

Comparison of Adenosine and Remifentanyl Infusions as Adjuvants to Desflurane Anesthesia

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Background: Because adenosine has been alleged to produce both anesthetic and analgesic sparing effects, a randomized, double-blinded study was designed to compare the perioperative effects of adenosine and remifentanyl when administered as intravenous adjuvants during general anesthesia for major gynecologic procedures.

Methods: Thirty-two women were assigned randomly to one of two drug treatment groups. After premedication with 0.04 mg/kg intravenous midazolam, anesthesia was induced with 2 μ g/kg intravenous fentanyl, 1.5 mg/kg intravenous propofol, and 0.6 mg/kg intravenous rocuronium, and maintained with desflurane, 2%, and nitrous oxide, 65%, in oxygen. Before skin incision, an infusion of either remifentanyl (0.02 μ g \cdot kg⁻¹ \cdot min⁻¹) or adenosine (25 μ g \cdot kg⁻¹ \cdot min⁻¹) was started and subsequently titrated to maintain systolic blood pressure, heart rate, or both within 10–15% of the preincision values.

Results: Adenosine and remifentanyl infusions were effective anesthetic adjuvants during lower abdominal surgery. Use of adenosine (mean \pm SEM, 166 \pm 17 μ g \cdot kg⁻¹ \cdot min⁻¹) was associated with a significantly greater decrease in systolic blood pressure and higher heart rate values compared with remifentanyl (mean \pm SEM, 0.2 \pm 0.03 μ g \cdot kg⁻¹ \cdot min⁻¹). Total postoperative opioid analgesic use was 45% and 27% lower in the adenosine group at 0–2 h and 2–24 h after surgery, respectively.

Conclusions: Adjunctive use of a variable-rate infusion of adenosine during desflurane–nitrous oxide anesthesia was associated with acceptable hemodynamic stability during the in-

traoperative period. Compared with remifentanyl, intraoperative use of adenosine was associated with a decreased requirement for opioid analgesics during the first 24 h after operation. (Key words: Antinociception; pain.)

A COMBINATION of intravenous and inhaled drugs commonly is used to maintain hemodynamic stability during the intraoperative period. Controversy exists regarding the optimal approach to controlling acute cardiovascular changes that occur in response to noxious surgical stimuli.¹ Although it is generally accepted that these acute hemodynamic responses are an indicator of inadequate anesthesia, analgesia, or both it is unclear whether these responses should be treated with analgesic, sedative-hypnotic, or sympatholytic drugs, or a combination of these.^{2,3}

Opioid analgesics are the most commonly used drugs to attenuate acute intraoperative hemodynamic responses. Remifentanyl, a novel esterase-metabolized opioid, rapidly and effectively suppress acute intraoperative hemodynamic responses without prolonging recovery time.^{4,5} However, the occurrence of severe pain on emergence from anesthesia and typical opioid-related side effects have been reported in the postoperative period.^{5,6} Adenosine, a naturally occurring nucleoside compound with potent sympatholytic properties, has been reported to potentiate the sedative effect of midazolam and to reduce the requirement for isoflurane and postoperative opioid analgesics.^{7–11} Sollevi¹⁰ suggested that a perioperative adenosine infusion of 70–130 μ g \cdot kg⁻¹ \cdot min⁻¹ could replace opioid administration during isoflurane and nitrous oxide (N₂O) anesthesia. Despite its extremely short plasma elimination half-life (less than 10 s), preliminary studies reported that adenosine possesses long-lasting sympatholytic and analgesic-like effects.⁹

Using a randomized, double-blinded study design, a variable-rate infusion of adenosine or remifentanyl was used to control acute hemodynamic responses to surgical stimulation during desflurane–nitrous oxide anesthe-

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sia in women undergoing major intraabdominal surgery. The primary objective of the study was to compare the two intravenous adjuvants with respect to their effects on early recovery and the postoperative opioid analgesic requirement.

Materials and Methods

After the local institutional review board approved the study, 32 adult women classified as American Society of Anesthesiologists physical status I or II and scheduled for elective abdominal hysterectomy or myomectomy procedures under general anesthesia were invited to participate in this study. Exclusion criteria included age less than 18 yr, obesity ($>130\%$ of ideal body weight), and a history of asthma; gout; or clinically significant cardiovascular, hepatic, renal, or endocrine dysfunction. Patients taking drugs with cardiovascular or analgesic effects or adenosine-antagonizing properties (*i.e.*, methylxanthines, dipyridamole) were excluded.

After patients gave written informed consent, they were randomly assigned to one of the two study treatment groups, remifentanyl or adenosine. Solutions of adenosine (5 mg/ml) and remifentanyl (4 $\mu\text{g}/\text{ml}$) were prepared in sodium chloride (0.9%) solution by the hospital pharmacy and provided in 500-ml glass bottles labeled with the patient's study number and initials. Neither the anesthesia staff nor the investigators were aware of the treatment assignment. A balanced salt solution, 5–10 ml/kg, was infused before induction of anesthesia. In the operating room, a pulse oximeter, automated blood pressure cuff, and electrocardiogram (lead II) were placed to obtain cardiovascular data. To monitor the effects of the two adjuvants on the central nervous system and to minimize the risk of intraoperative recall,¹² an electroencephalogram (EEG) device was used to record the bispectral (BIS) index values (Aspect Medical Systems, Boston, MA).

After obtaining baseline hemodynamic and BIS index values, patients were premedicated with 0.04 mg/kg intravenous midazolam. Subsequently, anesthesia was induced with 2 $\mu\text{g}/\text{kg}$ intravenous fentanyl and 1.5 mg/kg intravenous propofol. Endotracheal intubation was facilitated with 0.6 mg/kg intravenous rocuronium. After tracheal intubation, anesthesia was maintained with desflurane, 2% (inspired concentration) and N_2O , 65%, in oxygen. The desflurane concentration was changed only if the BIS value increased to more than 70 U or decreased to less than 30 U for more than 2 min.

Muscle paralysis was maintained with intermittent boluses of 5–10 mg intravenous rocuronium. Mechanical ventilation was used in all patients to maintain an end-tidal carbon dioxide concentration of 32–36 mmHg. Five minutes after tracheal intubation, a continuous infusion of the study drug was started at a rate of $0.3 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ (*i.e.*, $0.02 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ remifentanyl or $25 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ adenosine) through a second intravenous catheter using a Gemini PC-Z infusion pump (IMED Corp., San Diego, CA).

Systolic (SBP) and diastolic blood pressure, mean arterial pressure, and heart rate (HR) values, as well as the end-tidal desflurane concentration and the study drug infusion rate, were recorded at 5-min intervals before skin incision, at 1-min intervals during the initial 10-min interval after incision, and subsequently at 5-min intervals until the study drug infusion was stopped. Oxygen saturation and EEG-BIS index values were monitored continuously and recorded at 5-min intervals during surgery. Any spontaneous movements or clinical signs of increased autonomic activity (*e.g.*, lacrimation, mydriasis, facial flushing, or sweating) were noted. The age-adjusted average of the desflurane minimum alveolar concentration (MAC) over time (*i.e.*, $\text{MAC} \cdot \text{h} = \text{sum of end-tidal concentration divided by the MAC value multiplied by the duration [h] at that concentration}$) was also calculated.

The preincisional "baseline" hemodynamic values were defined as the values recorded during a 3- to 5-min interval after intubation, but before starting the study drug infusion. The study drug infusion was increased progressively in a stepwise manner at 30-s intervals until one of two "target" end points was achieved: (1) a SBP value that was 10–15% lower than the baseline value but not less than 90 mmHg, or (2) an HR value that was 10–15% lower than the baseline value but not less than 50 beats/min. Subsequently, the infusion rate was titrated incrementally ($\pm 25\%$ changes) to maintain the SBP and HR values in the targeted ranges. If the study drug infusion rate exceeded $19 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ (*i.e.*, $1.28 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ remifentanyl or $1,600 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ adenosine), a rescue medication (10 mg intravenous labetalol or 25 mg intravenous esmolol) was available to control any persistent hyperdynamic responses.

The following autonomic responses were considered indicative of inadequate intraoperative anesthesia, analgesia, or both: (1) sustained hypertension: $\text{SBP} > 125\%$ of baseline value or 180 mmHg for 1 min; (2) persistent tachycardia: $\text{HR} > 130\%$ of baseline value or 110 beats/min for 1 min; (3) somatic signs (*e.g.*, purposeful move-

ments, swallowing, grimacing, eye opening); and (4) autonomic signs (e.g., lacrimation or diaphoresis). These responses were treated by doubling the study drug infusion rate and increasing the inspired concentration of desflurane by 2% if the BIS index value was more than 70 U. Hypotension (defined as a SBP < 85% of baseline value or an absolute value of < 90 mmHg) was treated with additional fluids and by decreasing the study drug infusion rate by 50%. If the decrease in SBP persisted > 2 min in combination with tachycardia (HR > 110 beats/min), 100 g intravenous phenylephrine was administered. If hypotension was not associated with tachycardia, 5 mg intravenous ephedrine was given. When persistent hypotension was associated with BIS index values < 30 U, the inspired concentration of desflurane was decreased by 50%. For persistent bradycardia (HR < 50 beats/min lasting > 5 min), the study drug infusion was decreased by 50%, and 0.01 mg/kg intravenous atropine was administered.

At the end of the operation, residual neuromuscular blockade was reversed with 65 µg/kg intravenous neostigmine and 10 µg/kg intravenous glycopyrrolate. At skin closure, desflurane and N₂O were discontinued simultaneously, and the study drug infusion was decreased in increments of 50% until it was discontinued when the surgical dressing was applied. After extubation, patients reporting moderate or severe pain were given 25-g intravenous boluses of fentanyl until the pain was controlled adequately (which was defined as a visual analog scale pain score of 40 mm on a 100-mm scale, with 0 = none and 100 = severe).

Recovery times were calculated from the end of anesthesia (defined as the discontinuation of desflurane and N₂O). The following recovery end points were assessed at 1-min intervals: (1) spontaneous respiration, (2) eye opening, (3) response to verbal commands, (4) extubation, (5) orientation (place and date), (6) achievement of BIS index values of 80 U and 90 U, and (7) transfer from the operating room to the postanesthesia care unit (PACU). The total dose of the study drug (in milliliters) and requirements for fentanyl in the operating room were recorded, as were complications on emergence from anesthesia (e.g., laryngospasm, bronchospasm, coughing, respiratory depression, disorientation, excitation or agitation, shivering, or truncal rigidity).

When they arrived in the PACU, all patients were administered oxygen *via* nasal cannulas (2 l/min) and observed by a nurse who was unaware of the treatment group. Aldrete scores were recorded at 15-min intervals during PACU stay. If a patient reported pain, morphine

(1–3 mg given intravenously) was administered at 2- to 5-min intervals until the patient was comfortable (visual analog scale pain score of 40 mm on a 100-mm scale, with 0 = none and 100 = worst pain imaginable). Postoperative nausea and vomiting were treated with 10–20 mg intravenous metoclopramide. Standardized PACU discharge criteria required that the patient be alert and oriented; possess stable mean arterial pressure (MAP), HR, and respiratory rate values; oxygen saturation greater than 92% on room air; and have minimal residual side effects (e.g., nausea, pain). After discharge from the PACU, patients were permitted to self-administer morphine (in 2-mg intravenous boluses) at minimal intervals of 6 min using a patient-controlled analgesia device (Lifecare PCA Plus II Infusor, Abbott, Chicago, IL).

All postoperative evaluations were performed when patients were admitted to the PACU and subsequently at 1-, 2-, 3-, 6-, 12-, and 24-h intervals after surgery. Residual sedation was recorded using the observer's assessment of alertness-sedation scale¹⁵ (with a score of 1 indicating responsiveness to name spoken in normal tone and 5 indicating a failure to respond to mild prodding or shaking). Nausea was recorded using a 100-mm visual analog scale (with 0 = none and 100 = severe). The number of episodes of retching and vomiting was also recorded. Pain scores were measured similarly using the 100-mm visual analog scale. The cumulated morphine patient-controlled analgesia use was recorded at specific time intervals after surgery, as was the occurrence of side effects (e.g., pruritus, constipation). At 24- and 48-h intervals after surgery, a structured interview was conducted, and patients were asked: (1) "What is the very last thing you remember before going to sleep?"—based on the reply, the time of the last preinduction recall was determined, and (2) "What is the very next thing you remember?" Based on the patient's reply, the time of the first postinduction recall was determined. Finally, all patients were asked if they recalled any events (e.g., noise) during their operations. No specific questions relating to dreams were asked.

Statistical Analysis

Data were analyzed using the NCSS 6.0 statistical analysis program (Kaysville, UT). An *a priori* power analysis indicated that a sample size of 15 patients in each group would be adequate to detect a 30% reduction in the postoperative analgesic requirements with a power of 0.8 (alpha = 0.05). One-way analysis of variance was performed for all continuous variables, and when a sig-

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Table 1. Demographic Characteristics and Drug Dosages for the Two Treatment Groups*

	Adenosine	Remifentanyl
Number (n)	15	15
Age (yr)	47 ± 2	44 ± 1
Weight (kg)	75 ± 2	72 ± 3
Height (cm)	160 ± 2	160 ± 2
ASA physical status (I/II)	5/10	3/12
Chronic hypertension [n (%)]	4 (27)	3 (20)
Propofol (mg)	128 ± 3	127 ± 6
Fentanyl induction dose (μg)	123 ± 4	133 ± 5
Rocuronium (mg)	74 ± 3	78 ± 4
Desflurane (MAC · h)	1.1 ± 0.1	1.3 ± 0.1
Nitrous oxide (%)	66.1 ± 0.4	65 ± 0.9
Remifentanyl (mg)	NA	2.3 ± 0.3
Adenosine (mg)	1,400 ± 164	NA
Perioperative fluids (ml)	3,963 ± 262	3,986 ± 166
Intraoperative blood losses (ml)	595 ± 109	566 ± 49
Duration of surgery (min)	141 ± 10	160 ± 9
Duration of anesthesia (min)	171 ± 11	194 ± 10

Values are number and mean (± SEM).

NA = not applicable.

* No differences were found between the two groups.

nificant difference was noted, a Newman-Keuls test was performed for *post hoc* comparisons within and between groups. Nonparametric variables were evaluated using chi-square analysis. Demographic and recovery

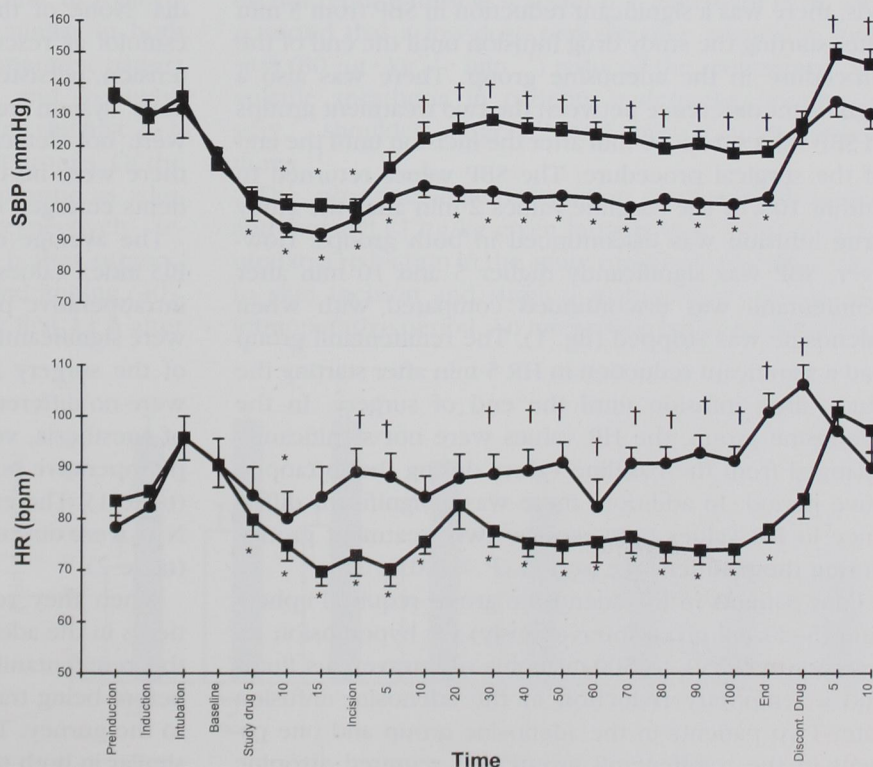
profile data were analyzed using the two-sample *t* test. Differences were considered significant if the *P* value was < 0.05. Values are expressed as the mean ± SEM.

Results

Of the 32 women studied, 2 were excluded because of unknown cocaine addiction and the occurrence of severe bronchospasm 5 min after starting the study drug (adenosine) infusion. There were no differences in the demographic characteristics or the type (or length) of the surgical procedures between the two treatment groups (table 1). The mean (± SEM and range) for the total adenosine dosage was 1.4 ± 0.2 g (0.4–3.6 g), and the mean ± SEM (and range) for the total remifentanyl dosage was 2.3 ± 0.3 mg (0.7–6 mg). The average infusion rates (and ranges) of adenosine and remifentanyl were 166 ± 17 μg · kg⁻¹ · min⁻¹ (72–290 μg · kg⁻¹ · min⁻¹) and 0.2 ± 0.03 μg · kg⁻¹ · min⁻¹ (0.02–0.38 μg · kg⁻¹ · min⁻¹), respectively.

Figure 1 summarizes perioperative SBP and HR values. As with SBP values, mean arterial pressure and diastolic blood pressure values followed a similar intraoperative pattern in both treatment groups (data not reported). Although both groups had similar SBP and HR values

Fig. 1. Perioperative systolic blood pressure (SBP) and heart rate (HR) values in patients receiving adjunctive therapy with either adenosine (n = 15 [circles]) or remifentanyl (n = 15 [squares]). Values are the mean ± SEM. **P* < 0.05 was considered significant when compared with baseline values; †*P* < 0.05 was considered to be significantly different between the two groups.



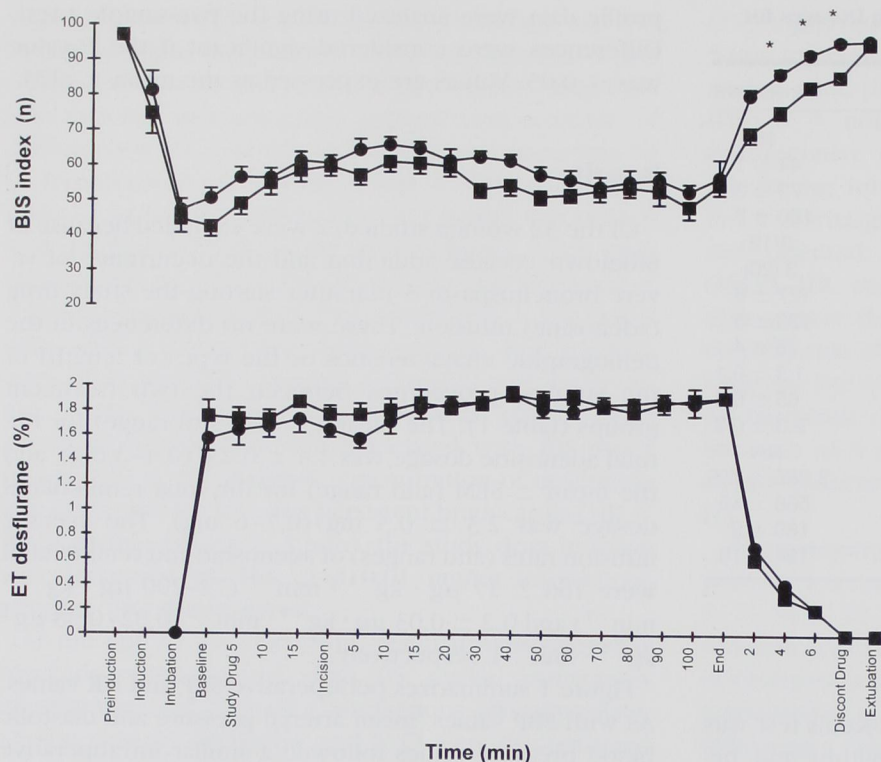


Fig. 2. Changes in the bispectral index values and the end-tidal concentration of desflurane during surgery in the two study groups, adenosine ($n = 15$ [circles]) or remifentanyl ($n = 15$ [squares]). Values are the mean \pm SEM; * $P < 0.05$ between the two groups.

during the induction, intubation, and preincision periods, there was a significant reduction in SBP from 5 min after starting the study drug infusion until the end of the procedure in the adenosine group. There was also a significant difference between the two treatment groups in SBP values from 10 min after the incision until the end of the surgical procedure. The SBP values returned to within 10% of the baseline values 2 min after the study drug infusion was discontinued in both groups. However, SBP was significantly higher 5 and 10 min after remifentanyl was discontinued compared with when adenosine was stopped (fig. 1). The remifentanyl group had a significant reduction in HR 5 min after starting the study drug infusion until the end of surgery. In the adenosine group, the HR values were not significantly changed from the baseline values during the intraoperative period. In addition, there was a significant difference in HR values between the two treatment groups during the maintenance period ($P < 0.01$).

Four patients in the adenosine group required ephedrine (5–20 mg given intravenously) for hypotension refractory to a 250- to 500-ml bolus of intravenous fluids and a temporary reduction in the adenosine infusion rate. Two patients in the adenosine group and one patient in the remifentanyl group also required atropine

(0.5–1 mg given intravenously) for prolonged bradycardia. None of the patients required either labetalol or esmolol as rescue medications for uncontrolled hypertension, persistent tachycardia, or both. Autonomic nervous system reactions and spontaneous movements were not detected in either treatment group. Finally, there were no complications in either group when patients emerged from anesthesia.

The average end-tidal desflurane concentrations and BIS index values were similar in both groups during the intraoperative period (fig. 2). However, the BIS values were significantly higher at 4 min and 6 min after the end of the surgery in the adenosine group (fig. 2). There were no differences in desflurane MAC-hours, duration of anesthesia, volume of fluids administered during the perioperative period, or in the intraoperative blood loss (table 1). The early recovery times after desflurane and N_2O were discontinued were also similar in both groups (table 2).

When they regained consciousness, 80% of the patients in the adenosine group and 86% of the patients in the remifentanyl group required fentanyl for analgesia before being transferred from the operating room table to the gurney. The dose of fentanyl (mean \pm SEM) was similar in both treatment groups: $73 \pm 8 \mu\text{g}$ (adenosine)

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Table 2. Recovery Times following Discontinuation of Desflurane and Nitrous Oxide in the Two Treatment Groups*

	Adenosine	Remifentanyl
Spontaneous ventilation (min)	3 ± 0.7	5 ± 0.7
Following commands (min)	6 ± 0.7	9 ± 0.5
Eye opening (min)	5 ± 0.7	7 ± 0.5
Extubation (min)	6 ± 0.7	9 ± 0.5
Orientation (min)	14 ± 1	15 ± 1
Transport to recovery (min)	13 ± 1	14 ± 0.7
Aldrete score of 10 (min)	73 ± 2	78 ± 4
PACU discharge (min)	76 ± 6	71 ± 4

Values are mean ± SEM.

PACU = postanesthesia care unit.

* No differences were found between the two groups.

and $76 \pm 7 \mu\text{g}$ (remifentanyl). When they arrived in the PACU, patients in the adenosine group had significantly lower visual analog scale pain scores than did those in the remifentanyl group, and this difference persisted for 12 h after operation (fig. 3). Similarly, patient-controlled analgesia morphine use was significantly higher in the remifentanyl group (compared with the adenosine group) during the first hour in the recovery room ($16 \pm 1 \text{ mg}$ vs. $9 \pm 0.9 \text{ mg}$) and at 6 h ($35 \pm 2 \text{ mg}$ vs. $25 \pm 2 \text{ mg}$), 12 h ($44 \pm 2 \text{ mg}$ vs. 33 ± 2), and 24 h (71 ± 4 vs. $51 \pm 2 \text{ mg}$) after surgery.

The duration of the PACU stay and the time to achievement of an Aldrete score of 10 were similar in both groups (table 2). The incidences of postoperative nausea (remifentanyl, 87%; adenosine, 67%) and vomiting (remifentanyl, 33%; adenosine, 27%) during the first 24 h did not differ between the two treatment groups. Of the patients receiving remifentanyl and adenosine as adjuvants during surgery, 73% and 67%, respectively, required rescue antiemetics in the first 24 h after surgery. The incidences of shivering (20–33%) and itching (40–53%) and the sedation scores during the first 12 h after

surgery also were similar in both groups. No patients in either group reported recalling any intraoperative events 24 and 48 h after surgery.

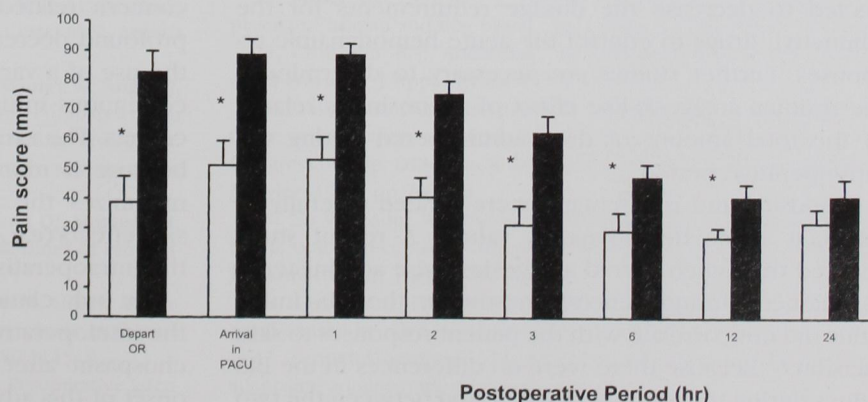
Discussion

Because it is difficult to evaluate the antinociceptive properties of adjunctive drugs during general anesthesia, we compared adenosine with remifentanyl, a potent opioid analgesic with the most similar pharmacokinetic profile. This study suggests that adenosine can control acute cardiovascular responses to surgical stimulation as effectively as the potent new rapid and ultrashort-acting opioid analgesic remifentanyl when administered as a continuous, variable-rate infusion to patients undergoing major intraabdominal gynecologic procedures.

In previous studies,^{14,15} adenosine was used to rapidly induce a stable and easily controllable level of hypotension without tachyphylaxis or rebound hypertension in patients undergoing cerebral aneurysm surgery¹⁴ and to control acute hypertensive crises while pheochromocytoma¹⁶ and neuroblastoma¹⁵ tumors were removed. Preliminary investigations have suggested that adenosine infusions ($70\text{--}130 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) can replace opioids during inhalation anesthesia for surgical procedures that do not require muscle relaxation.¹⁰ Segerdahl *et al.* also reported that a low-dose perioperative adenosine infusion ($80 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) reduced the requirement for volatile anesthesia in patients undergoing breast surgery,⁷ shoulder surgery,⁸ and hysterectomy procedures.¹¹

The pharmacologic interaction between adenosine and fentanyl ($2 \mu\text{g}/\text{kg}$ given intravenously) also contributed to a reduction in the acute cardiovascular responses to skin incision and surgical manipulation during the intraoperative period. An interaction between adenosine

Fig. 3. Visual analog scale pain scores for adenosine (clear bars) and remifentanyl (solid bars) groups at specific postoperative time intervals, with 0 = none to 100 = worst pain imaginable. Out OR = transfer from the operating room. PACU = arrival in the postanesthesia care unit. 1, 2, 3, 6, 12, 24 = time intervals after arrival in the PACU (expressed in hours). Values are mean ± SEM; *differences between groups in visual analog scale pain scores at the times indicated, $P < 0.05$.



and opioid receptors has been reported to alter the modulation of nociceptive transmission in the spinal cord.¹⁷ Furthermore, significant analgesic potentiation was observed when a combination of adenosine and morphine was used.¹⁸ Consistent with previous studies^{7,10,11,14} involving the use of an adenosine infusion as an adjuvant during surgery, a significant change in HR values was not observed. These findings differ from the HR effects associated with bolus-dose administration of adenosine.

Since all patients received 2 $\mu\text{g}/\text{kg}$ fentanyl intravenously for induction of anesthesia, and the surgical incision occurred at least 15 min after the study drug infusions were begun, a lower initial infusion rate was used compared with previous studies^{4,5,7,8,10} to avoid untoward hemodynamic effects. The mean overall infusion rate of adenosine ($166 \pm 17 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) used in this study was higher than the infusion rates used in previous studies, where it was reported to decrease the intraoperative requirements for volatile anesthetics^{7,11} and opioid analgesics.¹⁰ The mean remifentanyl infusion rate ($0.2 \pm 0.03 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) was in the range ($0.1\text{--}0.3 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) reported to suppress effectively responses to painful surgical manipulations in patients undergoing intraabdominal and orthopedic procedures under "balanced" anesthetic techniques.⁴

Because none of the patients experienced intraoperative recall, the use of a combination of desflurane (2%) and N_2O (65%), with a stable BIS index value in the 55–65 U range, provided an adequate hypnotic state. This finding is consistent with the study of Gonsowski *et al.*¹⁹ in which the use of 0.6 MAC desflurane prevented explicit and implicit learning. According to Daniel *et al.*,²⁰ 1.3 MAC desflurane with 60% N_2O blocks increases in HR and mean arterial pressure in response to a skin incision. Therefore, administration of higher concentrations of desflurane in this study would have been expected to decrease the dosage requirements for the adjunctive drugs to control the acute hemodynamic responses. Further studies are necessary to determine if the residual analgesic-like effect of adenosine is related to the total amount of drug administered during the intraoperative period.

Adenosine and remifentanyl were titrated carefully to maintain stable hemodynamic values. A recent study showed that when opioid analgesics were administered as adjuncts during general anesthesia, the BIS index value did not correlate with the patient responses to skin incision.²¹ Because there were no differences in the BIS values during the intraoperative period between the two

treatment groups, it would appear that the BIS monitor will not be useful for predicting acute autonomic responses when adenosine is used as an adjuvant during general anesthesia.

The postoperative analgesic requirements were high in both groups. However, the use of adenosine (compared with remifentanyl) was associated with a 45% decrease in the morphine requirement in the first hour and a 27% decrease in the first 24 h after surgery compared with remifentanyl. These data suggest that adenosine produces a more prolonged antinociceptive action than remifentanyl in the postoperative period. Although adenosine is eliminated rapidly from the blood (with a context-sensitive half-time of less than 10 s after an infusion is discontinued),²² a prolonged opioid-sparing effect was reported in previous studies when adenosine was administered during general anesthesia for breast surgery⁷ and hysterectomy procedures.¹¹ Although the precise mechanism responsible for the apparent opioid-sparing effects of adenosine is unknown, inhibition of neutrophilic chemotaxis and reduction of cytokine production,²³ and the modulation of central neuronal hyperexcitability,²⁴ are possible explanations for the sustained analgesic effect of adenosine. An alternative explanation for the differing effects of the two adjuvants on the postoperative opioid analgesic requirement relates to the development of "acute tolerance" to the analgesic effects of opioid compounds after the remifentanyl infusion is terminated. Further studies are needed to determine if adenosine has true analgesic effects or merely lacks the well-known ability of opioids to produce desensitization, downregulation of μ receptors, or both.²⁵

One criticism of this study relates to a possible bias introduced by "unblinding" as a result of the differing effects of the study drugs on the HR response. However, this difference was not apparent until after the study was complete. When the study was designed, an important concern related to the fact that adenosine produces profound decreases in HR. Another criticism relates to the use of a variable-rate infusion rather than fixed-rate continuous infusions for administering the study medications. The variable-rate infusion technique was chosen because it more closely mimics clinical practice and minimizes the possibility of untoward hemodynamic side effects (e.g., sinus arrest, severe hypotension) during the intraoperative period.

The only clinically significant side effect noted during the intraoperative period was an episode of acute bronchospasm after adenosine was initiated. Because the onset of this adverse reaction was related temporally to

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the administration of the study drug and it actually worsened when the adenosine infusion rate was increased, adenosine was thought to be a significant contributing factor. Although "light" anesthesia also may have played a role, previously adenosine was implicated as a cause of bronchospasm in patients with asthma, chronic obstructive pulmonary disease, and reactive airway disease.^{26,27} Although the incidence of postoperative nausea and vomiting and pruritus were high in the adenosine group, these side effects also occurred in a similar number of patients who received remifentanyl.

In conclusion, an infusion of adenosine was as effective as remifentanyl in providing satisfactory surgical anesthesia when it was used as an adjuvant to desflurane and N₂O in women undergoing lower abdominal procedures. Compared with remifentanyl, use of adenosine was associated with improved patient comfort and reduced opioid analgesic requirements during the first 24 h after surgery, suggesting that adenosine has longer-lasting antinociceptive effects in the postoperative period.

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