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Phase 2, Double-blind, Placebo-controlled, Dose-Response Trial of Intravenous Adenosine for Perioperative Analgesia

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Background: **Adenosine regulates pain transmission by actions at spinal, supraspinal, and peripheral sites. A few studies have suggested that administration of adenosine might be associated with anesthetic- and analgesic-sparing effects. The primary aim of this multicenter study was to determine the dose–response profile of adenosine with respect to perioperative analgesia.**

Methods: **Women undergoing major gynecologic surgery were enrolled. Subjects were randomly assigned to receive one of four doses of adenosine (25, 50, 100, or 200 $\mu g \cdot kg^{-1} \cdot min^{-1}$) or matching placebo. A dose-escalation cohort approach was followed. Study drug administration was started in the operating room at the time of skin incision and discontinued at the end of surgery. The anesthetic technique was standardized. Postoperative analgesia was provided with a standardized morphine patient-controlled analgesia system. Data were collected in the hospital and after discharge daily through postoperative day 7.**

Results: **A total of 166 subjects received treatment with study drug: 125 received adenosine and 41 received placebo. Except for height, there were no differences between treatment groups with respect to demographic or baseline characteristics. Cumulative opioid use during the initial 24-h period after extubation was not significantly different between treatment groups. There were also no differences between treatment groups with respect to cumulative anesthetic use, intraoperative opioid requirements, pain scores, sedation, time to readiness for discharge from the postanesthesia care unit, time to readiness for discharge from the hospital, opioid-related symptom distress scores, patient satisfaction with pain control, and occurrence of adverse events.**

Conclusions: **There were no differences between placebo and adenosine with respect to efficacy and safety for perioperative analgesia.**

OPIOIDS remain the mainstay for postoperative analgesia, especially after major surgery. However, pain is a multifactorial phenomenon that cannot be adequately controlled with simple monotherapy with opioids alone.[1] Furthermore, opioid use is associated with dose-related adverse effects such as respiratory depression, nausea, vomiting, urinary retention, itching, and sedation. Opioids also reduce gastrointestinal motility, which may contribute to postoperative ileus.[2,3] A multimodal approach involving the use of adjunct analgesics is therefore recommended to improve the quality of analgesia, produce opioid sparing, and reduce the incidence of opioid-related adverse effects.[4]

Adenosine is an endogenous substance and physiologically ubiquitous in the body. It is widely distributed in the whole body and is an important modulator of neurotransmission in many physiologic functions. In addition, adenosine regulates pain transmission by actions at spinal, supraspinal, and peripheral sites, with specific effects depending on receptor subtype and receptor localization.[5] The central nervous system contains adenosine A_1, A_{2A}, A_{2B}, and A_3 receptors. The A_1 receptor has an important role in antinociception at both the spinal and peripheral levels. At peripheral sites, A_{2A} and A_3 receptors facilitate pain transmission.[6] Systemic and intrathecal administration of adenosine have been found to possess antinociceptive and anesthetic-sparing effects in animal models.[7–9] Studies in healthy volunteers also showed that adenosine reduced ischemic, thermal, and chemically induced pain.[10–12] Several reports also provided evidence that adenosine alleviated neuropathic pain, hyperalgesia, and allodynia.[13–15] A few studies suggested that the perioperative administration of adenosine might be associated with anesthetic- and analgesic-sparing effects.[13,16–20] However, a number of dosing regimens were used in these studies. Furthermore, a dose response for the analgesic- and anesthetic-sparing effects of adenosine was not studied. The primary aim of this study was therefore to determine the dose–response profile of adenosine with respect to perioperative analgesia and opioid-sparing effects. A secondary objective was to determine its anesthetic-sparing effects and adverse events.

Materials and Methods

Nineteen centers across the United States participated in this study, conducted from October 5, 2005, to July 19, 2006. After institutional review board approval at each participating center and written informed consent,

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women aged 18–70 yr, with American Society of Anesthesiologists physical status classification I–III, undergoing open hysterectomy or other major gynecologic surgery during general anesthesia, were enrolled in this phase 2, randomized, double-blind, placebo-controlled, multicenter, dose-ranging study. Patients were excluded if they had a body mass index greater than 37 kg/m^2; were pregnant or lactating; had a history of asthma, gout, clinically significant cardiovascular, or renal disease; or received theophylline or dipyridamole within 48 h of surgery. Patients were also excluded if they had a history of chronic opioid use; were receiving opioids within 14 days before scheduled surgery or corticosteroids for longer than 3 months; or had a known hypersensitivity to adenosine, morphine, or hydrocodone.

Subjects were randomly assigned to receive one of four doses of adenosine (25, 50, 100, or 200 $\mu g \cdot kg^{-1} \cdot min^{-1}$) or matching placebo by an interactive voice response system according to a computer-generated randomization schedule. A dose-escalation cohort approach was followed. Blinded study medication (adenosine or matching normal saline placebo) was supplied in 500-ml glass bottles. Each bottle was identified by a unique number associated with active or placebo treatment. Bottle numbers were assigned by the interactive voice response system. To maintain blinding between the placebo and active arms, subjects were randomly assigned to a specified $ml \cdot kg^{-1} \cdot min^{-1}$ infusion rate. Study drug administration was started in the operating room *via* a dedicated peripheral intravenous line at the time of skin incision and was discontinued at the end of surgery. Study drug could be discontinued if there was hemodynamic instability (increase or decrease in systolic blood pressure [SBP] by 50% or SBP <80 or >200 mmHg, heart rate [HR] <45 or >120 beats/min despite treatment), clinically significant arrhythmia, high-grade conduction defect, or persistent electrocardiographic changes consistent with an ischemic pattern. Upon return of SBP and/or HR to within 25% of baseline or return of the electrocardiogram to baseline, the study drug could be reinstituted according to dose-reduction guidelines. If unacceptable hemodynamic or electrocardiographic changes recurred, the study drug was permanently discontinued. In the last cohort (200 $\mu g \cdot kg^{-1} \cdot min^{-1}$), study drug was started at the corresponding 100-$\mu g \cdot kg^{-1} \cdot min^{-1}$ rate and then increased by 25-$\mu g \cdot kg^{-1} \cdot min^{-1}$ increments every 2–3 min if the dose was tolerated. Immediately before each escalation in the dose of the study drug, a 6-s rhythm strip was obtained. If an adverse cardiovascular event or significant hemodynamic changes occurred during the gradual increase in dose, the dose was reduced back to the previously tolerated dose and maintained at that level throughout the procedure.

A baseline 12-lead electrocardiogram was performed for all patients. The anesthetic technique was standardized and consisted of premedication with 1–2 mg midazolam, and induction of anesthesia with 1.5–2.5 mg/kg propofol and 2 μg/kg fentanyl. A neuromuscular blocking drug of the anesthesiologist's choice was used for intubation and muscle relaxation. Anesthesia was maintained with isoflurane in $\geq$50% nitrous oxide–oxygen mixture. Ondansetron, 4 mg, was given for antiemetic prophylaxis at induction of anesthesia. Neuromuscular blockade was reversed at the end of the procedure using neostigmine and glycopyrrolate. Administration of prophylactic nonsteroidal antiinflammatory drugs or corticosteroids was not allowed. Depth of anesthesia was monitored with a target Bispectral Index (BIS) score of 40–60 using the BIS® monitor (Aspect Medical Systems, Inc., Norwood, MA). End-tidal isoflurane concentration was continuously monitored and recorded throughout the procedure. HR and SBP were continuously monitored with the aim of maintaining these values within 25% of baseline. The preincisional baseline hemodynamic values were defined as the values recorded during a 3- to 5-min interval after intubation but before skin incision.

The anesthetic regimen was adjusted according to a predefined algorithm based on hemodynamics and BIS values, ensuring that neuromuscular blockade was adequate (1 or no twitch response on train-of-four stimulation). If SBP or HR was above 25% of baseline and BIS was 40–50, a fentanyl bolus of 1 μg/kg was given. If BIS was 50–60, the volatile agent was increased by 0.5% increments. If BIS was greater than 60, a propofol bolus of 0.5 mg/kg was given and the volatile agent was increased by 0.5% increments. If SBP was below 25% of baseline and BIS was 50–60, a 200-ml fluid bolus of crystalloid or colloid was given. If BIS was less than 50, the volatile agent was reduced by 0.5%. If SBP remained less than 25% of baseline, 100 μg intravenous phenylephrine was given and repeated every 2 min if needed. If HR was less than 45 beats/min, 0.2 mg intravenous glycopyrrolate was given and repeated twice if needed. Other vasoactive drugs could be used if the above strategies did not keep the hemodynamic variables within the prescribed range or, if in the judgment of the investigator, these drugs were necessary to the safe conduct of anesthesia. An electrocardiogram rhythm strip was obtained at induction and was repeated to document evidence of adverse cardiovascular events necessitating intervention or interruption of study drug.

Postoperative analgesia was standardized. Upon arrival to the postanesthesia care unit (PACU), morphine patient-controlled analgesia was initiated using a bolus dose of 0.06 mg/kg with a lockout period of 6 min. The bolus dose could be increased by 0.01-mg/kg increments to maintain adequate analgesia (defined by a verbal rating scale [VRS] pain score of 4 or less). Rescue boluses of 0.04 mg/kg morphine could also be administered as needed. For pain uncontrolled by morphine, as defined

by a VRS greater than 6 for more than 30 min, 15 mg intravenous ketorolac could be administered once every 6 h. The patient-controlled analgesia system could be discontinued after 24 h if the subjects were tolerating oral fluids. Subjects were then given hydrocodone–acetaminophen or oxycodone–acetaminophen tablets every 4–6 h for pain control. For pain uncontrolled by oral hydrocodone–acetaminophen or oxycodone–acetaminophen tablets, as defined by a VRS pain score greater than 6 at 1 h after administration, 10 mg oral ketorolac or 15 mg intramuscular/intravenous ketorolac was given up to every 6 h.

Pain was assessed on an 11-point VRS (0 = no pain, 10 = worst possible pain). Pain assessments were performed at rest, followed by assessment after activity (performing incentive spirometry/pulmonary hygiene). Assessments of pain and vital signs were performed every 15 min in the PACU, then every hour for 4 h, and then every 4 h thereafter for the initial 48 h after surgery or until discharge, whichever occurred first. The modified Observer's Assessment of Alertness/Sedation scale was assessed at the same time points in the first 24 h.[21] An assessment of the subject's recovery using the Aldrete score was performed every 15 min while the patient was in the PACU. An Aldrete score of 9 out of 10 was used to determine time to readiness for discharge from the PACU. Twelve-lead electrocardiography was performed before discharge from the PACU. Adverse events and serious adverse events assessments were performed through day 7.

Opioid-related Symptom Distress Scale assessments were performed at 24 and 48 h. Patient satisfaction with pain control was also assessed at 24 and 48 h, using an 11-point VRS (0 = completely dissatisfied, 10 = completely satisfied). Clinical laboratory assessments (complete blood count with differential and platelet count, serum chemistry panel including liver function tests) were performed at approximately 24 h postoperatively or at discharge, whichever occurred first. If the subject was discharged before 48 h, study personnel contacted the subject *via* phone to perform necessary pain, satisfaction, and opioid-related Symptom Distress Scale assessments. After discharge, data were collected *via* diary cards completed daily through postoperative day 7 and returned to the study personnel *via* US mail. Data collected included opioid-related Symptom Distress Scale assessments daily through day 7, adverse events, serious adverse events, and concomitant medications.

Statistical Analysis

The primary outcome variable was the consumption of morphine in the initial 24 h after surgery. The sample size estimate was based on a previous study in women undergoing hysterectomy in which the mean (SD) 24-h morphine consumption was 59 (27) mg.[22] To demonstrate a 40% reduction in morphine consumption, with 10 subjects in the placebo group in every dose cohort in a dose-escalation design, we estimated that 26 patients per group would be required for an overall α of 0.05 and a power of 80%. To accommodate for dropouts, we aimed to randomize at least 30 subjects to each adenosine dose cohort.

SAS software (version 8.2; SAS Institute, Cary, NC) was used for statistical analyses. Results are presented as mean (SD) or median (interquartile range) for continuous variables, and as number (percentage) for categorical variables. Continuous variables were compared across the five treatments using analysis of variance. In the presence of an overall significant treatment effect, the Dunnett test was used for intergroup comparisons. For discrete variables, the Kruskal–Wallis test was performed to test the overall treatment effect. $P < 0.05$ was considered statistically significant.

Results

A total of 166 subjects received treatment with study drug: 125 received adenosine and 41 received placebo. Enrollment in each escalating-dose cohort was as follows: 25 $\mu g \cdot kg^{-1} \cdot min^{-1}$: 33 subjects received adenosine, 9 subjects received placebo; 50 $\mu g \cdot kg^{-1} \cdot min^{-1}$: 32 subjects received adenosine, 10 subjects received placebo; 100 $\mu g \cdot kg^{-1} \cdot min^{-1}$: 30 subjects received adenosine, 10 subjects received placebo; 200 $\mu g \cdot kg^{-1} \cdot min^{-1}$: 30 subjects received adenosine, 12 subjects received placebo. Of those 166 subjects, 143 (86.1%) completed the study as planned. A total of 23 subjects (13.9%) did not complete the full 7-day study period: 1 withdrew consent, 3 were withdrawn because of adverse events, 15 were lost to follow-up, and 4 withdrew for other reasons: the procedure was aborted in 1 subject, and 3 subjects lost or did not return their diary. However, primary endpoint data were available for 163 patients. With the exception of height, there were no significant differences between treatment groups with respect to demographic or baseline characteristics, baseline blood pressure, or HR (table 1).

Intraoperative data are summarized in table 2. There were no significant differences between the groups in the duration of surgery, intraoperative fentanyl use, intraoperative BIS score, or intraoperative use of phenylephrine and ephedrine. Significant overall differences were found in intraoperative end-tidal isoflurane concentration, intraoperative blood pressure, and HR. Between group comparisons showed that the systolic and diastolic blood pressures were significantly lower in the 100- and 200-$\mu g \cdot kg^{-1} \cdot min^{-1}$ adenosine groups compared with the placebo, 25-$\mu g \cdot kg^{-1} \cdot min^{-1}$ adenosine, and 50-$\mu g \cdot kg^{-1} \cdot min^{-1}$ adenosine groups. On the other hand, intraoperative HR was significantly higher in the 50-, 100-, and 200-$\mu g \cdot kg^{-1} \cdot min^{-1}$ adenosine groups compared with the placebo and 25-$\mu g \cdot kg^{-1} \cdot min^{-1}$ adenosine groups.

Table 1. Patient Demographics and Baseline Hemodynamics

	Placebo, n = 41	25 $\mu g \cdot kg^{-1} \cdot min^{-1}$ Adenosine, n = 33	50 $\mu g \cdot kg^{-1} \cdot min^{-1}$ Adenosine, n = 32	100 $\mu g \cdot kg^{-1} \cdot min^{-1}$ Adenosine, n = 30	200 $\mu g \cdot kg^{-1} \cdot min^{-1}$ Adenosine, n = 30	*P* Value
Age, yr	43 (7)	46 (8)	44 (8)	45 (7)	43 (8)	0.56
Height, cm	165 (8)	163 (7)	165 (7)	166 (6)	160 (7)	0.01
Weight, kg	78 (16)	74 (12)	74 (12)	76 (16)	74 (13)	0.68
BMI, kg/m^2	29 (5)	28 (4)	27 (4)	27 (6)	29 (5)	0.30
ASA						0.16
I	11 (27)	11 (33)	6 (19)	13 (43)	2 (7)	
II	28 (68)	20 (61)	22 (71)	15 (50)	25 (83)	
III	2 (5)	2 (6)	3 (10)	2 (7)	3 (10)	
Baseline SBP, mmHg	108 (16)	115 (20)	112 (14)	109 (15)	112 (12)	0.39
Baseline DBP, mmHg	62 (13)	65 (16)	64 (13)	62 (13)	62 (10)	0.80
Baseline HR, beats/min	76 (13)	77 (12)	79 (12)	75 (13)	82 (16)	0.33

Data are presented as mean (SD), except for American Society of Anesthesiologists (ASA) physical status classification, presented as n (%).
BMI = body mass index; DBP = diastolic blood pressure; HR = heart rate; SBP = systolic blood pressure.

Postoperative data are presented in table 3. There was no significant difference between the treatment groups in cumulative opioid use during the initial 24-h period after extubation (primary outcome measure). There were also no significant differences between treatment groups with respect to the 24–48 h morphine consumption or other secondary efficacy measures, including sedation scores; time to readiness for discharge from the PACU; time to readiness for discharge from the hospital; opioid-related symptom distress scores; patient satisfaction with pain control; use of rescue analgesics; and times to extubation, eye opening, and response to spoken command. There was also no difference between the groups in the incidence of postoperative nausea, vomiting, or pruritus. There were no differences between treatment groups in VRS pain scores at rest at 0–2 or 0–24 h. However, there was an overall difference between treatment groups in worst pain scores at rest between 24 and 48 h ($P = 0.03$), with VRS scores being significantly lower in the 25-$\mu g \cdot kg^{-1} \cdot min^{-1}$ adenosine group compared with the 200-$\mu g \cdot kg^{-1} \cdot min^{-1}$ group ($P = 0.028$). For the maximum pain scores after activity, there were no significant differences between the treatment groups at any of the time points.

No differences between the groups were identified with respect to laboratory assessments, electrocardiographic changes, or postoperative vital signs (table 4). Adverse events were not different between the groups. Of note, cardiac events were reported in 2.4% of patients in the placebo group and 5.6% of the combined adenosine groups, with a 10% incidence reported in both the 100- and 200-$\mu g \cdot kg^{-1} \cdot min^{-1}$ dose cohorts of adenosine. A total of 9 serious adverse events were reported by 8 (5%) of the 166 subjects who were treated with study drug (2 in the placebo group and 6 in the adenosine group). These events included postprocedural hemorrhage, respiratory depression, coagulopathy, pyrexia, hypovolemia, abnormal liver function test results, and gas-

Table 2. Intraoperative Data

	Placebo, n = 41	25 $\mu g \cdot kg^{-1} \cdot min^{-1}$ Adenosine, n = 33	50 $\mu g \cdot kg^{-1} \cdot min^{-1}$ Adenosine, n = 32	100 $\mu g \cdot kg^{-1} \cdot min^{-1}$ Adenosine, n = 30	200 $\mu g \cdot kg^{-1} \cdot min^{-1}$ Adenosine, n = 30	*P* Value
Duration of surgery, min	120 (94–166)	101 (91–150)	124 (103–186)	146 (110–173)	114 (96–171)	0.32
Intraoperative fentanyl, μg	142 (50)	144 (30)	134 (35)	144 (38)	140 (39)	0.81
End-tidal isoflurane, %	0.8 (0.2)	0.8 (0.2)	0.7 (0.2)	0.7 (0.2)	0.8 (0.3)	0.04
Intraoperative bradycardia	1 (2%)	0 (0%)	0 (0%)	0 (0%)	1 (3%)	0.81
Phenylephrine use	4 (10%)	6 (18%)	4 (13%)	10 (33%)	5 (17%)	0.11
Phenylephrine dose, μg	200 (82)	242 (128)	668 (1,192)	515 (606)	560 (418)	0.71
Ephedrine use	3 (7%)	1 (3%)	3 (9%)	5 (17%)	3 (10%)	0.46
Ephedrine dose, mg	8 (3)	5 (NA)	10 (5)	19 (27)	12 (3)	0.88
SBP, mmHg	118 (14)*	114 (12)†	111 (11)‡	102 (12)	110 (11)	<0.0001
DBP, mmHg	69 (11)§	66 (12)§	64 (9)‖	52 (10)	53 (9)	<0.0001
HR, beats/min	72 (12)#	72 (11)**	83 (13)	80 (10)	87 (11)	<0.0001
BIS score	44 (8)	46 (8)	48 (6)	49 (8)	47 (7)	0.10

Data are presented as mean (SD), median (interquartile range), or number of subjects (%).

* $P < 0.0001$ *vs.* 100 and 200 adenosine. † $P = 0.001$ *vs.* 100 adenosine and $P = 0.0005$ *vs.* 200 adenosine. ‡ $P = 0.03$ *vs.* 100 adenosine and $P = 0.016$ *vs.* 200 adenosine. § $P < 0.0001$ *vs.* 100 and 200 adenosine. ‖ $P = 0.0001$ *vs.* 100 adenosine and $P = 0.0003$ *vs.* 200 adenosine. # $P = 0.0018$ *vs.* 50 adenosine, $P = 0.0369$ *vs.* 100 adenosine, and $P < 0.0001$ *vs.* 200 adenosine. ** $P = 0.0032$ *vs.* 50 adenosine, $P = 0.0489$ *vs.* 100 adenosine, and $P < 0.0001$ *vs.* 200 adenosine.

BIS = Bispectral Index; DBP = diastolic blood pressure; HR = heart rate; NA = not applicable; SBP = systolic blood pressure.

Table 3. Postoperative Data

	Placebo, n = 41	25 $\mu g \cdot kg^{-1} \cdot min^{-1}$ Adenosine, n = 33	50 $\mu g \cdot kg^{-1} \cdot min^{-1}$ Adenosine, n =32	100 $\mu g \cdot kg^{-1} \cdot min^{-1}$ Adenosine, n = 30	200 $\mu g \cdot kg^{-1} \cdot min^{-1}$ Adenosine, n = 30	*P* Value
Opioid consumption, 0–24 h, mg	66 (33)	66 (35)	67 (46)	67 (26)	78 (50)	0.70
Opioid consumption, 24–48 h, mg	29 (19)	33 (24)	36 (32)	29 (18)	32 (23)	0.78
Need for rescue ketorolac	25 (63%)	18 (56%)	13 (42%)	18 (60%)	18 (62%)	0.44
Time to first dose of ketorolac after extubation, min	1,459 (122)	1,761 (608)	1,582 (417)	1,464 (63)	1,630 (461)	0.08
VRS worst pain at rest, 0–2 h	8.1 (2.0)	7.6 (2.4)	8.4 (1.9)	8.2 (1.9)	8.1 (2.2)	0.69
VRS maximum pain after activity, 0–2 h	8.2 (2.2)	7.9 (2.7)	8.8 (1.8)	8.4 (1.5)	8.5 (2.1)	0.57
VRS worst pain at rest, 0–24 h	8.2 (1.9)	7.7 (2.4)	8.4 (2.1)	8.2 (1.8)	8.3 (2.1)	0.68
VRS maximum pain after activity, 0–24 h	8.4 (2.1)	8.0 (2.6)	9.1 (1.4)	8.7 (1.3)	8.8 (1.9)	0.20
VRS worst pain at rest, 24–48 h	4.5 (2.3)	3.1 (2.1)*	4.3 (3.2)	3.7 (2.3)	5.1 (2.5)	0.03
VRS maximum pain after activity, 24–48 h	5.4 (2.2)	4.3 (2.4)	5.7 (2.7)	5.3 (2.2)	5.8 (2.7)	0.11
Patient satisfaction with pain control	8.8 (2.1)	8.9 (1.7)	8.7 (2)	8.3 (2.2)	8.5 (1.8)	0.78
Time to readiness for PACU discharge, min	30 (43)	30 (45)	39 (59)	29 (34)	49 (57)	0.42
Time to readiness for discharge from hospital, h	69 (21)	66 (21)	64 (15)	71 (35)	74 (21)	0.58
Nausea, 0–24 h	29 (73%)	19 (61%)	14 (45%)	18 (60%)	16 (55%)	0.22
Vomiting, 0–24 h	4 (10%)	3 (10%)	3 (10%)	7 (23%)	7 (24%)	0.22
Pruritus, 0–24 h	23 (58%)	16 (52%)	19 (61%)	19 (63%)	23 (79%)	0.25

Data are presented as mean (SD) or number (%).

* $P = 0.028$ *vs.* 200 $\mu g \cdot kg^{-1} \cdot min^{-1}$ adenosine.

PACU = postanesthesia care unit; VRS = verbal rating score.

tric cancer. None of these events were considered related to study drug.

Discussion

In this study, we found no significant differences between adenosine and placebo with respect to the analgesic efficacy for postoperative pain management. While this study was powered on the primary endpoint of 24-h opioid consumption, a *post hoc* sensitivity analysis was conducted using the observed mean 24-h worst VRS pain score at rest in the placebo group, and its SD pooled from all groups. This analysis found that a study with our sample size would have 95% power at an overall α of 0.05 to detect a reduction in VRS of 20% between placebo and the group with the lowest VRS, assuming a constant dose effect across treatments. Therefore, this study was adequately powered for both its primary endpoint and its main secondary endpoint.

Previous studies investigating the analgesic- and anesthetic-sparing effects of the perioperative administration of adenosine have yielded conflicting results. For example, three studies by one group of investigators evaluated the use of intravenous adenosine during breast surgery,[16] shoulder surgery,[18] and abdominal hysterectomy.[17] In each study, patients received an intravenous infusion of 80 $\mu g \cdot kg^{-1} \cdot min^{-1}$ adenosine or placebo during surgery. In the study involving hysterectomy, patients also received a reduced dose of intravenous adenosine (40 $\mu g \cdot kg^{-1} \cdot min^{-1}$) for 3 h after surgery. Postoperative analgesic requirements

Table 4. Cardiovascular Side Effects

	Placebo, n = 41	25 $\mu g \cdot kg^{-1} \cdot min^{-1}$ Adenosine, n = 33	50 $\mu g \cdot kg^{-1} \cdot min^{-1}$ Adenosine, n = 32	100 $\mu g \cdot kg^{-1} \cdot min^{-1}$ Adenosine, n = 30	200 $\mu g \cdot kg^{-1} \cdot min^{-1}$ Adenosine, n = 30
First-degree AV block	0 (0)	0 (0)	0 (0)	1 (3)	1 (3)
Second-degree AV block	0 (0)	0 (0)	0 (0)	0 (0)	1 (3)
Bradycardia, HR <45 beats/min	1 (2)	0 (0)	0 (0)	1 (3)	1 (3)
Myocardial ischemia	0 (0)	0 (0)	0 (0)	1 (3)	0 (0)
Tachycardia, HR >120 beats/min	0 (0)	1 (3)	0 (0)	0 (0)	1 (3)
ECG ST-segment depression	0 (0)	0 (0)	0 (0)	0 (0)	2 (5)
ECG T-wave abnormality	0 (0)	0 (0)	1 (4)	2 (8)	0 (0)

Data are presented as number (%).

AV = atrioventricular; ECG = electrocardiogram; HR = heart rate.

were reduced with adenosine in two studies.[16,17] Furthermore, there was an anesthetic-sparing effect, most pronounced in the hysterectomy study, where a 36% isoflurane-sparing effect was reported.[17] However, there was no reduction in opioid-related side effects in these studies. The authors also did not report improved recovery or a shortened duration of PACU or hospital stay as a result of opioid sparing. Some limitations of the methodology used in these studies have been highlighted, including the lack of description of well-defined variables to titrate anesthesia, inconsistent reporting of the doses of intraoperative opioids, no continuous monitoring of end-tidal isoflurane concentration, inconsistent description of the mode of delivery of postoperative opioids, and their intravenous or intramuscular administration on a *pro re nata* basis.[23]

Adenosine was also better than intravenous remifentanil in providing pain relief and reducing the need for opioid analgesia after hysterectomy and major orthopedic surgery performed during general anesthesia.[19,20] The dose of adenosine infusion used was variable, ranging from 50 to 500 $\mu g \cdot kg^{-1} \cdot min^{-1}$ and from 72 to 290 $\mu g \cdot kg^{-1} \cdot min^{-1}$ in these two studies.[19,20] Postoperative pain scores were also significantly lower during the postoperative period in patients who received adenosine, with pronounced and sustained relief lasting up to 48 h. The improved analgesia with adenosine in comparison with remifentanil could however be a result of the development of acute opioid tolerance or hyperalgesia after the use of remifentanil. This phenomenon has been reported in a number of studies, where a significant increase in pain scores and opioid consumption in the postoperative period followed the intraoperative use of remifentanil.[24,25]

Other studies did not report a useful analgesic effect of adenosine or adenosine receptor agonists in the postoperative period. In a multicenter study, the administration of a selective A_1 receptor agonist did not improve pain relief compared with placebo, in patients undergoing third molar extraction during general anesthesia.[26] Similarly, the intrathecal administration of 500–1,000 μg adenosine did not provide any anesthetic- or analgesic-sparing effects in women undergoing abdominal hysterectomy during general anesthesia.[27,28]

The lack of analgesic effect of adenosine in our study could have a number of explanations. First, this could be related to the timing of starting the administration of adenosine. Whereas the infusion of adenosine was started 5–15 min before skin incision in previous studies,[13,16–20] we started the administration of adenosine at the time of skin incision. This was done to avoid any untoward hemodynamic changes after induction of anesthesia before the start of surgical stimulation. It is possible that the preemptive administration of adenosine is important for its analgesic effect. However, although the evidence for preemptive analgesia in animal studies is convincing,[29] results from human studies remain equivocal and agent dependent.[30] Second, the dose of adenosine used could have been insufficient to achieve an analgesic effect. This is unlikely, however, because studies that investigated a constant infusion regimen used a dose of 80 $\mu g \cdot kg^{-1} \cdot min^{-1}$,[13,16–18] which lies within the range of doses that we used in our study. These doses were selected for evaluation in this study based on the range of doses that were found to be efficacious and safe, and we also included doses above and below what was published in perioperative trials comparing adenosine with placebo. In the two studies comparing adenosine with remifentanil, a variable infusion regimen was used. In one study,[19] the mean (SD) dose of 292 (82) $\mu g \cdot kg^{-1} \cdot min^{-1}$ is higher than the dose that we used, while in the other study,[20] the mean (SD) dose of 166 (17) $\mu g \cdot kg^{-1} \cdot min^{-1}$ is lower than the dose than we used in cohort 4. However, because we had a 10% incidence of cardiovascular side effects in the 100- and 200-$\mu g \cdot kg^{-1} \cdot min^{-1}$ cohorts, it is likely that higher doses of adenosine might be associated with even a higher incidence of cardiovascular side effects and therefore would not be well tolerated in the perioperative period. Third, because the main site of action of adenosine is likely to be spinal, it is possible that intravenous administration does not deliver the drug in sufficient concentrations. For example, in patients with neuropathic pain, intrathecal administration of 2 mg adenosine was effective in reducing allodynia and hyperalgesia, whereas intravenous administration of the same dose was not effective.[31] However, two studies investigating the intrathecal administration of adenosine in the perioperative period did not show any useful anesthetic- or analgesic-sparing effects.[27,28] In this study, we only included women undergoing gynecologic abdominal surgery. This provided a homogeneous patient population but did not allow us to examine whether the results would have been different if we had also included men. Although it has been suggested that sex may affect response to some analgesics, such as opioids,[32] there are no data to suggest that this might be the case with adenosine. Finally, it is possible that despite its potential analgesic efficacy in other pain states, such as neuropathic pain,[15,31] adenosine does not possess a useful analgesic effect in the perioperative period, and the positive findings in some of the previous investigations were due to limitations in the methodology or secondary to the hyperalgesia after remifentanil administration, as previously highlighted.

In summary, the use of intraoperative adenosine infusion did not provide a useful analgesic effect in women undergoing major gynecologic surgery during general anesthesia. Because this study was adequately powered for both its primary and main secondary endpoints, we believe that further investigation of intravenous adenosine for perioperative analgesia is unwarranted.

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