General Anesthesia

Intraoperative infusion of dexmedetomidine reduces perioperative analgesic requirements

[Une perfusion peropératoire de dexmédétomidine réduit les besoins analgésiques périopératoires]

Alp Gurbet MD, Elif Basagan-Mogol MD, Gurkan Turker MD, Fatih Ugun MD, F. Nur Kaya MD, Berin Ozcan MD

Purpose: This prospective, randomized, double-blind study was designed to assess whether intraoperative infusion of dexmedetomidine provides effective postoperative analgesia. Postoperative pain scores and morphine consumption were compared in a treated group and a placebo group, both of which received patient-controlled morphine after total abdominal hysterectomy.

Methods: Fifty women were randomly assigned to two groups. Group D ($n = 25$) received a loading dose of dexmedetomidine 1 $\mu g \cdot kg^{-1}$ *iv* during induction of anesthesia, followed by a continuous infusion at a rate of 0.5 $\mu g \cdot kg^{-1} \cdot hr^{-1}$ throughout the operation. Group P ($n = 25$) received a volume-matched bolus and infusion of placebo (0.9% saline). For each case, heart rate, peripheral oxygen saturation, and systolic and diastolic blood pressure were recorded intraoperatively and for 48 hr postoperatively. Patients used a patient-controlled analgesia device to receive bolus doses of morphine after surgery. Total morphine consumption, pain scores, and sedation scores were recorded for the first 48 hr (two hours in the postanesthesia care unit and 46 hr on the ward).

Results: The groups were similar with respect to mean times to extubation of the trachea. Pain and sedation scores were also similar between groups at all corresponding times throughout the 48-hr period of observation. Group D patients consumed significantly less morphine in the postanesthesia care unit and on the ward ($P < 0.05$ and $P < 0.01$, respectively). Fewer patients in Group D experienced itching or nausea/vomiting ($P < 0.05$).

Conclusion: Continuous *iv* dexmedetomidine during abdominal surgery provides effective postoperative analgesia, and reduces postoperative morphine requirements without increasing the incidence of side effects.

Objectif *: La présente étude prospective, randomisée et à double insu a été réalisée pour déterminer si une perfusion peropératoire de dexmédétomidine fournit une analgésie postopératoire efficace. Les scores de douleur et la consommation de morphine postopératoires ont été comparés entre un groupe expérimental et un groupe témoin, les deux recevant de la morphine autocontrôlée après une hystérectomie abdominale totale.*

Méthode *: Cinquante femmes ont été réparties au hasard en deux groupes. Celles du groupe D ($n = 25$) ont reçu une dose initiale de dexmédétomidine iv de 1 $\mu g \cdot kg^{-1}$ pendant l'induction de l'anesthésie, puis une perfusion continue à 0,5 $\mu g \cdot kg^{-1} \cdot hr^{-1}$ pendant l'opération. Celles du groupe P ($n = 25$) ont reçu un bolus de volume apparié et une perfusion de solution saline à 0,9 %. La fréquence cardiaque, la saturation en oxygène du sang périphérique et la tension artérielle systolique et diastolique ont été enregistrées pendant l'opération et pendant 48 h après. Les patientes ont utilisé une pompe d'analgésie autocontrôlée pour recevoir des bolus de morphine postopératoire. La consommation totale de morphine, les scores de douleur et de sédation ont été notés pendant les 48 premières heures (deux heures à la salle de réveil et 46 h à la chambre).*

Résultats *: L'extubation endotrachéale a été faite à des temps similaires dans les deux groupes. La douleur et la sédation ont aussi été semblables pour tous les enregistrements faits pendant les 48 h d'observation. Une quantité significativement plus basse de morphine a été utilisée dans le groupe D, en salle de réveil et à la chambre (respectivement $P < 0,05$ et $P < 0,01$). Moins de patientes du groupe D ont eu du prurit ou des nausées et des vomissements ($P < 0,05$).*

Conclusion *: La perfusion iv continue de dexmédétomidine, administrée pendant une opération abdominale, fournit une analgésie postopératoire efficace et réduit les besoins postopératoires de morphine sans augmenter l'incidence d'effets secondaires.*

From the Department of Anesthesiology and Reanimation, Uludag University Faculty of Medicine, Bursa, Turkey.

Address correspondence to: Dr. Alp Gurbet, Uludag, Department of Anesthesiology and Reanimation, University Faculty of Medicine, Gorukle, 16049 Bursa, Turkey. Phone: 90-224-4428039; Fax: 90-224-4428958; E-mail: agurbet@uludag.edu.tr

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DEXMEDETOMIDINE is a highly selective α_2-adrenergic receptor agonist that is most often used for short-term sedation in patients in intensive care who are on mechanical ventilation.[1] The main advantage of this drug is that it does not cause serious respiratory side effects.[2] In addition, it has an opioid-sparing effect.[3,4] The analgesic, sedative/hypnotic and anxiolytic properties of dexmedetomidine make this drug potentially useful for painful surgical procedures.

Systemic administration of the α_2-agonists dexmedetomidine and clonidine has been reported to cause sedative effects and reduce opioid requirements in the perioperative period.[5–10] Such features are indirect evidence that these drugs have analgesic action. However, studies conducted in the perioperative period involve numerous confounding factors, and it is difficult to distinguish whether analgesic or sedative effects are responsible for the reduced opioid requirements.[11] The analgesic activity of α_2-agonists seems to be mediated by both supraspinal and spinal mechanisms. It is thought that central α_2-adrenoceptors in the locus ceruleus (a supraspinal site) and in the dorsal horn of the spinal cord are involved in this activity.[12,13] Dexmedetomidine has also been shown to have antihyperalgesic action in rats with neuropathic pain originating in the peripheral nervous system.[14] This drug enhances the effects of analgesics without increasing the incidence of side effects.[15]

The aim of this study was to evaluate whether intraoperative infusion of dexmedetomidine provides effective postoperative analgesia. To address this question, we compared findings after intraoperative administration of dexmedetomidine or placebo to patients who underwent major abdominal surgery and then received morphine postoperatively via patient-controlled analgesia (PCA). Side effects related to dexmedetomidine were also investigated.

Methods

Institutional Ethics Committee approval was obtained for this prospective study, and all participants gave informed consent. The subjects were 50 women who underwent total abdominal hysterectomy and received morphine via PCA for postoperative pain control. All patients were ASA physical status I or II, and their ages ranged from 35 to 65 yr. The exclusion criteria were weight exceeding 100 kg, inability to use the PCA device, renal or hepatic dysfunction, cardiac failure, ischemic or valvular heart disease, long-term use of certain medications (ß-blockers, analgesics, sedatives or tricyclic antidepressants), psychiatric illness, alcohol abuse, and heavy smoking habit. The night before surgery, an anesthesiologist instructed each patient regarding use of the PCA device.

A computer-generated randomization table was used to assign each woman to the placebo group (Group P, $n = 25$) or the dexmedetomidine group (Group D, $n = 25$). An anesthesiologist (who was not one of the observers for the study) prepared injectable solutions containing either dexmedetomidine or 0.9% saline. The dexmedetomidine was supplied in 2-mL ampoules of 100 $\mu g \cdot mL^{-1}$ concentration (Abbott, Chicago, IL, USA), and this volume was diluted with 98 mL of normal saline to yield a final concentration of 2 $\mu g \cdot mL^{-1}$. For each patient in Group P, a 100 mL volume of 0.9% saline solution was prepared.

Routine monitoring consisted of non-invasive blood pressure, electrocardiography and peripheral oxygen saturation (SpO_2) monitoring. Induction of anesthesia was achieved with thiopentone 3 to 5 $mg \cdot kg^{-1}$ *iv* and fentanyl 3 $\mu g \cdot kg^{-1}$ *iv*. Vecuronium 0.1 $mg \cdot kg^{-1}$ *iv* was given to facilitate tracheal intubation, and anesthesia was maintained with 0.5 to 2% (end-tidal concentration) sevoflurane in 60% nitrous oxide and 40% oxygen. In each case, the aim was to maintain mean arterial blood pressure (MAP) within 80–120% of baseline values. Mean arterial blood pressure rise of more than 20% above baseline was treated by administering a 2 $\mu g \cdot kg^{-1}$ *iv* bolus of fentanyl and raising the end-tidal sevoflurane concentration to 2%. Mean arterial blood pressure drop of more than 20% below baseline was treated initially with reduction of the end-tidal sevoflurane concentration to 0.5%. Supplemental boluses of vecuronium 0.05 $mg \cdot kg^{-1}$ *iv* were administered as required to maintain muscle relaxation during surgery.

Each Group D patient received an initial loading dose of dexmedetomidine1 $\mu g \cdot kg^{-1}$ over 30 min prior to induction, followed by an infusion started at 0.5 $\mu g \cdot kg^{-1} \cdot hr^{-1}$. The infusion was discontinued when surgery ended. Group P patients received the same volume of 0.9% saline as a sham loading dose, followed by a saline infusion. Heart rate, SpO_2, and MAP were recorded at specific time points (zero, five, 15, 30, 60, 90 and 120 min) during the surgical procedure. The total amount of fentanyl administered during each operation was also recorded.

Upon completion of surgery, each patient was extubated when she was able to execute simple verbal commands. All subjects were transferred to the postanesthesia care unit (PACU), where they were monitored and received nasal O_2 supplementation. Each woman was reminded of how to operate a PCA system (Abbott Pain Management Provider, Chicago, IL, USA) after receiving an initial bolus of morphine

TABLE Demographic and intraoperative data

	Group P (n = 25)	*Group D (n = 25)*
Age (yr)	49 ± 9	43 ± 7
Weight (kg)	70 ± 10	69 ± 11
Height (cm)	161 ± 5	163 ± 4
ASA (I/II)	15/10	12/13
Duration of surgery (min)	109 ± 25	101 ± 25
Intraoperative data		
HR (beats·min^{-1})	69 ± 11	65 ± 10
MAP (mmHg)	82 ± 8	80 ± 7
SpO_2 (%)	98 ± 1	98 ± 2
End-tidal sevoflurane (%)	1.4 ± 0.2	1.3 ± 0.3
Intraoperative fentanyl (μg)	325 ± 17	255 ± 16 *

Group P = placebo group; Group D = dexmedetomidine group; HR = heart rate; MAP = mean arterial pressure; SpO_2 = peripheral oxygen saturation. Data are mean ± standard deviation or number of patients. Intraoperative data are over entire surgery. * $P < 0.05$, Group P *vs* Group D.

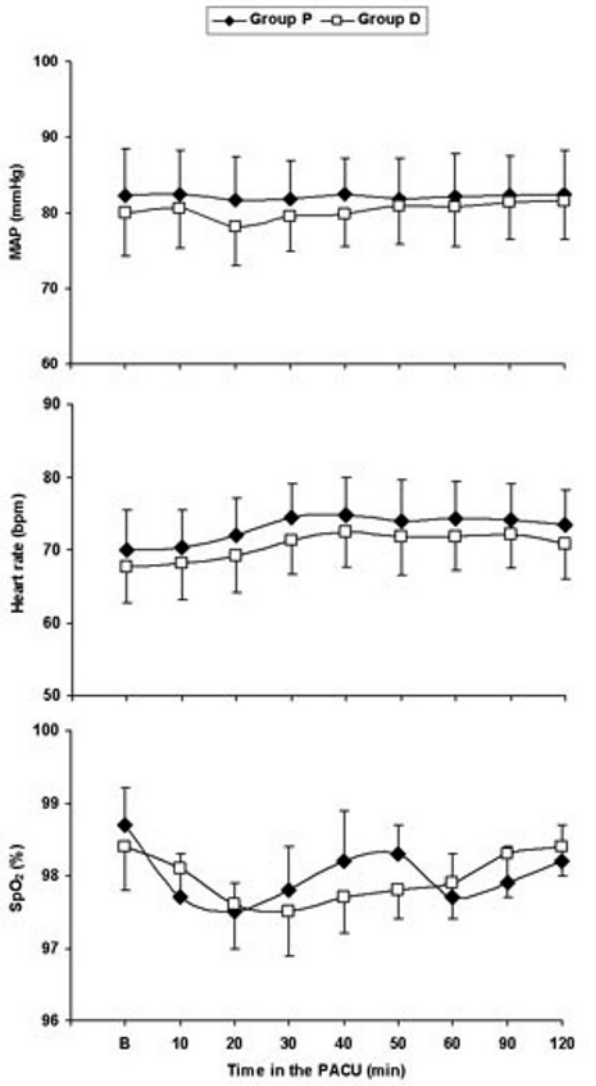

FIGURE 1 Cardiorespiratory variables after surgery while in the PACU (mean ± SD). Group P = placebo group; Group D = dexmedetomidine group; B = preoperative baseline value; MAP = mean arterial pressure; SpO_2 = peripheral oxygen saturation; PACU = postanesthesia care unit.

3 mg *iv*. The PCA machine was set to deliver morphine boluses 1 mg *iv* with a lockout interval of five minutes. Morphine was delivered only via PCA; no morphine infusions were provided. This PCA regimen was continued for 48 hr (in the PACU and on the ward). Patients were encouraged to push the analgesic-demand button when they experienced pain, and to repeat until they felt pain relief. Diclofenac 75 mg *iv* was administered for rescue analgesia if the pain scores at rest remained higher than 3.

Each patient remained in the PACU for two hours, and was transferred thereafter to the ward. Data for pain scores (see details below), heart rate, MAP, and sedation scores (see details below) were recorded at ten, 20, 30, 40, 50, 60, 90 and 120 min in the PACU, at arrival on the ward, and at three, four, eight, 12, 16, 24, 32, 40 and 48 hr postoperatively. Each subject's mean SpO_2 value in the PACU was also recorded. Observers who recorded data were blinded with respect to patients' group allocation. The observer was never the anesthesiologist providing clinical care of the patient.

Pain intensity was assessed using an 11-point visual analogue scale (VAS) on which 0 indicated no pain and 10 indicated the worst pain imaginable. At each assessment period after surgery, the patient assessed her pain at rest (VAS_R) and during movement (VAS_M). Sedation levels were also recorded at the same time intervals. The degree of sedation was assessed using the Ramsay sedation scale. In this system, 1 = agitated and uncomfortable, 2 = cooperative and orientated, 3 = can follow simple directions, 4 = asleep but strong response to stimulation, 5 = asleep and slow response to stimulation, and 6 = asleep and no response to stimulation.

Times to extubation of the trachea, and side effects possibly related to opioid or dexmedetomidine administration [nausea and vomiting, urinary retention, bradypnea (fewer than 8 breaths·min^{-1}), and itching] were recorded for each case.

Statistical considerations

Based on previous data from Unlugenc *et al.*,[9] 23 patients per group would detect a 30% reduction in PCA morphine requirements, relative to the placebo group, during the first 24 hr with a 5% one-tailed type I error rate and 80% power. Kruskal-Wallis, Chi-square and Mann-Whitney U tests were employed as appropriate, and P values < 0.05 were considered significant.

Results

Five patients refused consent. A total of 50 patients consented to participate at the preoperative anesthesia visit and no patient was excluded at any stage of the study. Demographic and intraoperative outcomes are shown in the Table. Groups were similar with respect to age, body weight, height, proportions of ASA I and ASA II patients, and duration of surgery. There were no differences in intraoperative heart rate, MAP and SpO_2 between groups. The mean amount of intraoperative fentanyl administered in Group D was significantly lower than that in Group P ($P < 0.05$). The intraoperative concentrations of sevoflurane were similar in both groups.

Intergroup comparisons of MAP, heart rate and SpO_2 findings in the PACU revealed no significant differences (Figure 1). The groups' mean sedation scores at each time point in the PACU and on the ward were similar (Figures 2 and 3). There were also no significant differences between the groups' mean VAS_R scores at each time point assessed in the PACU and on the ward after surgery, and the same was true for the mean VAS_M scores (Figures 2 and 3).

The times from PACU admission to first analgesic (PCA) demand were similar in the two groups (8 ± 6 *vs* 9 ± 7 min, Groups P and D, respectively; $P > 0.05$). Group P had significantly higher mean cumulative morphine consumption than Group D (19.5 ± 1 *vs* 12 ± 0.7 mg, respectively; $P < 0.05$) during the PACU stay (Figure 2).

During the time patients were assessed on the ward (i.e., from arrival on the ward to 48 hr postoperatively), Group P patients had significantly higher mean cumulative morphine consumption than Group D patients (65.8 ± 20.6 *vs* 28.6 ± 10.7 mg, respectively; $P < 0.01$), (Figure 3).

A significantly higher number of patients in Group P experienced itching (13 *vs* 4 patients for Group P *vs* Group D, respectively; $P < 0.05$). Nausea and vomiting requiring treatment was also lower in the dexmedetomidine group (15 *vs* 6 patients, respectively; $P < 0.05$). Also, seven patients in Group P needed rescue analgesia in contrast to only two patients in Group

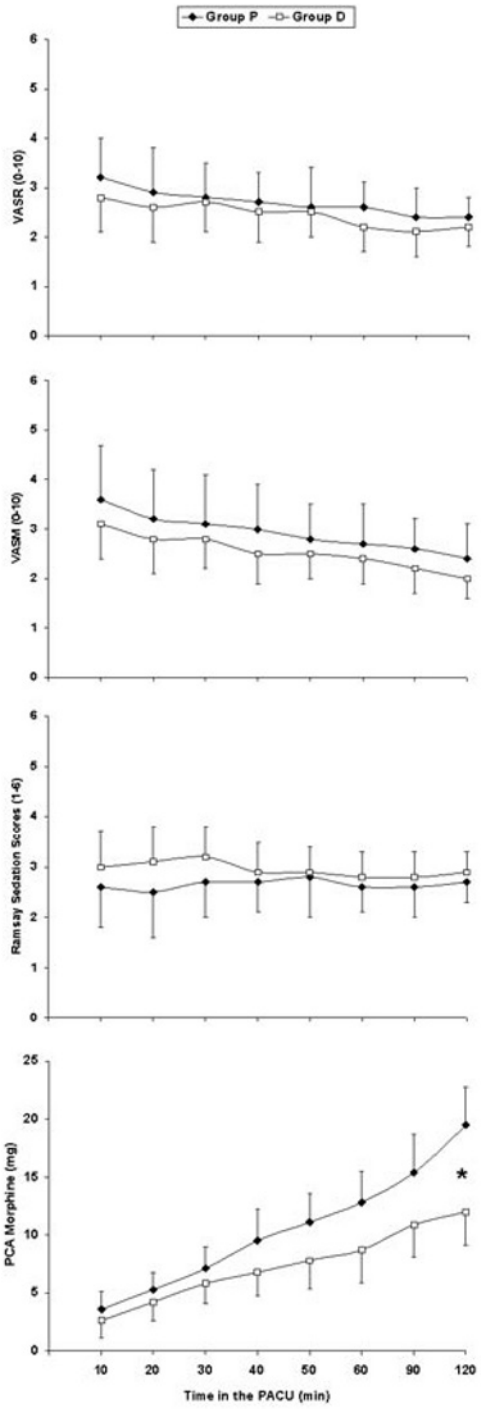

FIGURE 2 Pain scores at rest and during movement, sedation scores and cumulative PCA morphine consumption in the PACU (mean ± SD). Patients receiving intraoperative dexmedetomidine consumed significantly less PCA morphine during the PACU stay (*$p < 0.05$). There were no significant differences in other end-points. Group P = placebo group; Group D = dexmedetomidine group; VAS_R = visual analogue scale at rest; VAS_M = visual analogue scale during movement; PCA = patient-controlled analgesia; PACU = postanesthesia care unit.

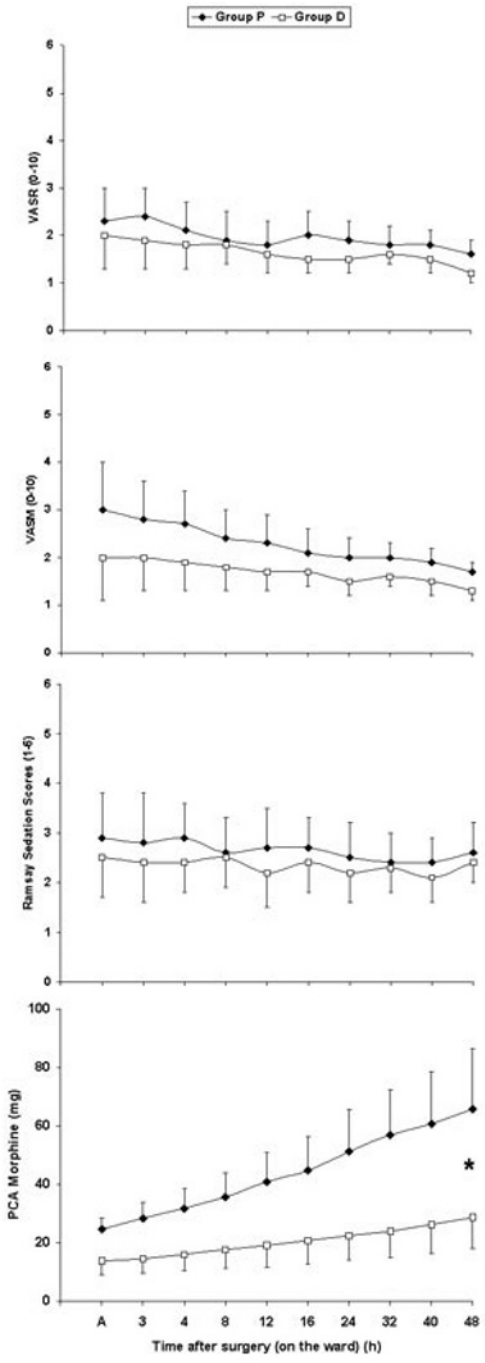

FIGURE 3 Pain scores at rest and during movement, sedation scores and cumulative PCA morphine consumption while on the ward (mean ± standard deviation). Patients receiving intraoperative dexmedetomidine had significantly lower mean cumulative morphine consumption than placebo patients on the ward (*$P < 0.01$). There were no significant differences in other end-points. Group P = placebo group; Group D = dexmedetomidine group; A = arrival on the ward; VASR = visual analogue scale at rest; VASM = visual analogue scale during movement; PCA = patient-controlled analgesia.

D ($P < 0.05$). No patient in either group developed urinary retention or bradypnea. None of the patients in either group developed any opioid-related complications that delayed PACU or hospital discharge.

Discussion

Our findings indicate that intraoperative *iv* dexmedetomidine reduces PCA morphine consumption after total abdominal hysterectomy during the first 48-hr after surgery.

Animal studies have shown that *iv* dexmedetomidine significantly reduces sevoflurane anesthetic requirements.[16] The analgesic effects of dexmedetomidine observed in our study correlate well with previous findings in both animals and humans. Experiments with thermal pain models in animals have shown that systemic administration of clonidine or dexmedetomidine has significant analgesic effects.[17,18] Jaakola *et al.*[4] evaluated analgesia after systemic administration of different doses of dexmedetomidine (0.25, 0.50, and 1 $\mu g \cdot kg^{-1}$) and fentanyl (2 $\mu g \cdot kg^{-1}$) in healthy volunteers, and found that dexmedetomidine had a moderate analgesic effect that was maximized at 0.5 $\mu g \cdot kg^{-1}$. In line with this, Cortinez *et al.*[1] showed that a 0.6 $ng \cdot mL^{-1}$ target control infusion (equivalent to 0.5 $\mu g \cdot kg^{-1}$) of *iv* dexmedetomidine had analgesic effects in humans. These doses of dexmedetomidine are similar to the amounts which patients received in the current study.

Several experimental pain studies in human volunteers used the cold pressor test after administration of dexmedetomidine or clonidine. These investigations indicate a 20% to 30% decrease in pain VAS scores for subjects who receive either of these drugs at doses associated with moderate to severe sedation.[2,18,19] However, conflicting results were documented in one study in an experimental model of secondary hyperalgesia, where volunteers who received clonidine at a dose known to produce moderate to severe sedation experienced no anti-hyperalgesic or anti-allodynic effects.[20] Our results add to evidence that suggests dexmedetomidine does not have broad analgesic efficacy when administered systemically at doses that produce mild to severe sedation.

One study[4] revealed that both dexmedetomidine and fentanyl have significant analgesic effects on ischemic pain induced by a sphygmomanometer cuff. The authors found that the analgesic action of dexmedetomidine was not dose-dependent; they observed an apparent ceiling effect at 0.5 $\mu g \cdot kg^{-1}$. In our study, we observed that an intraoperative loading dose of dexmedetomidine 1 $\mu g \cdot kg^{-1}$ followed by an infusion at a rate of 0.5 $\mu g \cdot kg^{-1} \cdot hr^{-1}$ provided good analgesia for

at least 48 hr after total abdominal hysterectomy. This was reflected by the significantly lower requirements for *iv* PCA morphine analgesia in the dexmedetomidine group. Arain *et al.*[5] examined the efficacy of dexmedetomidine *vs* morphine for postoperative analgesia after major inpatient surgery. Thirty minutes before the end of the surgery, one group received an initial loading dose of dexmedetomidine 1 $\mu g \cdot kg^{-1}$ followed by an infusion at a rate of 0.4 $\mu g \cdot kg^{-1} \cdot hr^{-1}$, discontinued at the end of surgery. Prior to the end of surgery, the other group received an *iv* bolus of morphine 0.08 $mg \cdot kg^{-1}$. Upon recovery from anesthesia, patients in both groups received morphine 2 mg *iv* whenever the VAS pain score was > 5. The groups had similar pain scores but the morphine group required 66% more morphine to achieve this analgesic effect. Similarly, in our study we observed no differences between the VAS pain scores (at rest or during movement) for the placebo and dexmedetomidine groups at any of the time after surgery. However, the patients who received dexmedetomidine required a lower cumulative amount of morphine during the first 48 hr after surgery.

Animal studies indicate that systemic administration of α_2-adrenergic receptor agonists results in dose-dependent antinociception and sedation responses.[21] Human data reveal a clear dose-response relationship for sedation, but not for analgesia, with systemic administration of these drugs.[6,22] One possible explanation of the variances between animal and human studies is that many of the animal experiments involved drug doses several orders of magnitude larger than those used in human trials.[3,18,19] In human research, it is usually not possible to administer systemic doses of α_2-agonists that will provide effective analgesia, because such doses can heavily sedate subjects or even render them unconscious. In our study, we did not observe clinically important sedation in any patient who received intraoperative dexmedetomidine infused at a rate of 0.5 $\mu g \cdot kg^{-1} \cdot hr^{-1}$.

Previous research has shown that *iv* target infusions of dexmedetomidine (0.5, 0.8, 1.2, 2.0, 3.2, 5.0, and 8.0 $ng \cdot mL^{-1}$) decrease heart rate and blood pressure in a dose-dependent fashion. These cardiovascular effects are well documented for the plasma concentrations of dexmedetomidine that have been investigated to date.[2] Arain *et al.*[5] administered dexmedetomidine at an initial loading dose of 1 $\mu g \cdot kg^{-1}$ followed by an infusion at 0.4 $\mu g \cdot kg^{-1} \cdot hr^{-1}$ initiated 30 min before the end of elective inpatient surgery. Slower mean heart rates were observed in the dexmedetomidine-treated group during the early postoperative period. However, no patient who received dexmedetomidine in our study developed clinically important bradycardia, either during surgery or postoperatively.

Venn *et al.*[23] investigated the postoperative effects of postoperatively administered dexmedetomidine in 119 cardiac surgery and general surgery patients who required mechanical ventilation and sedation in an intensive care unit. The patients were divided into two groups that received either dexmedetomidine or placebo. In both groups, midazolam and morphine were used for rescue sedation and analgesia, respectively. The authors found that dexmedetomidine had an analgesia-sparing effect and resulted in reduced need for rescue sedation. The elimination half-life of dexmedetomidine is two to three hours, and the authors speculated that the analgesic-sparing effect of dexmedetomidine would have persisted for up to 24 hr postoperatively. In our study, we observed that the dexmedetomidine group had significantly lower morphine requirements than the placebo group during the first 48 hr after abdominal surgery. One explanation for prolonged postoperative analgesia with dexmedetomidine may be the anxiolytic and thymoanaleptic properties of α_2-agonists, which act on the emotional component of postoperative pain.[24]

In summary, our results indicate that intraoperatively administered dexmedetomidine has specific analgesic properties and provides effective visceral pain relief. We found that continuous infusion of dexmedetomidine during abdominal surgery significantly reduces the amount of PCA morphine that patients require to remain comfortable postoperatively, without affecting time to extubation. Intraoperative, systemically administered dexmedetomidine was also associated with fewer morphine-related side effects compared with placebo.

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