Intraoperative clonidine enhances postoperative morphine patient-controlled analgesia

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In this prospective study, the postoperative analgesic effects of intraoperative iv clonidine were evaluated. Two hundred consecutive patients undergoing major abdominal surgery were randomly assigned to either balanced anaesthesia with iv clonidine (Group 1) or balanced anaesthesia alone (Group 2). A PCA infuser was connected immediately after tracheal extubation. It was programmed to deliver morphine "on demand" iv boluses at doses of 1 mg for patients >65 yr and 1.5 mg for women or 2 mg for men <65 yr old. A blinded observer assessed postoperative analgesia by recording the analgesic demands (both met and unmet), patient pain scores, sedation scores, and any side effects during the first 36 hr after surgery. Intraoperative clonidine reduced the number of analgesic demands during the observation period (45 ± 27 demands in Group 1 vs 81 ± 60 in Group 2, P = 0.0001). This resulted in a reduction in morphine delivered (55.4 ± 30.6 mg vs 67.1 ± 45.1 mg, P < 0.05), mainly during the first 12 hr (19.7 ± 11.1 mg vs 27.6 ± 18.1, mg P < 0.001) and the unmet demand rate was also reduced at all time intervals (P < 0.01). Clonidine did not exacerbate sedation or side effects. However, clonidine provided better analgesia in men and in patients <65 yr of age. Intraoperative iv clonidine enhances morphine analgesia after abdominal surgery.

Cette étude prospective a pour but d'évaluer les effets analgésiques postopératoires de la clonidine administrée par voie iv durant la chirurgie. Deux cents patients admis pour chirurgie abdominale majeure sont distribués de façon aléatoire en deux groupes égaux selon la technique anesthésique utilisée : les patients du groupe 1 ont une anesthésie balancée incluant de la clonidine iv, et ceux du groupe 2, une anesthésie balancée sans clonidine. L'analgésie postopératoire est débutée immédiatement après l'extubation trachéale à l'aide d'une pompe contrôlée par le patient. La pompe permet une administration à la demande de morphine iv. Les doses de morphine sont de 1 mg pour les patients âgés de plus de 65 ans, 1,5 mg pour les femmes et 2 mg pour les hommes de moins de 65 ans. L'intervalle entre les doses est de 7 minutes, avec un maximum de 30 mg pour chaque période de 4 heures. Un observateur non informé de la technique anesthésique utilisée pour chaque patient évalue l'analgésie postopératoire. Les paramètres évalués sont le total des demandes analgésiques (celles avec ou sans administration de morphine), l'échelle de douleur, l'échelle de sédation et les effets secondaires durant les 36 heures suivant la chirurgie. Le nombre de demandes analgésiques est de 45 ± 27 dans le groupe 1 versus 81 ± 60 dans le groupe 2 (P = 0,0001). Ceci se traduit par une moindre utilisation de morphine dans le groupe 1, soit 55,4 ± 30,6 mg versus 67,1 ± 45,1 mg dans le groupe 2 (P < 0,05) ; cette différence est plus marquée dans les 12 premières heures après la chirurgie (19,7 ± 11,1 mg versus 27,6 ± 18,1 mg ; P < 0,001). L'administration de clonidine iv n'est pas associée à une sédation plus importante ou une incidence plus élevée d'effets secondaires. Les effets analgésiques de la clonidine sont plus marqués chez les hommes et chez les patients de moins de 65 ans. En conclusion, la clonidine iv administrée durant la chirurgie augmentent les effets analgésiques de la morphine suite à une chirurgie abdominale.

Key words
ANALGESIA: postoperative;
ANALGESICS: morphine;
SYMPATHETIC NERVOUS SYSTEM: pharmacology, clonidine.

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Adequate postoperative analgesia has become a priority. Besides providing patient comfort, it reduces the incidence of complications and the length of hospitalization.[1] Despite the progress of technology, the exclusive management of pain by epidural or parenteral opiates cannot be achieved without close surveillance or complications.[2] Kehlet recently introduced the concept of postoperative "balanced analgesia" using, among other drugs, opiates,

local anaesthetics, nonsteroidal or steroidal anti-inflammatory drugs.[3,4]

Clonidine, a centrally acting imidazole alpha$_2$ adrenergic agonist, interacts with anaesthesia. It diminishes the requirements for halogenated anaesthetics[5,6] and improves haemodynamic stability.[7] It also makes recovery from anaesthesia smoother by avoiding shivering[8] or, at least, its high metabolic cost.[9] Moreover, clonidine is analgesic via a non-opiate mechanism.[10] The use of alpha$_2$ adrenergic agonists for balanced anaesthesia is currently under investigation.[11]

In this prospective study, the postoperative analgesic effects of intravenous clonidine administered intraoperatively were evaluated by the analgesic demands of patients using a patient-controlled analgesia device.

Methods

The study was approved by the institutional Ethics Committee. Two hundred consecutive patients, ASA physical status I–III, aged 20 to 75 yr, undergoing major abdominal surgery and scheduled for postoperative pain control using morphine patient-controlled analgesia (PCA) were prospectively studied during a five month period.

Exclusion criteria were: emergency procedures, impaired renal or hepatic function, cardiac conduction disturbances, ischaemic or valvular heart disease, chronic use of clonidine, beta-blockers, tricyclic antidepressants or high-dose benzodiazepines, psychiatric illness, alcohol abuse, heavy smokers unable to stop at least one week before surgery. Patients unable to understand PCA pain control or the study protocol at the preoperative visit were also excluded.

All patients gave their informed consent.

The night before surgery, patients were instructed on how to use the PCA device. They were asked to push the analgesic delivery button any time they experienced pain and were encouraged to push again until the pain was relieved. The PCA device was used as an objective way to measure pain as initially described by Sechzer.[12]

Patients were randomly assigned either to Group 1, which received balanced anaesthesia and intravenous clonidine, or Group 2, which were anaesthetized by balanced anaesthesia alone. Preanaesthetic medication consisted of 2 mg sublingual lorazepam and 0.5 mg *im* atropine given 45 min before surgery.

In Group 1, a loading dose of clonidine (4 $\mu g \cdot kg^{-1}$ over 30 min) was started during the induction of anaesthesia and before skin incision; this was followed by an infusion of clonidine 2 $\mu g \cdot kg^{-1} \cdot hr^{-1}$ which was continued until closure of the peritoneum. A pilot study of ten patients conducted in our institution showed that this clonidine infusion regimen provided blood levels of clonidine, measured by radioimmunoassay, of 2.5 $\pm$ 0.5 $ng \cdot ml^{-1}$ after the loading dose and 1.7 $\pm$ 0.4 $ng \cdot ml^{-1}$ at the end of the infusion. A serum concentration of 1.5–2 $ng \cdot ml^{-1}$ is known to be effective in the management of chronic hypertension.[13]

General anaesthesia was induced with 4–6 $mg \cdot kg^{-1}$ thiopentone and 5 $\mu g \cdot kg^{-1}$ fentanyl. Tracheal intubation was performed after the administration of 0.1 $mg \cdot kg^{-1}$ pancuronium. Normocapnia was achieved with mechanical ventilation. Anaesthesia was maintained with 66% nitrous oxide in oxygen and supplemented with isoflurane. Additional doses of fentanyl (1.5 $\mu g \cdot kg^{-1}$) were given as necessary (an increase of 20% or more of basal heart rate or arterial blood pressure). Pancuronium was used for muscle relaxation during surgery. At the end of surgery, the trachea were extubated when the patients were able to execute simple verbal commands. All patients were transferred pain-free to the recovery room.

Immediately after their arrival, patients were connected to a PCA device (Abbott Life Care 4200) and reminded how to self-administer analgesia. The PCA settings were as follows:

(a) morphine hydrochloride bolus doses of 1 mg for patients over 65 yr, and if <65 yr, 1.5 mg for women and 2 mg for males, according to epidemiological variations in postoperative pain.[14]
(b) lockout interval seven minutes.
(c) four-hour limit of 30 mg morphine.
(d) no loading dose.

Patients were encouraged to push the analgesic demand button any time they experienced pain and until a relief was obtained. Because of the lockout interval, not every demand was satisfied. The met and unmet analgesic demands were kept in the PCA computer memory and printed at 12, 24, 36 hr after extubation.

The quality of postoperative analgesia was inferred, for each subject, from the rate and timing of both the met and unmet morphine demands. This method has been suggested as a more objective way to measure analgesic effects than the use of subjective rating scales.[15]

The interval between extubation and first analgesic demand was also recorded.

Patients were asked to quote their analgesia every four hours after surgery according to a four-point analgesia scale: 0 = no pain, 1 = moderate pain, good control with PCA, 2 = moderate pain, poor control with PCA, 3 = unbearable pain.

The degree of sedation was determined every two hours during the first 12 hr, and every four hours afterwards according to a three-point sedation scale: 0 = alert, 1 = sleeping and arousable by verbal command, 2 = sleeping and difficult to arouse by tactile stimulation.

Patients were also observed for bradypnoea (<8 $breaths \cdot min^{-1}$), nausea, vomiting and hallucinations every

TABLE I Patient data and intraoperative characteristics (mean ± SD)

	Group 1 (n = 96)	*P*	*Group 2 (n = 91)*
Male/Female	53/43	ns	50/41
Patients >65 yr	18	ns	20
Age (yr)	52.7 ± 15.6	ns	52.3 + 15.8
Weight (kg)			
– male	75.4 ± 19.8	ns	76 ± 18.6
– female	65.1 ± 16.1	ns	64.6 ± 13.8
Duration of surgery (hr)	4.64 ± 1.6	<0.001	3.98 ± 1.4
Type of surgery			
– gastric	30	ns	24
– colonic	45	ns	37
– pancreatic	9	ns	5
– hepaticojejunostomy	12	ns	25
Fentanyl			
– induction $\mu g \cdot kg^{-1}$	5.7 ± 1.8	ns	5.5 ± 2.0
– incision $\mu g \cdot kg^{-1}$	1.8 ± 1.41	0.01	2.9 ± 1.1
– procedure $\mu g \cdot kg^{-1}$	3.8 ± 3	ns	6.6 ± 7.4
Intraoperative clonidine $\mu g \cdot kg^{-1}$	12.5 ± 3.4		0
Extubation delay min	48 ± 27	ns	43 ± 32

Statistical significance levels: t test and Fischer Exact t test for contingency tables.

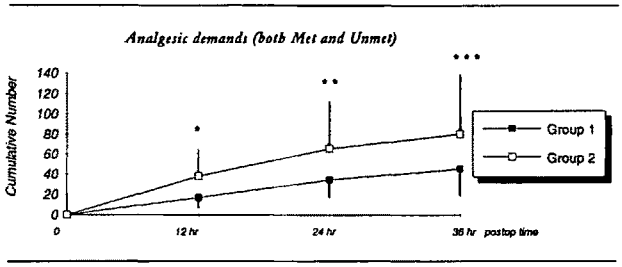

FIGURE 1 Evolution of the analgesic demands of patients in Group 1 (intraoperative *iv* clonidine $n = 96$) and in Group 2 ($n = 91$). 0 = extubation time. Results are expressed as medians ± SD. ★$P = 0.00001$. ★★$P = 0.0001$. ★★★$P = 0.000001$ (Mann-Whitney pairs test).

TABLE II Morphine delivered (mg) (mean ± SD)

	Group 1 (n = 96)	*P*	*Group 2 (n = 91)*
0–12 hr	19.7 ± 11.1	<0.001	27.6 ± 18.1
12–24 hr	20.9 ± 13.6	ns	24.3 ± 18.2
24–36 hr	14.9 ± 12.5	ns	16.4 ± 15.2
0–36 hr	55.4 ± 30.6	<0.05	67.1 ± 45.1

Morphine delivered for each 12 hr period postoperatively (MANOVA). Group 1 = clonidine, Group 2 = no clonidine.

two hours during the first 12 hr after surgery and every four hours until the end of the use of the PCA device. Other postoperative complications were also recorded (e.g., prolonged ileus, hypotension, bradycardia, rebound hypertension) during the first postoperative week. Urinary retention was not evaluated as all patients had a bladder catheter inserted for surgery.

At the end of the observation period, patients were asked to evaluate their postoperative pain management according to a three point satisfaction scale: 2 = excellent, 1 = good, 0 = bad.

The patient's treatment group was blinded to the observer who assessed postoperative pain relief and occurrence of side effects. The observer was never the anaesthetist in charge of the patient.

Statistical analysis of the data was performed using Student's t test for parametric comparison of groups, Fisher's exact t test for analysis of contingency tables of distribution of patients within groups and Mann-Whitney pairs test for non-parametric comparison of independent groups when appropriated. Differences between parametric data were analyzed by multifactorial analysis of variance. The frequency table (patients' pain score) was analysed using the multi-way frequency table technique.

A P value of <0.05 was considered significant.

Results

Of the 200 patients enrolled in this study, 13 were withdrawn (four in Group 1 and nine in Group 2) because it was decided during surgery to ventilate their lungs postoperatively (haemorrhagic procedures, allergic reactions, thoracic extension of surgical field). The remaining patients in both groups were comparable regarding age, sex and weight. Patients in Group 1 were randomly assigned to more profound surgical procedure which explains the longer duration of surgery in this group (Table I). There was no difference between groups with respect to allocation of morphine bolus doses.

Intraoperative administration of clonidine (Group 1) decreased the total demand (0–36 hr) (both met and unmet) for analgesia (45 ± 27 demands in Group 1 vs 81 ± 60 in Group 2, $P = 0.0001$). The analgesic demand rate was also lower in Group 1 at any 12-hr interval considered ($P < 0.001$) (Figure 1).

The reduction of total (0–36 hr) morphine delivery in Group 1 was mainly by a reduction of the requirements during the first 12 hr after surgery (Table II). The unmet demands rate in this group remained lower (median 5 range interval 81 vs 25 range interval 252, $P < 0.01$) at any time interval considered.

The influence of intraoperative clonidine on postoperative analgesic demands was evaluated at each level of morphine bolus dose.

For the patients >65 yr (1 mg bolus dose), intraoperative *iv* clonidine did not reduce the analgesic demands nor the morphine requirements at any 12-hr interval considered

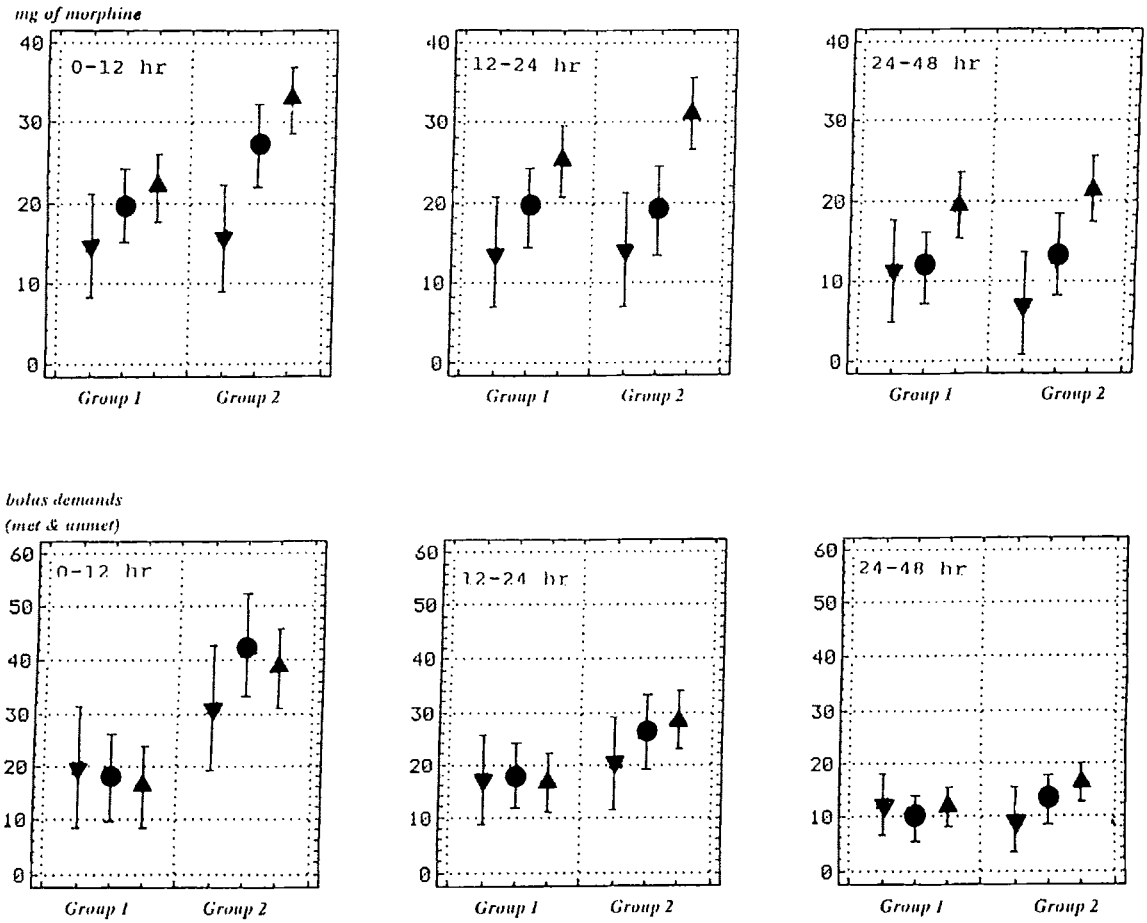

FIGURE 2 Morphine administered and analgesic demands (met and unmet) printed according to the various morphine doses. Group 1: *iv* clonidine (n = 96). Group 2: no *iv* clonidine (n =91). ▼ = 1 mg bolus = patients >65 yr. ● = 1.5 mg bolus = women <65 yr. ▲ = 2 mg bolus = male <65 yr (mean ± SD).

(Figure 2). The unmet demand rate was reduced only during the first 12 hr (n = 3.5 in Group 1 versus 15 in Group 2, P = 0.01).

For patients <65 yr, clonidine reduced the analgesic demands at all time intervals (P < 0.001). The total (0–36 hr) morphine amount decreased from 85.7 ± 47.5 to 62.8 ± 33.6 mg (P < 0.05) for men and from 59.5 ± 42.2 to 57.8 ± 34.5 mg (NS) for women. The most important reduction occurred in both sexes 12 hr after surgery (P < 0.05).

The patients' pain scores are also in accordance with better postoperative pain control in Group 1 than in Group 2 (Figure 3).

The interval between tracheal extubation and the first analgesic demand was not prolonged in Group 1: 96.3 ± 94 vs 77.7 ± 88.9 in Group 2 (NS).

Sedation Scores did not vary among the two groups at any time interval considered (Figure 4).

The incidence of other side effects was low in both groups. There was no bradypnoea or hallucinations and no hypotensive or bradycardic episodes were recorded intra or postoperatively. None of the patients who received clonidine developed rebound hypertension during the one week observation period.

The clinical course was uncomplicated in all patients.

Twenty patients of Group 1 complained of nausea versus 28 in Group 2 (NS). Vomiting, related to the use of PCA, occurred in two patients of Group 2 (NS).

At the end of the observation period, 72% of the patients in Group 1 evaluated their pain management as exellent, 25% as good and 3% as bad. In Group 2, 44% found it excellent, 51% good, 5% bad (P < 0.001).

Discussion

Despite the wide individual variability in the demand for analgesia after major abdominal surgery,[16] our results disclose that the intraoperative administration of intravenous clonidine improved the quality of postoperative

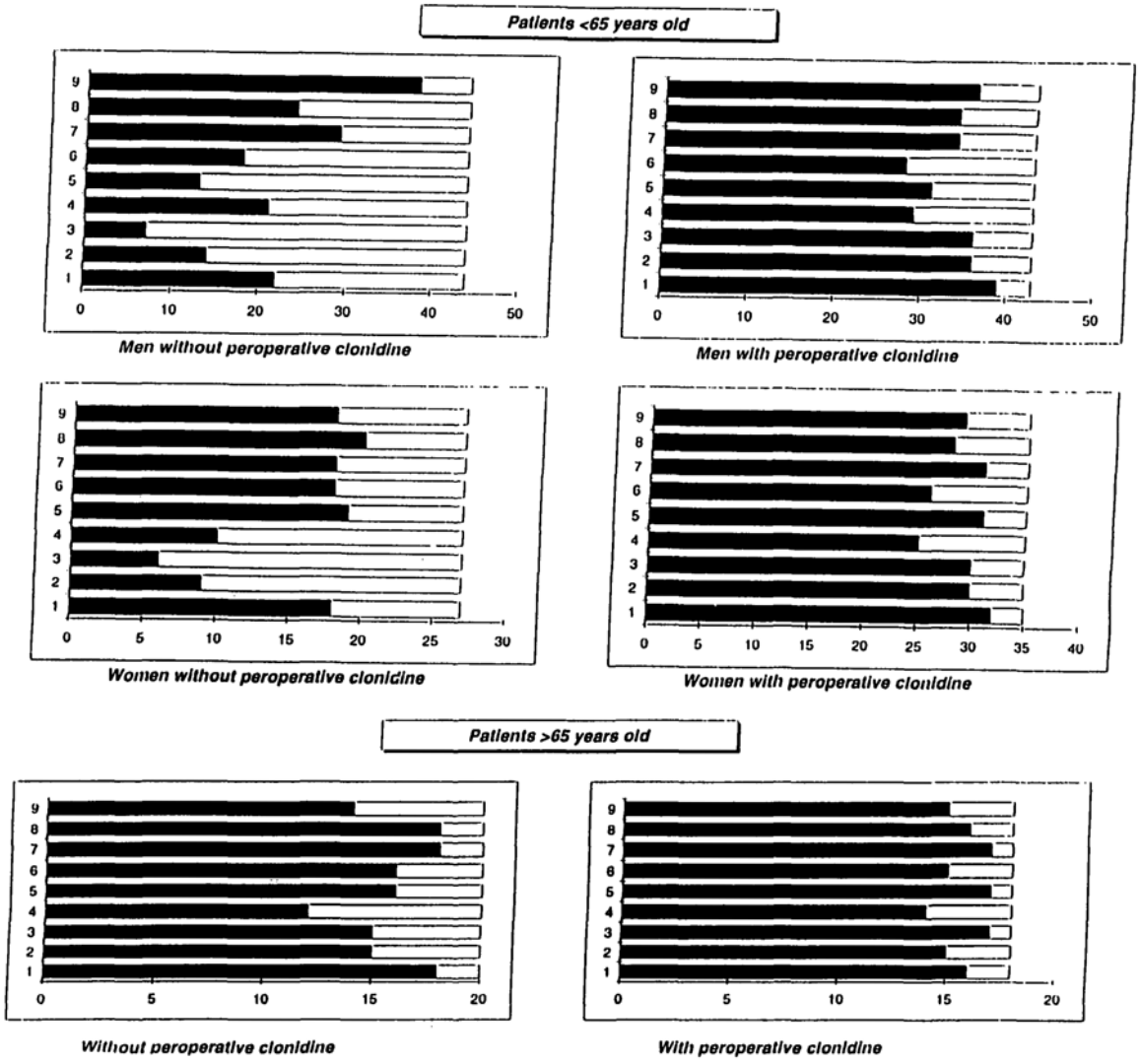

FIGURE 3 Patients' pain scores during four-hour period until 36 hr after surgery (1 = 0–4 hr, 2 = 4–8 hr, 3, 4, 5, 6, 7, 8, 9 = 30–36 h) divided according to sex, age <65, and clonidine treatment. Frequency table for patients <65 yr grouped by sex having received clonidine or not during the operation. Multi-way frequency table analysis: pain × sex × time, $P < 0.05$; pain × clonidine × time, $P = 0.000001$. Frequency table for patients >65 yr old. Multi-way frequency table analysis: pain × clonidine, $P < 0.05$.

morphine PCA. Patients in the clonidine group had a reduced rate of analgesic demands during the observation period. Less morphine was delivered by the PCA device and the unmet demand rate was lower. Patient pain scores were in accordance with these findings which were not the result of excessive sedation impairing patients' ability to self-administer analgesia. Moreover, intraoperative use of clonidine did not induce side effects nor exacerbate morphine side effects. Clonidine enhanced the quality of postoperative analgesia.

There is physiological and biochemical evidence for the existence of different systems that modulate the processing of nociception at different levels in the central nervous system.[17] There are, among others, neuronal pathways using opiate- and alpha$_2$ adrenergic receptor agonists.[18] Their actions are additive and complementary.[19] Clonidine, a central acting alpha$_2$ adrenergic agonist relieves pain when administered enterally, parenterally, epidurally or intrathecally.[20–22] Animal studies have shown that some groups of noradrenergic neurons in the brainstem have axonal connection with the spinal dorsal horn and are involved in the control of pain.[23] Stimulation of those central noradrenergic neurons by alpha$_2$ agonists increases nociceptive thresholds.[24] In clinical practice, clonidine

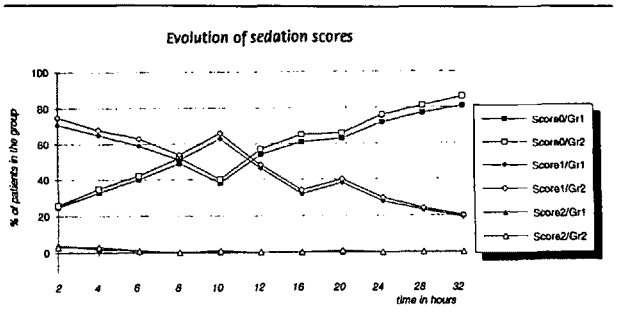

FIGURE 4 Sedation scores. Group 1: *iv* clonidine ($n = 96$). Group 2: no *iv* clonidine ($n = 91$). Score: 0 – alert. 1 – sleeping and arousable by verbal command. 2 – sleeping, difficult to arouse by tactile command no statistically significant differences at any time interval.

relieves pain resistant to morphine such as neurogenic and cancer pain.[25] Clonidine has also been reported to have a selective antinociceptive effect on visceral pain.[26]

Several experimental and clinical studies have demonstrated a potentiation of the antinociceptive effect of morphine by systemic clonidine administration.[27–29] Recruitment of other neurotransmitters (acetylcholine, adenosine, growth hormone) and inhibition of the release of substance P by clonidine may also have an additive analgesic effect.[30,31]

A prophylactic effect of intraoperative clonidine on postoperative pain may be suspected. It has recently been established that nociceptive impulses from the operative field may induce a prolonged and widespread exacerbation in spinal cord excitability and supraspinal perception leading to hyperalgia.[32,33] This constitutes one of the pathophysiological mechanisms underlying postoperative pain. Balanced anaesthesia alone cannot prevent such an hyperexcitable state.[34] A large dose of clonidine (4 $\mu gr \cdot kg^{-1}$) given before the surgical stimulus may enhance the central noradrenergic inhibitory control on the dorsal horn interneurone and prevent this spinal hyperexcitability phenomenon or its consequences.

If a reduction in morphine requirements during the first 12 hr after surgery is in accordance with the reported terminal half-life of acute intravenous clonidine (8–10 hours),[35] effective circulating levels cannot account for a reduction of unmet demands lasting 36 hr. A pharmacokinetic interaction between clonidine and morphine as reported for alfentanil[36,37] also cannot explain those differences.

A prolonged effect on postoperative analgesia may be explained by the anxiolytic[38,39] and thymoanaleptic[40] properties of the alpha$_2$ agonists that help to reduce the emotional component of postoperative pain. The reduced rate of unmet demands and the better satisfaction scores in the clonidine group may support this hypothesis.

Age and sex are two important epidemiological variables concerning postoperative analgesia.[15] The analgesic benefits of intraoperative clonidine decrease for men, women and elderly patients respectively. Intraoperative clonidine is more effective in young middle-aged men. Age and sex-related variations in noradrenergic pain modulation pathways may account for these differences.[41] This observation may provide a new insight into the physiological mechanisms underlying the sex variation in pain perception.[42]

The occurrence of morphine side effects was not increased by clonidine as reported here and detailed by others.[43] No adverse haemodynamic effects were noted in the clonidine group. Rebound hypertension after discontinuing clonidine occurs generally 20 hr after discontinuation of chronic treatment and this syndrome is probably rare considering the large number of patients treated.[13]

Clonidine has specific analgesic properties, shows synergistic analgesic effects with opiates and is particularly effective for visceral pain relief. A prophylactic action on postoperative pain perception could be discussed having in mind its anxiolytic properties. In this study, intraoperative clonidine improved the quality of postoperative analgesia after abdominal surgery. This effect is, however, more important for patients >65 than for those <65 yr of age. Considering the absence of side effects with the dosage used, clonidine should be considered as a constituent of the postoperative "balanced" analgesia.

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