significantly lower consumption of analgesics during the 72-h observation period. Furthermore, less epidural and intravenous bolus injections of analgesics were required. Figure 1 shows the time course of postoperative pain relief during continuous epidural infusion of morphine and clonidine compared to the relief caused by epidural infusion of morphine alone. The pain scores of the two groups differed significantly throughout the study ($P < 0.05$). Because of the low loading dose, the amount of additional administered epidural bolus injections of morphine hydrochloride (2 mg) and of intravenous meperidine (50 mg) was highest during the first 24-h period. During the first 4 h postoperatively, the additional amount of epidural morphine was 24 mg in both groups, and 500 mg and 400 mg of meperidine were additionally given to groups 1 and 2, respectively. Although supplemental opioid use did not differ for the first 4 h, patients in group 1 reported lower pain scores after 4 h. Group 1 required less additional epidural and intravenous bolus injections during the 72-h observation period as compared to group 2 (table 3).

Patients receiving epidural morphine and clonidine had lower systolic and diastolic blood pressure and heart rate as compared to patients with epidural morphine alone ($P < 0.05$; figs. 2 and 3). Five patients in group 1 experienced a decrease in systolic blood pressure greater than 30% from preanesthetic levels during the first 24-h period that responded to iv colloid fluid (250 ml) administration. One patient during the first and one patient during the second

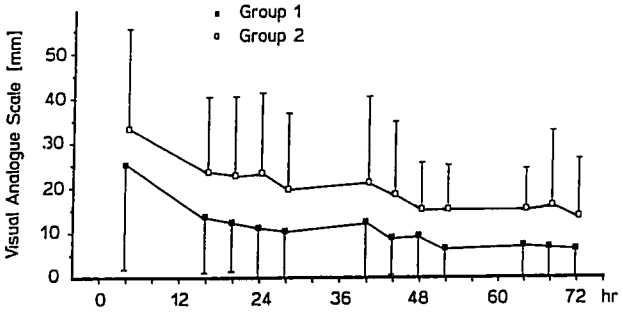

FIG. 1. Pain scores (10-cm linear analogue scale according to Scott and Huskisson[20]) during continuous infusion of epidural clonidine and morphine (group 1) and epidural morphine (group 2) at each assessment time during the study period. Each point represents the mean ± SD. Groups differ by one-way ANOVA ($P < 0.05$).

§ SPSS-X, Inc.: User's Guide, 3rd edition. Chicago, SPSS Inc, 1988 (ISBN 0-918469-51-1).

TABLE 3. Supplemental Epidural Morphine and Intravenous Meperidine Injections

Type of Bolus Injection	Group	Time (h) 0–24	24–48	48–72	Σ
Epidural	1 (n = 45)	22 (44)	7 (14)	4 (8)	33 (66)
	2 (n = 46)	31 (62)	24 (48)	13 (26)	68 (136)
Intravenous	1 (n = 45)	14 (700)	2 (100)	2 (100)	18 (900)
	2 (n = 46)	16 (800)	8 (400)	6 (300)	30 (1500)

Number of supplemental epidural morphine and intravenous meperidine injections on demand in patients of group 1 (morphine and clonidine) and group 2 (morphine alone) during the entire observation period.

Significant difference beween group 1 and 2 ($P < 0.05$, chi-squared test). The total amount of supplemental epidural morphine and intravenous meperidine is given in parentheses ($P < 0.05$, one-way ANOVA).

24-h period required a vasopressor in addition to iv infusion. In patients with a history of hypertension, blood pressure decreased more than in normotensive patients. Decreased heart rate did not require treatment.

As a result of major abdominal surgery, FVC was depressed by almost 46% and 52% in groups 1 and 2, respectively, compared to preoperative levels; however, FVC was significantly ($P < 0.05$) less depressed in group 1 than in group 2 (fig. 4). Respiratory rate was not significantly different between the two groups. None of the patients had a respiratory frequency of less than 10 breaths per min and no case of delayed respiratory depression occurred.

The incidence of side effects was similar in both groups (chi-squared test; $P > 0.05$; fig. 5). The sedation score did not differ between groups.

Discussion

To measure the analgesic effect of the epidural drugs tested, both a standardized visual analogue scale[20] and the cumulative consumption of additional epidural and intravenous bolus injections of analgesics were used.[22]

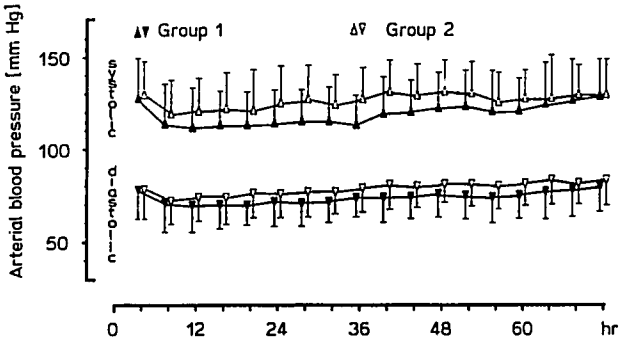

FIG. 2. Systolic and diastolic arterial pressure after the continuous epidural infusion of clonidine and morphine (group 1) or morphine (group 2) at each assessment during the first 72 h after operation. Each point represents the mean ± SD. Groups differ by one-way ANOVA ($P < 0.05$).

Both methods of assessing postoperative pain relief require cooperative (not heavily sedated) patients. After major abdominal surgery, the individual demand for analgesics shows a wide range of amounts.[23] We therefore used a combined approach to initiate and sustain analgesia for postoperative pain control. Basic analgesia was provided by a low dose of epidural morphine infused continuously.[24] The lowest effective doses per 24 h of epidural morphine were taken from pilot studies that also showed that during the first 72 h after an operation, the amount of analgesics for adequate pain relief declines gradually. Supplemental analgesia was provided by additional epidural bolus injections of morphine and intravenous meperidine given immediately after request of the patients by the medical staff of the ICU according to the study protocol. Our approach for supplemental analgesia has a small disadvantage compared to specialized patient-controlled analgesia (PCA) equipment in that patients must first request an analgesic supplement and must then wait until it is received. However, the response time was short and ranged from 2–8 min in this setting. Therefore, the pain score and the dosage of supplemental analgesics were taken as a measure of the analgesic efficacy of the epidural drugs tested.[22]

Studies on epidural clonidine analgesia following surgery are conflicting with respect to pain relief, duration

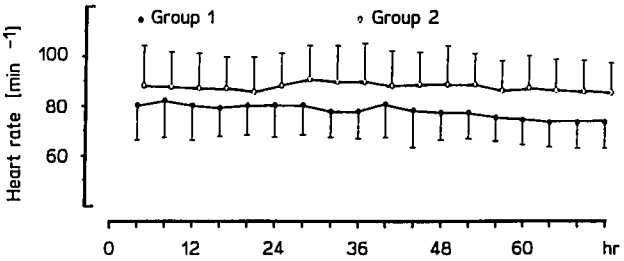

FIG. 3. Heart rate at each assessment time during the study period. Group 1 received epidural clonidine and morphine, and group 2, epidural morphine alone. Each point represents the mean ± SD. Groups differ by one-way ANOVA ($P < 0.05$).

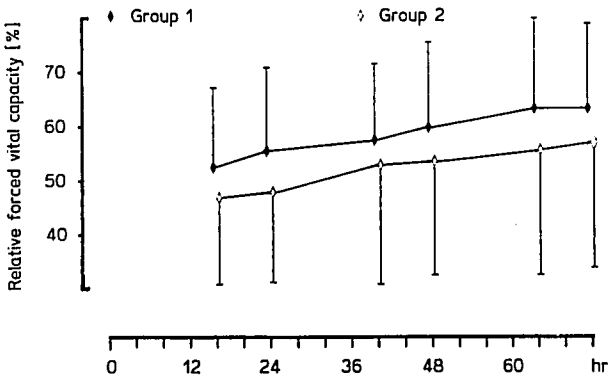

FIG. 4. Forced vital capacity in relation to preoperative values at each assessment time during the study period. Group 1 received epidural clonidine and morphine, and group 2, epidural morphine. Each point represents the mean ± SD. Groups differ by one-way ANOVA ($P < 0.05$).

of action, and effective dose.[10,11,17,25] However, in a recent dose–response study, a dose-dependent analgesic effect of epidural clonidine on postoperative pain was demonstrated.[22] This is supported by animal studies on epidural[2,26] and intrathecal clonidine,[3,14,15,27] with clonidine being ten times as potent as morphine on tail flick reflex.[13,28]

Our results demonstrate a potent interaction on pain relief from the combined administration of epidural morphine and clonidine after major abdominal surgery. The addition of 450 μg per 24 h clonidine to low-dose epidural morphine infusion enhanced postoperative analgesia. When the significantly lower pain scores are considered in conjunction with the reduced requirement for supplementary opioids and the significantly better postoperative FVC, it is evident that the combination of epidural clonidine and morphine provided better control of postoperative pain than did epidural morphine alone within the constraints of this dosage regimen. In addition, it is evident that a graded record of deep breath such as FVC is an objective measure for postoperative pain.[29] When clonidine and morphine are concomitantly infused epidurally, the potential risk of late respiratory depression[30] is minimized due to a lower total consumption of epidural and iv opioids for sufficient pain control.

In a previous study, the combined administration of epidural clonidine (75 μg) and morphine (2 mg) produced an analgesic effect lasting for 15 h after surgery involving resection of the 12th rib for nephrectomy in 20 patients, whereas epidural morphine (2 mg) alone failed to produce an adequate analgesic effect.§ In our study, during the first 4 h after surgery, 75 μg epidural clonidine was infused. Since supplemental analgesics consumption did not differ between both groups during this period, it might be assumed that a total dose of 75 μg clonidine given by epidural infusion might be necessary to reach steady-state concentrations with a significant effect as confirmed by a lower pain score. Also, one might suggest that clonidine relieves pain (*e.g.*, neurogenic) not responding to morphine.[5,8,9] Similar hourly clonidine infusion rates during epidural clonidine–morphine infusions provided adequate pain control in cancer patients for periods up to 5 months.[31] This morphine–clonidine interaction was also described in a patient suffering from severe neuropathic pain.[8] Additionally, in cancer patients, the coadministration of intrathecal clonidine and morphine[5,6,¶] or hydromorphone[32] relieved intractable cancer pain when morphine tolerance developed. These and our findings are supported by experimental data demonstrating a positive interaction between morphine and clonidine at the spinal level.[3,14,15] Moreover, other studies demonstrated a potentiation of the antinociceptive effect of systemically administered morphine[3,33] and of intrathecal morphine by systemic clonidine.[34]

Heart rate and blood pressure were decreased by coadministration of epidural clonidine (450 μg per 24 h) with morphine. Epidural clonidine produces hypotension by actions at brain stem sites[35] and direct spinal inhibition of preganglionic sympathetic outflow.[36] Hypotension was more likely in patients with a history of hypertension[22,31] and the presence of postoperative hypovolemia. This dose-dependent effect[22,31] is possibly explained by a lower spinal and a higher peripheral clonidine concentration following epidural injection, while intrathecal clonidine injection produces a more pronounced decrease in blood pressure.[5] The observed decrease in heart rate did not require specific therapeutic measures, although clonidine may decrease velocity through cardiac conduction systems and produce dangerous dysrhythmias.[22,31] Furthermore, the higher levels of blood pressure and heart rate in the patients treated with epidural morphine (group 2) might also be explained by sympathetically mediated cardiovascular responses due to an increased sympathetic tone and insufficient analgesia.[37] The other observed side effects were similar in both groups. Even side effects like dry mouth or sedation occurred to the same extent in both groups and are likely to be explained by perioperative factors instead of a specific clonidine-related side effect. In our patients, no signs or symptoms of neurologic sequelae or toxic effects became evident after epidural administration of 1,350 μg clonidine during a 72-h period. The safety margin of epidural and intrathecal clonidine administration has been well established in animal studies and in patients with terminal cancer or postoperative pain.[22,31,38–40]

¶ Motsch J: Treatment of cancer pain. Schmerz Pain Doleur 7:68–74, 1986.

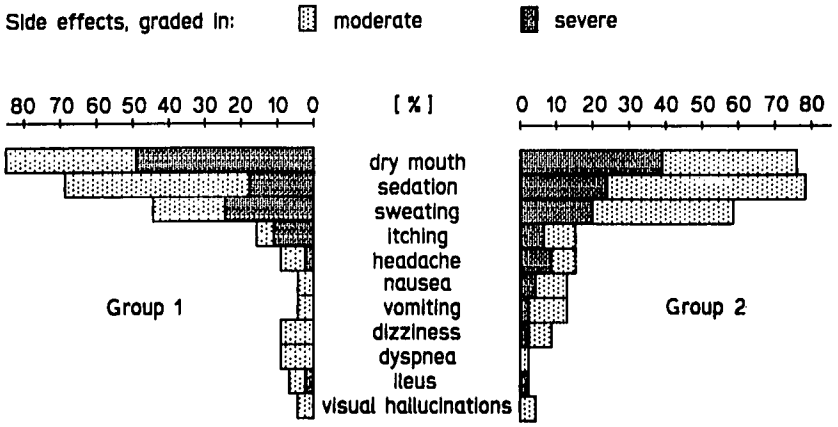

FIG. 5. Postoperative observed side effects, graded moderate and severe. For postoperative pain relief, group 1 received epidural clonidine and morphine, and group 2, epidural morphine alone. No significant differences were found between the two groups ($P > 0.05$, chi-squared test).

We conclude that epidural clonidine increases the analgesic effect of epidural morphine after major abdominal surgery without increasing side effects. We also suggest that the circulatory effects resulting from a combined administration of epidural clonidine and morphine should be considered when using such combined therapy.

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References

1. Yaksh TL: Pharmacology of spinal adrenergic systems which modulate spinal nociceptive processing. Pharmacol Biochem Behav 22:845–858, 1985
2. Eisenach JC, Dewan DM, Rose JC, Angelo JM: Epidural clonidine produces antinociception, but not hypotension, in sheep. ANESTHESIOLOGY 66:496–501, 1987
3. Yaksh TL, Reddy SVR: Studies in the primate on the analgetic effects associated with intrathecal actions of opiates, α-adrenergic agonists, and baclofen. ANESTHESIOLOGY 54:451–467, 1981
4. Gordh Jr T, Tamsen A: A study of the analgetic effect of clonidine in man. Acta Anaesthesiol Scand Suppl 27:(Suppl 87):72, 1983
5. Coombs DW, Saunders RL, LaChange D, Savage S, Ragnarsson TS, Jensen LE: Intrathecal morphine tolerance: Use of intrathecal clonidine, DADLE, and intraventricular morphine. ANESTHESIOLOGY 62:358–363, 1985
6. Van Essen EJ, Bovill JG, Ploeger EJ, Beerman H: Intrathecal morphine and clonidine for control of intractable cancer pain. A case report. Acta Anaesthesiol Belg 39:109–112, 1988
7. Bonnet F, Diallo A, Saada M, Belon M, Guilbaud M, Boico O: Prevention of tourniquet pain by spinal isobaric bupivacaine with clonidine. Br J Anaesth 63:93–96, 1989
8. Tamsen A, Gordh Jr T: Epidural clonidine produces analgesia. Lancet ii:231–232, 1984
9. Glynn CJ, Teddy PJ, Jamous MA, Moore RA, Lloyd JW: Role of spinal noradrenergic system in transmission of pain in patients with spinal cord injury. Lancet ii:1249–1250, 1986
10. Kalia PK, Madan R, Batra RK, Latha V, Vardan V, Gode GR: Clinical study on epidural clonidine for postoperative analgesia. Indian J Med Res 83:550–552, 1986
11. Gordh Jr T: Epidural clonidine for treatment of postoperative pain after thoracotomy. A double-blind placebo-controlled study. Acta Anaesthesiol Scand 32:702–709, 1988
12. Rawal N, Arner S, Gustafsson LL, Allvin R: Present state of extradural and intrathecal opioid analgesia in Sweden. Br J Anaesth 59:791–799, 1987
13. Spaulding TC, Fielding S, Venafro JJ, Lal H: Antinociceptive activity of clonidine and its potentiation of morphine analgesia. Eur J Pharmacol 58:19–25, 1979
14. Wilcox GL, Carlson KH, Joachim A, Jurna I: Mutual potentiation of antinociceptive effects of morphine and clonidine on motor and sensory responses in rat spinal cord. Brain Res 405:84–93, 1987
15. Ossipov MH, Suarez LJ, Spaulding TC: Antinociceptive interactions between alpha$_2$-adrenergic and opiate agonists at the spinal level in rodents. Anesth Analg 68:194–200, 1989
16. Mok MS, Wang JJ, Chan JH, Liu SE, Lippmann M: Analgesia effect of epidural clonidine and nalbuphine in combined use (abstract). ANESTHESIOLOGY 69:A398, 1988
17. Petit J, Oksenhendler G, Colas G, Leroy A, Winckler C: Comparison of the effects of morphine, clonidine and a combination of morphine and clonidine administered epidurally for postoperative analgesia (abstract). ANESTHESIOLOGY 71:A647, 1989
18. Eysenck HJ, Eysenck SBG: Manual of the Eysenck Personality Inventory. London, University of London Press, 1971
19. Boyle P, Parbrook GD: The interrelation of personality and post operative factors. Br J Anaesth 49:259–264, 1977
20. Scott J, Huskisson EC: Graphic representation of pain. Pain 2: 175–184, 1976
21. Nie HH, Hull CH, Jenkins JG, Steinbrenner K, Bent DH: SPSS Statistical Package for Social Sciences. New York, McGraw-Hill, 1975
22. Eisenach JC, Lysak StZ, Viscomi ChM: Epidural clonidine analgesia following surgery: Phase I. ANESTHESIOLOGY 71:640–646, 1989
23. Tamsen A, Hartvig P, Dahlström B, Holmdahl MH: Patient controlled analgetic therapy in the early postoperative period. Acta Anaesthesiol Scand 23:462–470, 1979
24. Chrubasik J, Wiemers K: Continuous-plus-on-demand epidural infusion of morphine for postoperative pain relief by means of a small, externally worn infusion device. ANESTHESIOLOGY 62: 263–267, 1985
25. Bonnet F, Boico O, Rostaing S, Saada M, Loriferne JF, Touboul C, Abhay K, Ghinone M: Extradural clonidine analgesia in postoperative patients. Br J Anaesth 63:465–469, 1989
26. Post C, Gordh Jr T, Minor BG, Archer T, Freedman J: Antinociceptive effects and spinal cord tissue concentrations after intrathecal injection of guanfacine or clonidine in rats. Anesth Analg 66:317–324, 1987
27. Reddy SVR, Maderdrut JL, Yaksh TL: Spinal cord pharmacology

of adrenergic agonist-mediated antinociception. J Pharmacol Exp Ther 213:525–533, 1980
28. Fielding S, Spaulding TC, Lal H: Antinociceptive actions of clonidine, Psychopharmacology of Clonidine. Edited by Lal H, Fielding S. New York, Alan R Liss, 1981, pp 225–242
29. Parkhouse J, Holmes CM: Assessing postoperative pain relief. Proc R Soc Med 56:579–585, 1963
30. Gustafsson LL, Schildt B, Jakobsen K: Adverse effects of extradural and intrathecal opiates: Reports of a nationwide survey in Sweden. Br J Anaesth 54:479–486, 1982
31. Eisenach JC, Rauck RL, Buzzanell Ch, Lysak StZ: Epidural clonidine analgesia for intractable cancer pain: Phase I. ANESTHESIOLOGY 71:647–652, 1989
32. Coombs DW, Saunders RL, Fratkin JD, Jensen LE, Murphy CA: Continuous intrathecal hydromorphone and clonidine for intractable cancer pain. J Neurosurg 64:890–894, 1986
33. Dranser K, Fields HL: Synergy between the antinociceptive effects of intrathecal clonidine and systemic morphine in the rat. Pain 32:309–312, 1988
34. Sagen J, Proudfit HK: Effect of intrathecally administered noradrenergic antagonists on nociception in rat. Brain Res 310: 295–301, 1984
35. van Zweiten PA, Thoolen JMC, Timmermans PBMWM: The hypotensive activity and side effects of methyldopa, clonidine and guanfacine. Hypertension 6(Suppl II):1128–1132, 1984
36. Gueyenet PG, Cabot JB: Inhibition of sympathetic preganglionic neurons by catecholamines and clonidine: Mediation by an α-adrenergic receptor. J Neurosci 1:908–917, 1981
37. Ghignone M, Quintin L, Duke PC, Kehler CH, Calvillo O: Effects of clonidine on narcotic requirements and hemodynamic response during induction of fentanyl anesthesia and endotracheal intubation. ANESTHESIOLOGY 64:36–42, 1986
38. Yaksh TL, Collins JG: Studies in animals should precede human use of spinally administered drugs (editorial). ANESTHESIOLOGY 70:4–6, 1989
39. Eisenach JC, Castro MI, Dewan DM, Rose JC: Epidural clonidine analgesia in obstetrics: Sheep studies. ANESTHESIOLOGY 70:51–56, 1989
40. Eisenach JC, Dewan DM: Intrathecal clonidine in obstetrics: Sheep studies. ANESTHESIOLOGY 72:663–668, 1990