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Dexmedetomidine as an Adjunct to Epidural Analgesia After Abdominal Surgery in Elderly Intensive Care Patients: A Prospective, Double-Blind, Clinical Trial

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ABSTRACT

BACKGROUND: The ideal postoperative analgesia management of elderly surgical patients in intensive care units (ICUs) is continually being investigated.

OBJECTIVE: The purpose of this study was to assess the effectiveness and tolerability of IV administration of dexmedetomidine as an adjunct to a low-dose epidural bupivacaine infusion for postoperative analgesia after abdominal surgery in elderly patients in the ICU.

METHODS: ICU patients aged >70 years undergoing abdominal surgery were eligible for the study. A lumbar epidural catheter was inserted at the beginning of the surgery with no medication. On arrival at the ICU, the catheter was loaded with 0.25% bupivacaine 25 mg at the T8 to T10 sensory level, and a continuous infusion of 0.125% bupivacaine was started at 4 to 6 mL/h in combination with patient-controlled epidural analgesia (PCEA) of fentanyl (4 μg/bolus) for pain treatment. Patients in the treatment group received dexmedetomidine as an IV loading dose of 0.6 μg/kg for 30 minutes followed by continuous infusion at 0.2 $\mu g/kg \cdot h^{-1}$. Patients in the control group were not administered dexmedetomidine. The effectiveness of the pain relief was determined using a visual analog scale (VAS) (0 = no pain to 10 = worst pain imaginable) at rest. VAS score, heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure, and arterial blood gases were monitored periodically for 24 hours after surgery. If required, tenoxicam (20-mg IV bolus) was used to ensure a VAS score of ≤3. The number of times PCEA and tenoxicam were administered and the occurrence of adverse events (AEs) were also recorded.

RESULTS: Sixty patients (34 men, 26 women; mean [SD] age, 75.96 [4.25] years; mean [SD] weight, 74.13 [10.62] kg) were included in the study. VAS scores were significantly lower in the dexmedetomidine group compared with the control group at hours 1, 2, and 12 (VAS [hour 1]: 2.8 [0.4], $P < 0.001$; VAS [hour 2]: 2.7 [0.5], $P < 0.001$; and VAS [hour 12]: 0.9 [0.7], $P = 0.044$). The mean number of administrations of fentanyl via PCEA was significantly greater in the control group compared with the dexmedetomidine group (2.20 vs 6.63 times; $P < 0.001$). The mean number of administrations of tenoxicam was significantly lower in the treatment group than the control group (0.27

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vs 1.07 times; $P < 0.001$). In the control group, the decreases in sedation at 0, 8, 12, 16, and 20 hours were significant compared with baseline ($P = 0.024$, $P = 0.001$, $P = 0.020$, $P < 0.001$, and $P = 0.005$, respectively). Mean HR, SBP, and AEs (eg, bradycardia [HR <60 beats/min], respiratory depression [respiratory rate <8 breaths/min], hypotension [SBP <90 mm Hg], oversedation, hypoxia, and hypercapnia) decreased significantly in the dexmedetomidine group (all, $P < 0.05$). Significantly more patients in the dexmedetomidine group rated their satisfaction with postoperative pain control as excellent compared with the control group (12 vs 6 patients; $P = 0.014$).

CONCLUSION: Intravenous dexmedetomidine was effective and generally well tolerated as an analgesic adjunct to epidural low-dose bupivacaine infusion for pain treatment, with lower need for opioids after abdominal surgery in these elderly intensive care patients than in the control group. (*Curr Ther Res Clin Exp.* 2008;69:16–28) © 2008 Excerpta Medica Inc.

KEY WORDS: postoperative analgesia, elderly patients, dexmedetomidine, epidural analgesia.

INTRODUCTION

Elderly surgical patients in intensive care units (ICUs) manifest specific characteristics, including cardiac conditions, systemic pathologies, and increased sensitivities to sedatives and analgesics, that require additional attention when choosing the appropriate analgesic routes of administration and drugs.[1–3]

Epidural analgesia is the most commonly recommended method for postoperative pain management of this age group.[4] However, choosing the optimal epidural drug is still the subject of many investigations.[2,4] Using only local anesthetics at effective doses raises concerns about adverse events (AEs), such as hypotension, bradycardia, motor weakness, and elevation in block level.[3] Opioid combinations may not provide satisfactory results, as they are associated with respiratory failure, nausea, and vomiting.[2,3]

Because of its effective sedative properties, use of the α_2-agonist dexmedetomidine in intensive care patients is under study.[5–7] Its use in pain management has also been studied because of its analgesic attributes.[8–11] However, as with other α_2-agonists, the AEs associated with dexmedetomidine (eg, bradycardia, hypotension), which are caused by its central sympatholytic effects, are still being investigated.[7,12]

The aim of this study was to investigate the effectiveness and tolerability of the analgesia obtained by combining a low-dose local anesthetic in epidural analgesia with IV dexmedetomidine infusion for postoperative pain management of elderly surgical intensive care patients.

PATIENTS AND METHODS

The ethics committee of Baskent University School of Medicine, Adana, Turkey, approved the study, which was designed as a prospective clinical investigation with patients aged >70 years who were to undergo major abdominal surgery and to be monitored postoperatively in the ICU of the university. Patients with advanced heart failure (ejection fraction <30%); respiratory failure; indications for mechanical ventilation; a

diagnosis of kidney or liver failure; use of long-term narcotic drugs for any reason; or a history of vertebral surgery, coagulation defect, bleeding diathesis, sepsis, shock, or a neurologic pathology similar to dementia that might hamper their ability to cooperate were excluded from the study. Written informed consent was obtained from all participants prior to study enrollment.

Anesthesia was induced using IV thiopental sodium 5 mg/kg and fentanyl 1 μg/kg; IV vecuronium 0.1 mg/kg was administered for muscle relaxation. After endotracheal intubation, anesthesia was to be maintained using 1% isoflurane and nitrous oxide in 50% oxygen. The patient was placed in the left lateral position, and an 18-gauge epidural catheter (Portex® Epidural Minipack, Smiths Medical, Hythe, United Kingdom) was inserted into the L3 to L4 intervertebral space. Surgery was performed without sending any medication or saline through the catheter.

After surgery, patients were extubated and transferred to the ICU. No vasoactive drug was administered to the patients. Fluid was administered to maintain central venous pressure at 7 to 9 mm Hg and hematocrit >30%. After the initial administration of 0.25% plain bupivacaine 25 mg (AstraZeneca LP, Wilmington, Delaware) epidurally as the loading dose, 0.125% plain bupivacaine was started at an infusion rate of 4 to 6 mL/h to achieve analgesia at the T8 to T10 sensory level.

The study was designed as a pseudorandomized clinical trial. After achieving adequate analgesia, the patients were divided into 2 groups based on the order in which they were admitted to the ICU. The patients and the investigators assessing responses and AEs were blinded to treatment allocation. Dexmedetomidine* was administered to the treatment group at an infusion rate of 0.6 μg/kg for 30 minutes and maintained at 0.2 μg/kg · h^{-1}. The control group was not administered dexmedetomidine.

A visual analog scale (VAS) (0 = no pain to 10 = worst pain imaginable) was used to assess pain intensity and a sedation-agitation scale (SAS) (1 = unarousable to 7 = dangerous agitation) was used to assess sedation level.[13] Analgesia was planned to assure a VAS score ≤3 in both groups. The analgesia level could be increased when required (ie, VAS score >3 after 30 minutes of analgesia) using patient-controlled epidural analgesia (PCEA) with fentanyl 2-mL/bolus (2 μg/mL) and a lockout time of 10 minutes. In addition, tenoxicam (20-mg IV bolus) could be administered, if required (ie, VAS score >3 after 30 minutes of epidural fentanyl administration).

Analgesia level, hemodynamic parameters (heart rate [HR], systolic blood pressure [SBP], and diastolic blood pressure [DBP]), arterial blood gases, peripheral oxygen saturation, and sedation level at 0, 0.5, 1, 2, 4, 8, 12, 16, 20, and 24 hours were recorded for all study patients. Hemodynamic parameters, blood gas analysis, and respiratory function were used to assess the effectiveness and tolerability of pain treatment. AEs (eg, bradycardia [HR <60 beats/min], respiratory depression [respiratory rate <8 breaths/min], hypotension [SBP <90 mm Hg], oversedation, hypoxia, and hypercapnia) were assessed throughout the study. The number of PCEA administrations of fentanyl and the number of tenoxicam doses were determined at the end of the 24-hour postsurgical period. The patients were also asked if they experienced any AEs, and they were

*Trademark: Precedex® (Hospira Inc., Lake Forest, Illinois).

specifically asked about nausea and vomiting, pruritus, or unexpected headache (all epidural catheters were inserted very carefully to prevent spinal headache). At the end of the study, patient satisfaction with postoperative pain control was investigated using a validated scale (1 = bad, 2 = moderate, 3 = good, 4 = excellent).[14]

STATISTICAL ANALYSIS

Statistical analysis was performed using the Statistical Package for Social Sciences, version 11.0 (SPSS Inc., Chicago, Illinois). The Student *t* test and paired *t* test were used to analyze normally distributed data. Data that were not normally distributed were assessed using the Mann-Whitney *U* test and Wilcoxon signed-rank test. $P < 0.05$ was considered to be statistically significant. A sample size of 22 patients per group was determined, through power analysis ($\alpha = 0.05$; $\beta = 0.90$), to be needed to detect a decrease in VAS score to three 1 hour postoperatively with an SD of 1. Thirty patients were enrolled per group to account for dropouts.

RESULTS

Sixty patients (34 men, 26 women; mean [SD] age, 75.96 [4.25] years; mean [SD] weight, 74.13 [10.62] kg) were included in the study. No significant differences were found between the groups in age, sex, weight, height, or duration or type of surgery (**Table**).

During the course of the study, hemodynamic parameters (HR, SBP, DBP) in the dexmedetomidine and control groups decreased significantly compared with baseline values (all, $P < 0.05$) (**Figure 1**). While the mean HR in the treatment group was significantly lower at hour 2 compared with the control group (86.43 [5.26] vs 93.03

Table. Baseline demographic and clinical characteristics of elderly intensive care patients requiring abdominal surgery (N = 60).*

Variable	Dexmedetomidine Group (n = 30)	Control Group (n = 30)
Age, mean (SD), y	75.66 (3.86)	76.26 (4.66)
Sex, no. (%)		
Male	16 (53.3)	18 (60.0)
Female	14 (46.7)	12 (40.0)
Weight, mean (SD), kg	73.43 (9.98)	74.83 (11.35)
Height, mean (SD), cm	167.03 (8.45)	158.80 (23.82)
Duration of surgery, mean (SD), min	269.33 (78.86)	269.00 (89.03)
Type of surgery, no.		
Whipple surgery	7	7
Total or hemicolectomy	11	9
Intestinal resection	8	9
Radical cystectomy	4	5

*No significant between-group differences were found.

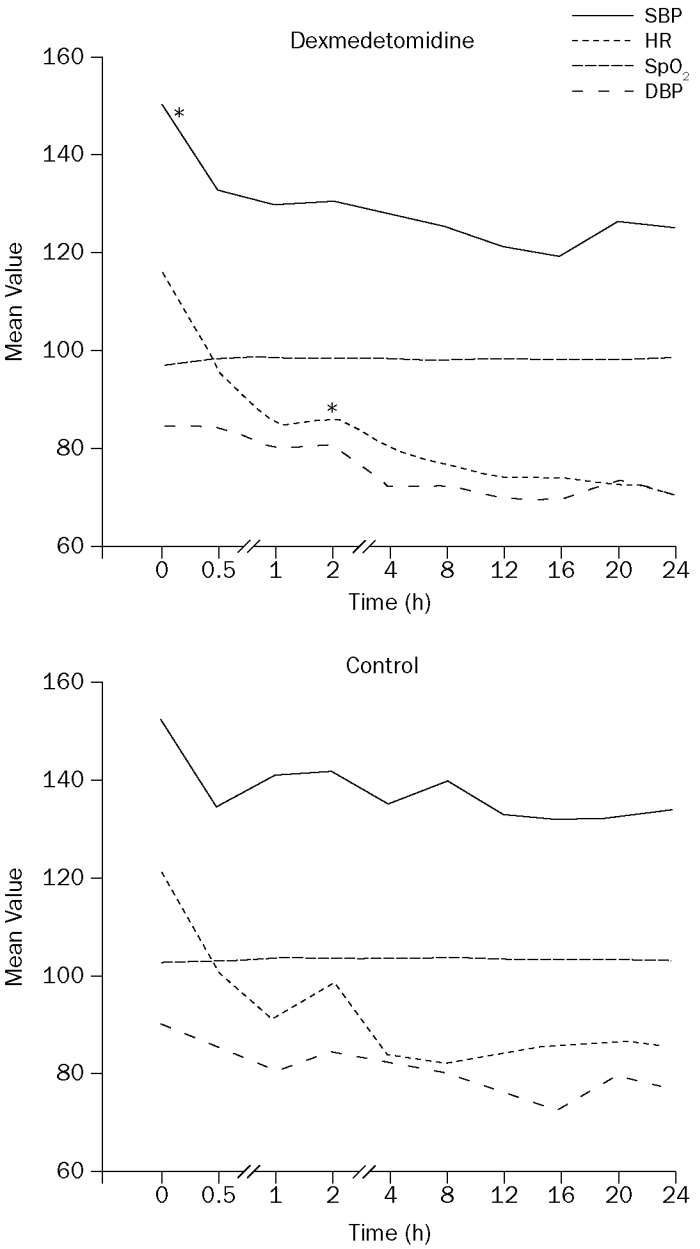

Figure 1. Hemodynamic parameters (heart rate [HR] in beats per minute, systolic blood pressure [SBP] in mm Hg, diastolic blood pressure [DBP] in mm Hg) and peripheral oxygen saturation (SpO_2) in mm Hg by treatment group in elderly intensive care patients requiring abdominal surgery (N = 60). *$P < 0.001$ versus control.

[9.49] beats/min; $P < 0.001$), there were no other significant between-group differences in HR. Whereas the decrease in HR in the treatment group was significantly lower than in the control group, after 16 hours none of the HR values were found to be outside the normal range (16-hour mean HR of treatment group: 73.63 [4.27] beats/min). Although SBP values were within the normal range, they were found to be decreased significantly in the treatment group beginning with hour 1 compared with baseline. SBP values were significantly decreased throughout the 24-hour period (all, $P < 0.001$). Except at hour 1 in the treatment group (79.86 [6.62]; $P = 0.007$), there were no significant between-group differences in DBP. No significant differences were found in blood gas analysis or peripheral oxygen saturation between groups.

After 1 hour, VAS scores indicated that analgesia was effective in both groups compared with baseline values. VAS scores were significantly lower in the dexmedetomidine group compared with the control group at hours 1, 2, and 12 (VAS [hour 1]: 2.8 [0.4], $P < 0.001$; VAS [hour 2]: 2.7 [0.5], $P < 0.001$; and VAS [hour 12]: 0.9 [0.7], $P = 0.044$) (**Figure 2**).

The mean number of administrations of fentanyl via PCEA was significantly greater in the control group compared with the dexmedetomidine group (2.20 vs 6.63 times; $P < 0.001$) (**Figure 3**). The mean number of administrations of tenoxicam was also significantly lower in the dexmedetomidine group than in the control group (0.27 vs 1.07 times; $P < 0.001$).

SAS scores decreased in both groups compared with baseline values. In the control group, the decreases at 0, 8, 12, 16, and 20 hours were significant (SAS [hour 0]: 5.1 [1.0], $P = 0.024$; SAS [hour 8]: 2.4 [0.5], $P = 0.001$; SAS [hour 12]: 3.2 [0.6], $P = 0.020$; SAS [hour 16]: 3.1 [0.3], $P < 0.001$; and SAS [hour 20]: 3.3 [0.4], $P = 0.005$) (**Figure 4**).

In the control group, 5 patients (16.7%) were administered atropine sulfate (0.5 mg IV) for the treatment of bradycardia and 4 patients (13.3%) required volume replacement due to hypotension. Five patients (16.7%) in the control group and 1 patient (3.3%) in the dexmedetomidine group had postoperative nausea. No other AEs were experienced in the treatment group.

Significantly more patients in the dexmedetomidine group compared with the control group rated their satisfaction with postoperative pain control to be excellent (12 vs 6 patients; $P = 0.014$) (**Figure 5**). In both groups, 18 patients rated the experience as good. Six patients in the control group compared with none in the treatment group were not adequately satisfied with postoperative pain control.

DISCUSSION

The number of surgeries performed in elderly patients has been increasing rapidly.[3] Particularly after major surgeries, such as intra-abdominal surgery, these patients are closely monitored in the ICU with hemodynamic and respiratory follow-up, bleeding control, and effective postoperative analgesia and sedation.[2]

Appropriate sedation and analgesia levels during the postoperative period in geriatric patients are known to significantly affect morbidity and mortality by decreasing delirium and preventing age-related pharmacodynamic and pharmacokinetic changes.[1,15]

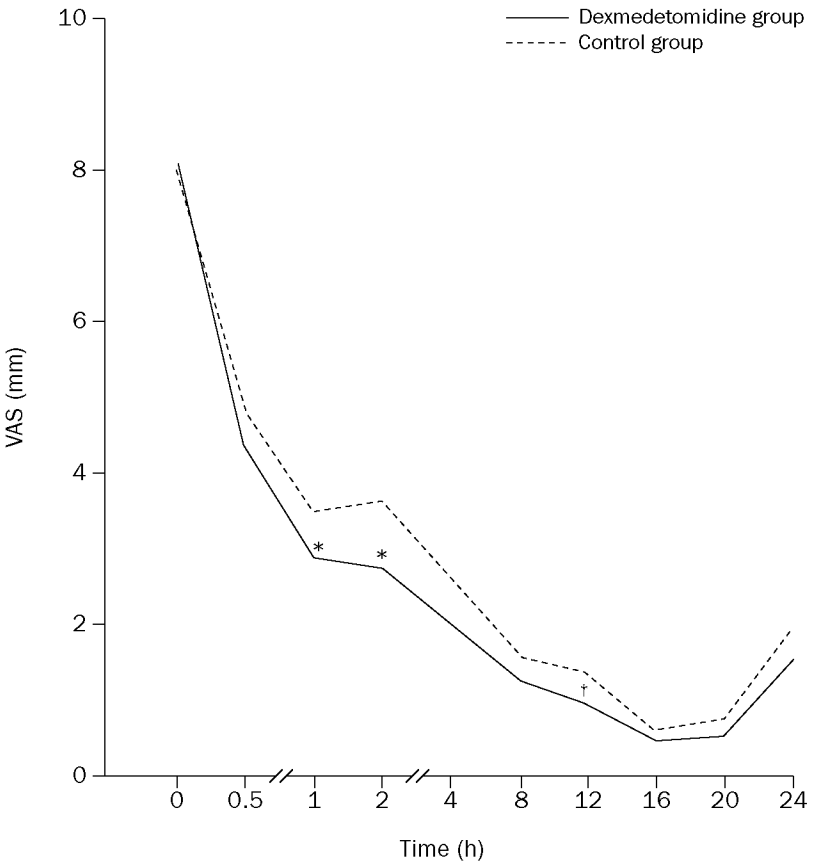

Figure 2. Visual analog scale (VAS) scores for pain level by treatment group in elderly intensive care patients requiring abdominal surgery (N = 60). Scale: 0 = no pain to 10 = worst pain imaginable. *$P < 0.001$ versus control; †$P = 0.044$ versus control.

The importance of pain management in postoperative delirium, which is seen commonly in elderly patients, is a significant factor in delaying recovery.[9,15–18] While the analgesia plan to be used during the postoperative period varies depending on the age of the patient, the type of surgery, and the overall health status of the patient, ideal methods and drugs to be used for analgesia are still under investigation. Physiologic and systemic pathologic changes occurring in elderly patients contribute to the importance of the postoperative analgesia method.[1,2]

Epidural techniques are commonly used in postoperative analgesia for elderly patients, with the combination of a local anesthetic and an opioid being preferred.[3,4] However, the occurrence of serious AEs (eg, hypotension, respiratory depression, deep bradycardia) and unwanted AEs (eg, nausea, vomiting, motor block) with these analge-

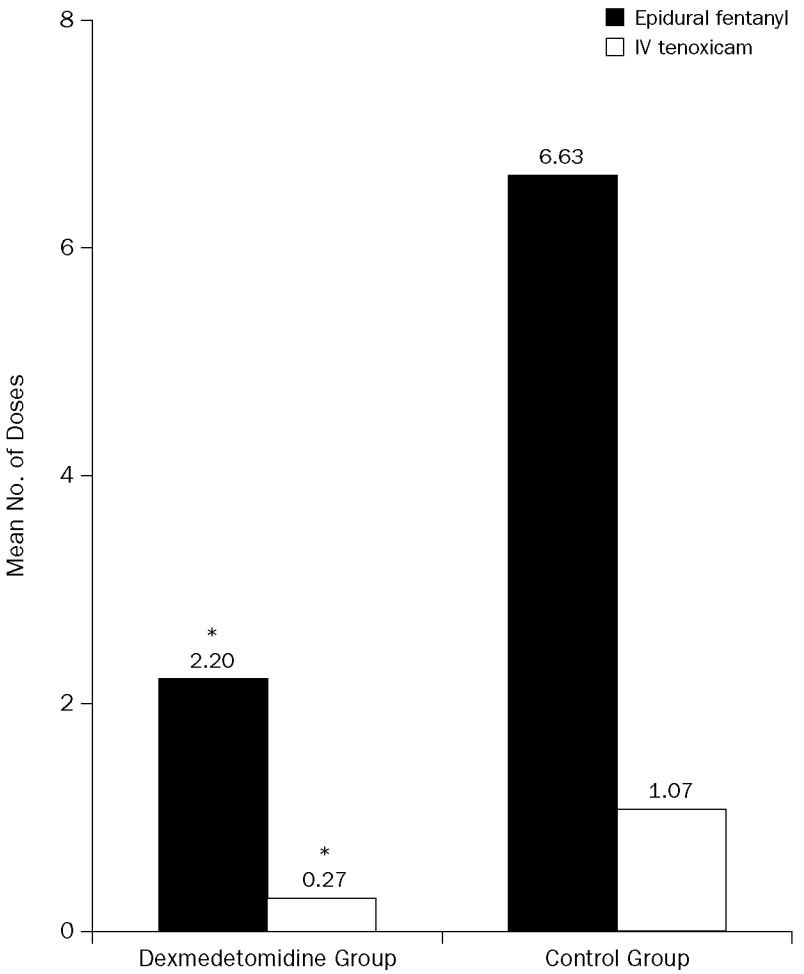

Figure 3. Mean number of doses of epidural fentanyl and IV tenoxicam by treatment group in elderly intensive care patients requiring abdominal surgery (N = 60). *$P < 0.001$.

sic regimens make it necessary to continue research about different and more optimal analgesia methods.[1,3] The α_2-agonists, particularly the combination of clonidine with local anesthetics administered via the epidural or spinal route, has been found to be effective in pain management.[19–21] Dexmedetomidine, another α_2-receptor agonist, is commonly used in ICUs for sedation of patients with psychological problems, including delirium.[6,7,22] The dose range of this drug, preferably used intravenously, varies depending on the severity of the sedation (SAS ≤3; difficult to arouse but awakens to verbal stimuli and drifts off again).[23] In various clinical studies, dexmedetomidine has been found to reduce the doses of opioids, benzodiazepines, propofol, and antipsychotic drugs

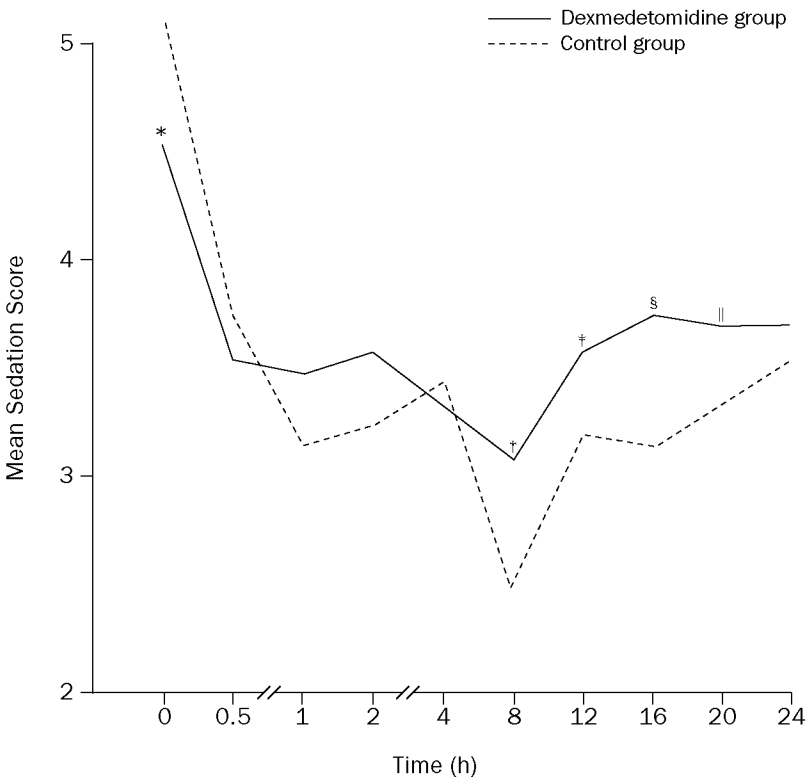

Figure 4. Mean sedation-agitation scale scores by treatment group in elderly intensive care patients requiring abdominal surgery (N = 60). Scale: 1 = unarousable to 7 = dangerous agitation. *P = 0.024 versus control; †P = 0.001; ‡P = 0.020; §P < 0.001; ‖P = 0.005.

in ICUs.[6,7] The effective analgesia obtained with dexmedetomidine has been widely discussed.[8–11] Its effect on increasing sedation and analgesia via its central influence on the locus ceruleus and the posterior horn of the spinal cord has been reported.[24] However, clinical studies on its spinal and epidural use are limited.

The aim of this study was to determine the effectiveness and tolerability of a moderate dose of IV dexmedetomidine on postoperative pain relief combined with a continuous low-dose local anesthetic administered epidurally. Because sedation and hemodynamic AEs associated with dexmedetomidine may be a problem for geriatric patients,[10] the drug was used in moderate doses. The required analgesic dose for all the patients was supported by low-level epidural fentanyl administration at intervals via PCEA. In cases where the epidural technique was insufficient, intravenous tenoxicam was added to the treatment.

During the study we used a VAS to assess the effectiveness of pain relief; maintaining a VAS score ≤3 was the main goal of the study. In the present study, adequate

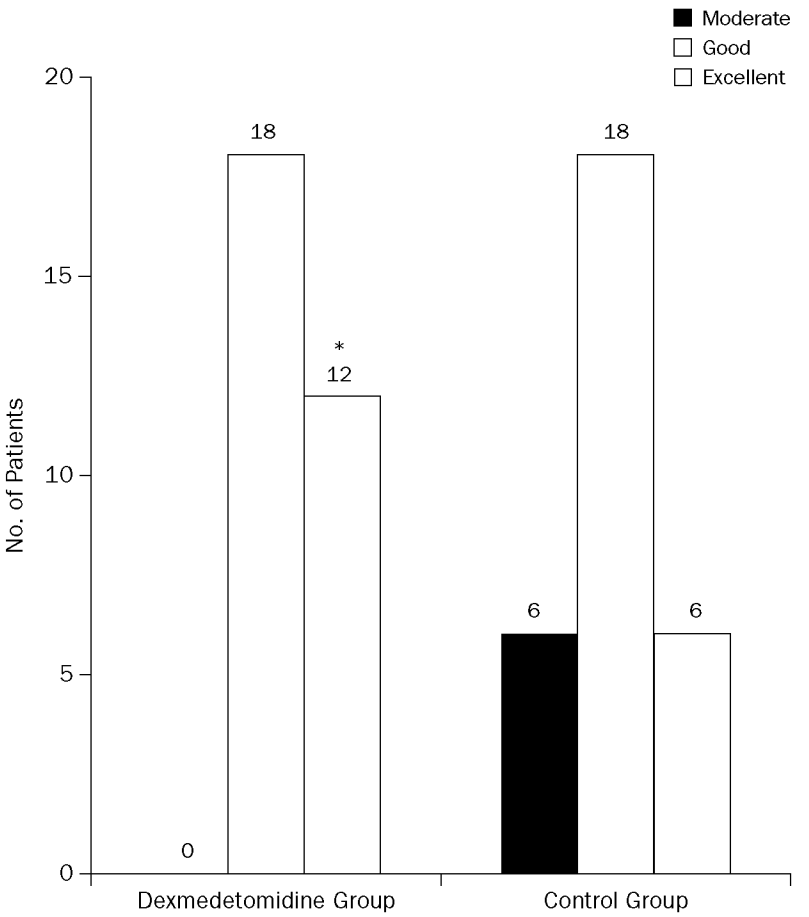

Figure 5. Patient satisfaction scale scores for postoperative pain control by treatment group in elderly intensive care patients requiring abdominal surgery (N = 60). Scale: 1 = bad, 2 = moderate, 3 = good, 4 = excellent. *$P < 0.014$ versus control.

analgesia levels were achieved in both groups. However, the fact that although VAS values in the dexmedetomidine group were significantly lower than in the control group at some measurement times, the need for a significantly lower number of doses of fentanyl may be an important advantage. This result supports the systemic analgesic attribute of dexmedetomidine.[8–11,25] Therefore, a lower number of doses of fentanyl and tenoxicam may be associated with fewer AEs and lower sedation, which may contribute to more a comfortable postoperative period for patients.

Dexmedetomidine was reported to increase the sedative effects of opioids but was as effective as opioids when used as monotherapy.[8,26] In this study, a more continuous and moderate sedation level was observed in the dexmedetomidine group. However, while

the sedation level in the control group was different from baseline and compared with the treatment group at most times, occasional occurrences of deep sedation were thought to be associated with the frequency of the fentanyl boluses. Administering dexmedetomidine via infusion for sedation of ICU patients is particularly recommended to achieve good continuous sedation.[10] In this study, use of dexmedetomidine infusion at a moderate dose (0.2 μ/kg · h^{-1}) in patients administered a low dose of local anesthetic (0.125% bupivacaine 4–6 mL/h) via epidural catheter was found to be effective.

While local anesthetics administered epidurally are associated with AEs (eg, respiratory and cardiac events), α_2-agonists are also associated with AEs, such as bradycardia and hypotension.[3,7,12] The advantage of a minimal risk for respiratory depression with IV dexmedetomidine in patients with bradycardia and hypotension has been reported in studies on ICU sedation.[12,26] In the present study, while mean HR and SBP were significantly lower in the dexmedetomidine group, they remained within normal limits which was an advantage in these geriatric patients. This may be associated with appropriate analgesia and sedation levels in the dexmedetomidine group and minimal cardiovascular AEs of the drug.[7,8,10,27] In addition, a significant reduction of nausea and vomiting in the dexmedetomidine-treated patients may have been associated with the lower amount of fentanyl they used.

Although paracetamol and NSAIDs are known to be well tolerated, they are not sufficient for pain management after major abdominal surgery.[1,28] In the present study, the NSAID tenoxicam was added to the pain management regimen if needed to achieve sufficient and safe analgesia.[2] However, a significantly lower requirement for tenoxicam in the dexmedetomidine group was found and was one of the advantages of dexmedetomidine as a coanalgesic in elderly patients.[10,11]

Patient satisfaction with postoperative pain control was found to be significantly higher in the dexmedetomidine group, in which effective analgesia and sedation were achieved with minimal AEs compared with the control group.

This study was designed as a pseudorandomized clinical trial in which the study patients and the investigator assessing the study parameters were blinded to the drugs being used. The limitations of this method might be selection bias. Other limitations include the small sample size of the study.

CONCLUSIONS

In both groups of elderly patients undergoing abdominal surgery, adequate and effective pain treatment with hemodynamic stability was provided by IV dexmedetomidine in addition to epidural fentanyl. The combination of an epidural low-dose local anesthetic administered with moderate doses of IV dexmedetomidine was effective and was associated with significantly lower opioid use and greater patient satisfaction.

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