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Treatment of Stress Response during Balanced Anesthesia

Comparative Effects of Isoflurane, Alfentanil, and Trimethaphan

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Acute hypertensive responses during nitrous oxide–opioid–relaxant anesthesia are a common clinical problem. In adult men undergoing radical prostatectomy procedures and anesthetized with a standardized technique, we evaluated the effectiveness of alfentanil, isoflurane, and trimethaphan in treating acute hemodynamic and stress hormone responses to surgical stimulation. Stress hormone concentrations were measured 1 min before skin incision, after the onset of an acute hypertensive response, and after returning the mean arterial pressure to within 10% of the preincision values with one of the three treatment modalities. Pretreatment plasma alfentanil concentrations (151 ± 47 to 156 ± 47 ng · ml^{-1}) and end-tidal nitrous oxide concentrations (66 ± 2 to 68 ± 2%) were similar in all three groups. Acute hypertensive events were associated with significantly increased concentrations of catecholamines and vasopressin (antidiuretic hormone [ADH]). Whereas intravenous alfentanil returned all hormone concentrations to preincision values, norepinephrine and glucose concentrations were significantly increased after adjunctive isoflurane administration. Although trimethaphan decreased the norepinephrine concentration, the epinephrine, β-endorphin, cortisol, ADH, and glucose concentrations were significantly increased compared to preincision values. However, the persistent elevation in the posttreatment ADH concentration in the trimethaphan group was the only significant difference between the three groups. Mean (± standard deviation) times to awakening (2.8 ± 3.3 to 3.8 ± 4.2 min), extubation (8.1 ± 4.8 to 10.3 ± 8.5 min), and orientation (19.6 ± 20.4 to 24.6 ± 19.1 min) were similar in all three groups. Naloxone was required more frequently in patients in the alfentanil (35%) and isoflurane (24%) groups than in the trimethaphan group (4%). However, fewer alfentanil-treated patients required antihypertensive therapy in the postanesthesia care unit (12% *vs.* 48% and 38% in the isoflurane and trimethaphan groups, respectively). Postoperative analgesic requirements and hospital discharge times were similar in all three groups. We conclude that the choice of adjunctive therapy to maintain hemodynamic stability during balanced anesthesia did not appear to effect outcome after radical prostatectomy procedures. (Key words: Anesthetics, volatile: isoflurane. Hormones: catecholamines; vasopressin; β-endorphin; cortisol. Analgesics, opioid: alfentanil. Pain, postoperative: patient-controlled analgesia. Pharmacology: trimethaphan. Sympathetic nervous system, catecholamines: epinephrine; norepinephrine.)

WITH THE AVAILABILITY of potent, rapid, and shorter-acting opioid analgesics, nitrous oxide–opioid–relaxant ("balanced") anesthetic techniques have become more widely used for maintenance of general anesthesia. Although these techniques are associated with a rapid and smooth emergence from anesthesia, acute increases in blood pressure occur during the operation in response to changing surgical stimuli.[1]

Although it is generally agreed that these hemodynamic responses require an increased "depth of anesthesia," it is unclear whether this should be accomplished by administering additional analgesic, sedative–hypnotic, and/or sympatholytic medication. Unfortunately, there is little scientific information to guide the clinician in the use of intravenous (iv) anesthetics.[2] Studies with the rapid, short-acting opioid alfentanil suggest that it is possible to maintain hemodynamic stability by varying the rate of opioid administration in response to changes in the surgical stimulus.[3–5] However, the high opioid concentrations that may be required to blunt potent stimuli can contribute to postoperative side effects (*e.g.*, ventilatory depression and nausea or vomiting). Therefore, many anesthesiologists treat these acute hemodynamic responses with volatile agents (*e.g.*, isoflurane). Since volatile anesthetics can add to the central nervous system depressant effects of opioid analgesics, alternative approaches have been sought (*e.g.*, sympatholytic drugs).[1]

Using a randomized, single-blind protocol design, we compared the intraoperative hemodynamic and stress hormone responses, as well as the recovery profiles, when alfentanil, isoflurane, or trimethaphan was used to treat acute hypertensive responses in patients anesthetized with alfentanil and nitrous oxide.

Materials and Methods

The study was approved by the Washington University Human Studies Committee. Eighty-eight consenting adult men, ASA physical status 1, 2, or 3, scheduled for elective radical prostatectomy procedures under general anesthesia, were assigned to one of three treatment groups according to a randomized, single-blinded protocol. Exclusionary criteria included history of allergic reaction to the study medications, chronic opioid or sedative use, obesity (> 130% of ideal body weight), clinically significant hepatic or renal dysfunction, endocrine disease, and uncontrolled hypertension. All patients received midazolam, 0.1 mg · kg^{-1} intramuscularly, 30–45 min prior to arrival in the preoperative holding area, where peripheral venous and arterial catheters were inserted.

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After obtaining preinduction (baseline) hemodynamic values, anesthesia was induced with alfentanil 30 $\mu g \cdot kg^{-1}$, thiopental 2.5 $mg \cdot kg^{-1}$, and vecuronium 0.1 $mg \cdot kg^{-1}$, iv. After tracheal intubation, anesthesia was maintained with an alfentanil infusion, 0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$, and nitrous oxide 67% in oxygen, and paralysis was maintained with vecuronium 0.8 $\mu g \cdot kg^{-1} \cdot min^{-1}$. Ventilation was controlled with a volume-cycled ventilator to maintain end-tidal carbon dioxide tension (PET_{CO_2}) at 34 ± 3 mmHg (mean ± standard deviation). Mean arterial pressure (MAP) and heart rate (HR) were continuously monitored using an integrated monitor (Cardiocap II®, Datex Medical Instrumentation, Tewksbury, MA). Central venous pressure was monitored *via* a catheter in an internal jugular vein and was maintained between 3 and 8 mmHg throughout the study period by administration of crystalloid and/or blood products.

Blood samples were obtained from the central venous catheter for determination of plasma catecholamines, vasopressin (antidiuretic hormone [ADH]), β-endorphin, cortisol, and glucose concentrations at 1–2 min before skin incision (preincision) and 3–5 min after the onset of the hypertensive response to the retropubic dissection (pretherapy). Blood for catecholamine analysis was collected into heparinized glass tubes, while the blood samples for the remainder of the hormone assays were collected into EDTA-treated tubes. These samples were immediately placed on ice and the plasma separated using a refrigerated centrifuge. All samples were stored at −40° C until the assays were performed. Epinephrine and norepinephrine concentrations were determined using high-performance liquid chromatography (with assay sensitivities of 10 $pg \cdot ml^{-1}$ and coefficients of variation equal to ± 10%), while all other hormone concentrations were determined using radioimmunoassay (RIA) techniques by Nichols Laboratory (San Juan Capistrano, CA). Plasma alfentanil concentrations were also measured using a standardized RIA.[6] The coefficients of variation for all RIA techniques were less than 15%. The lower limit of sensitivity of the RIA assays for ADH, β-endorphin, cortisol, and alfentanil were 1 $pg \cdot ml^{-1}$, 8 $pg \cdot ml^{-1}$, 0.5 $\mu g \cdot dl^{-1}$, and 5 $ng \cdot ml^{-1}$, respectively.

Patients exhibiting an increase in MAP of 25% or more above their preincision MAP for a minimum of 3 min were treated using one of three different therapeutic modalities. Alfentanil 20–60 $\mu g \cdot kg^{-1}$ iv, isoflurane 0.5–2.0% (inspired), or trimethaphan 0.05–0.15 $mg \cdot kg^{-1}$ iv, was administered to return the MAP to within 10% of the preincision value. In the alfentanil group, patients initially received a 10-$\mu g \cdot kg^{-1}$ bolus, and the infusion rate was increased by 0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$. This alfentanil treatment regimen was repeated every 2–3 min until the MAP decreased. Isoflurane treatment was initiated at 0.5% (inspired) and increased by 0.5% every 2–3 min until the MAP returned to within 10% of the preincision value. In the trimethaphan group, an infusion of 1 $mg \cdot min^{-1}$ was initiated and this was increased by 50–100% every 2–3 min until the MAP was ± 10% of the preincision value. After maintaining a stable MAP for 20 min, repeat blood samples were obtained for determination of posttherapy endocrine and alfentanil concentrations.

The adjunctive therapy was adjusted to maintain hemodynamic stability throughout the remainder of the operative period. If the MAP remained within 10% of the preincision MAP for a period of 15–30 min, the initial infusion rate or concentration of adjunctive therapy administration was decreased by 50%. If the MAP remained stable, the adjunctive therapy was further decreased every 15–30 min until the minimum effective supplemental dose of each adjunctive therapy was determined during the maintenance period. Adjunctive therapy was discontinued if MAP decreased below the preincision value for more than 5 min.

Upon initiating skin closure, the vecuronium and alfentanil infusions and the adjunctive therapy were discontinued. At the end of surgery, residual neuromuscular blockade was reversed with neostigmine 0.07 $mg \cdot kg^{-1}$ and glycopyrrolate 0.01 $mg \cdot kg^{-1}$, followed by discontinuation of nitrous oxide. The times from discontinuation of nitrous oxide until spontaneous eye-opening, purposeful response to verbal commands, adequate spontaneous ventilation, tracheal extubation, and orientation (to person, place, and time) were recorded by an individual blinded to the treatment regimen. The recovery endpoints were evaluated at 5–10-s intervals after spontaneous eye-opening. If adequate spontaneous ventilation did not occur within 10 min (in the presence of an PET_{CO_2} of 40–45 mm Hg), naloxone, 0.04 mg iv boluses, were administered every 60 s until spontaneous ventilation was adequate ($PET_{CO_2} < 50$ mm Hg).

Upon arrival in the postanesthesia care unit (PACU), the patients were administered 40% oxygen *via* face mask and observed by a nurse blinded to the treatment group until they returned to their baseline mental status and met the standardized PACU discharge criteria. In addition, the need for analgesic, antiemetic, and antihypertensive therapy in the PACU was recorded. If a patient complained of pain, morphine sulfate 1–2 mg iv was administered at 2–5-min intervals until the patient was comfortable. An acute hypertensive response was defined as a postoperative MAP value exceeding 25% of the preoperative baseline value for > 5 min. If hypertension persisted after achieving adequate pain control, labetalol 5–10 mg iv or hydralazine 2.5–5 mg iv was administered as needed to return the MAP value to within 10% of the preoperative baseline value. Patients complaining of postoperative nausea and/or vomiting received metoclopramide 10–20 mg iv. Prior to discharge from the PACU,

patients were given a patient-controlled analgesia (PCA) device (Baxter Infusor®, Chicago, IL) which allowed them to self-administer morphine sulfate 2 mg (0.5 ml) at minimum intervals of 6 min. The patients were visited daily to evaluate their overall recovery status and analgesic usage. On the fifth postoperative day, the patients completed a questionnaire regarding their satisfaction with the anesthetic technique and the postoperative PCA therapy.

Data Analysis

Data were analyzed with the STATA® statistical analysis program, using one-way analysis of variance and chi-square analysis. Changes over time were evaluated using repeated measures of analysis of variance and Student's *t* test with a Bonferroni correction for multiple comparisons. Intergroup differences were evaluated using a Tukey's *post hoc* test. Differences were considered to be statistically significant if the P value was < 0.05. Values are expressed as mean ± standard deviation (unless otherwise specified).

Results

With the standardized nitrous oxide–alfentanil–vecuronium anesthetic technique, 81 patients (92%) exhibited a significant hypertensive response after entry into the retropubic space and were randomized to one of the three treatment groups. There were no differences in age, weight, height, and baseline hemodynamic values among the three groups (table 1). In addition, all groups had a similar incidence of preexisting hypertension, coronary artery disease, and chronic use of β and calcium-channel blocking drugs (table 1).

All patients received the same preanesthetic and induction medications. The mean dose of intramuscular midazolam was 8.4 ± 1.6 mg, and the induction doses (and ranges) were: alfentanil 2.5 ± 0.3 mg (1.7–3.0 mg), thiopental 214 ± 48 mg (150–350 mg), and vecuronium 10.0 ± 1.5 mg (7–14 mg). The plasma alfentanil concentrations were similar in all groups at the preincision (146 ± 32 to 171 ± 39 ng · ml^{-1}) and pretherapy (151 ± 47 to 156 ± 47 ng · ml^{-1}) time intervals. As expected, the post-treatment alfentanil concentration was significantly higher in the alfentanil-treated patients (489 ± 135 ng · ml^{-1}) compared to the two other groups (154 ± 44 and 164 ± 63 ng · ml^{-1}, with isoflurane and trimethaphan, respectively). The total alfentanil dose (and range) in the alfentanil group was 31.2 ± 11.4 mg (14.7–67.2 mg). In the isoflurane and trimethaphan groups, the total alfentanil doses (and ranges) were 12.6 ± 2.6 mg (6.3–18.6 mg) and 13.1 ± 4.1 mg (5.7–19.2 mg), respectively. The total trimethaphan dose (and range) in that treatment group was 77 ± 49 mg (14–179 mg). In the isoflurane group, the average intraoperative inspired isoflurane concentration (and range) was 1.2 ± 0.4% (0.5–2%).

Perioperative changes in hemodynamic variables are summarized in figures 1 and 2. The three groups had similar baseline MAP values (fig. 1). However, after induction with alfentanil–thiopental, there was a significant decrease in MAP that persisted until the time of laryngoscopy. With tracheal intubation, MAP increased in all three groups and returned to baseline values within 1 min postintubation. Upon entry into the retropubic space (13.4 ± 6.2 to 14.5 ± 8.0 min after skin incision), the MAP values increased 31–36% (fig. 1). The times required for the MAP values to return to within 10% of the preincision value were similar with alfentanil (10.7 ± 8.2 min), isoflurane (8.8 ± 4.9 min), and trimethaphan (9.0 ± 7.5 min) therapy. MAP values were subsequently maintained within 10% of preincision values in all three groups. Posttherapy stress hormone concentrations were obtained after maintaining a stable MAP for 20 min. There were no significant differences in MAP among the

TABLE 1. Demographic Characteristics, Baseline Hemodynamic Values, and Alfentanil Levels for the Three Treatment Groups

	Alfentanil	Trimethaphan	Isoflurane
Number (n)	26	26	29
Age (yr)	64 ± 9	64 ± 9	66 ± 8
Weight (kg)	85 ± 12	82 ± 12	81 ± 12
Height (cm)	177 ± 7	176 ± 8	175 ± 8
Mean arterial blood pressure (mmHg)	97 ± 12	95 ± 15	99 ± 14
Heart rate (beats per min)	70 ± 12	67 ± 12	68 ± 11
Chronic hypertension (n)	8	11	11
Coronary artery disease (n)	10	11	10
β-blocker therapy (n)	5	6	4
Calcium-channel blocker therapy (n)	5	2	5
Alfentanil concentration (ng · ml^{-1})			
Preincision	146 ± 32	171 ± 39	161 ± 38
Pretherapy	154 ± 35	151 ± 47	156 ± 47
Operative time (min)	254 ± 54	229 ± 77	229 ± 57

Numbers or mean values ± SD.

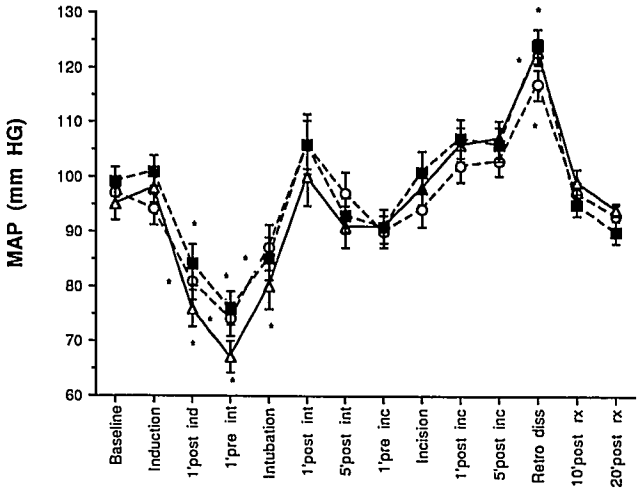

FIG. 1. Perioperative mean arterial blood pressure values in patients receiving adjunctive therapy with either alfentanil, n = 26 (circles), trimethaphan, n = 26 (triangles), or isoflurane, n = 29 (squares). Values are means ± SEM; .*$P < 0.05$ was considered statistically significant when compared to preinduction baseline values for each group. Ind = induction; inc = incision; retro diss = retropubic dissection; rx = therapy.

three treatment groups at any given time during the remainder of the procedure.

The three groups also had a similar mean baseline HR (fig. 2). There was a significant decrease in HR in all groups after induction, and the HR remained significantly decreased from baseline in all groups at 1 min preintubation; however, HR returned to baseline values after tracheal intubation. Prior to skin incision (preincision), HR values were significantly lower than baseline and remained unchanged until the retropubic space was entered. Six patients (two in each group) received an antimuscarinic, glycopyrrolate 0.2 mg iv, to treat bradycardia prior to skin incision. With retropubic dissection, HR increased in all groups. After treatment of the hypertensive response, HR values in alfentanil-treated patients were significantly lower than those in the other two treatment groups.

All patients experienced significant increases in epinephrine, norepinephrine, and ADH concentrations 3–5 min after the acute hypertensive response to retropubic dissection (table 2). In the group treated with alfentanil, these hormone concentrations returned to baseline. Isoflurane therapy returned epinephrine and ADH concentrations to baseline values, but norepinephrine concentrations remained significantly elevated. The norepinephrine concentration returned to its preincision value with trimethaphan treatment; however, epinephrine and ADH concentrations remained significantly increased after the return of MAP to preincision values. Plasma β-endorphin concentrations were unchanged in the alfentanil and isoflurane groups during the study period, but were significantly increased in the trimethaphan-treated patients after blood pressure control was achieved. Cortisol concentrations were also unchanged in all groups at the time of the hypertensive response; however, cortisol was significantly increased after treatment with trimethaphan. Statistically significant increases in glucose concentrations were seen after blood pressure control in both the trimethaphan and isoflurane-treated patients. Nevertheless, the only intergroup difference was the persistent elevation in the ADH concentration in the trimethaphan-treated patients (table 2).

There were no differences in the duration of surgery (table 1) or recovery times among the three groups (table 3). Compared to the isoflurane (n = 7) and alfentanil (n = 9) treatment groups, significantly fewer trimethaphan-treated patients (n = 1) required postoperative opioid antagonists. All groups had similar MAP values (105 ± 17 to 110 ± 19 mmHg) and HR (77 ± 14 to 85 ± 18 beats/min) on arrival in the PACU. However, patients in the trimethaphan and isoflurane groups were more likely to require antihypertensive therapy during their PACU stay (12% for alfentanil *vs.* 38% and 48% for trimethaphan and isoflurane, respectively). There were no differences in the requirements for antiemetic therapy, duration of PACU stay, or length of hospitalization among the three groups (table 3).

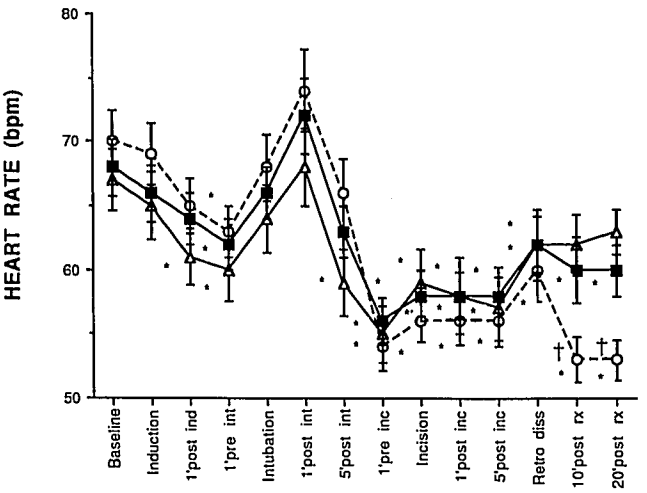

FIG. 2. Perioperative heart rate values in patients receiving adjunctive therapy with either alfentanil, n = 26 (circles), trimethaphan, n = 26 (triangles), or isoflurane, n = 29 (squares). Values are means ± SEM; *$P < 0.05$ was considered statistically significant when compared to preinduction baseline values for each group. †$P < 0.05$ was considered significant when compared to preinduction baseline values for each group. †P was considered to be significantly different when compared to the other two groups at the same time interval. Ind = induction; inc = incision; retro diss = retropubic dissection; rx = therapy.

TABLE 2. Intraoperative Changes in Stress Hormone Levels in the Three Treatment Groups

	Epinephrine (pg/ml)	Norepinephrine (pg/ml)	ADH (pg/ml)	Beta-endorphin (pg/ml)	Glucose (mg/dl)	Cortisol (μg/dl)
Alfentanil						
Preincision	27 ± 11	372 ± 203	3.4 ± 4.4	27 ± 12	104 ± 15	11 ± 4
Pretherapy	74 ± 72*	506 ± 253*	15.6 ± 4.0*	61 ± 57	106 ± 13	13 ± 6
Posttherapy	39 ± 12	407 ± 193	3.1 ± 4.0	36 ± 26	108 ± 13	12 ± 6
Trimethaphan						
Preincision	28 ± 14	281 ± 132	4.2 ± 5.9	25 ± 11	108 ± 21	13 ± 6
Pretherapy	88 ± 73*	539 ± 395*	37.2 ± 22.0*	47 ± 49	110 ± 18	13 ± 4
Postherapy	53 ± 45*	330 ± 295	58.1 ± 83.0*†	47 ± 26*	120 ± 22*	17 ± 10*
Isoflurane						
Preincision	33 ± 24	381 ± 209	5.4 ± 8.1	30 ± 13	101 ± 20	11 ± 4
Pretherapy	123 ± 158*	531 ± 230*	29.8 ± 28.1*	33 ± 14	105 ± 26	14 ± 5
Posttherapy	45 ± 33	504 ± 328*	6.7 ± 11.5	31 ± 11	123 ± 34*	12 ± 6

Mean values ± SD.
* Significantly different from pre-incision, $P < 0.05$.
† Trimethaphan posttherapy value significantly different from alfentanil and isoflurane posttherapy values, $P < 0.05$.

There were also no differences among the three groups in morphine usage in the PACU or on the postsurgical ward (table 3). The postoperative follow-up questionnaire revealed that patients were highly satisfied with their PCA therapy (96–100%) and would request a PCA device for pain control in the future (92–94%). The incidence of postoperative nausea (9–12%) and itching (12–17%) was low in all three treatment groups. Although 25% of the patients remembered entering the operating room, none of the patients experienced any recall of intraoperative events.

Discussion

Acute hypertensive responses frequently occur during balanced anesthesia with a nitrous oxide–opioid–muscle relaxant combination.[1] With this alfentanil-based anesthetic technique, patients achieved a preincision alfentanil concentration (159 ± 35 ng·ml^{-1}) that was previously reported to provide adequate analgesia for superficial surgical procedures.[4,7] Although this alfentanil concentration effectively prevented the clinical signs of inadequate analgesia immediately after skin incision, 92% of patients subsequently experienced an acute hypertensive response during the more stressful retropubic dissection. Although autonomic responsiveness is an indirect indicator of stimulus intensity, these data suggest that skin incision is a less noxious stimuli than retropubic dissection. This observation is in agreement with the findings of Ausems *et al.*[4] The plasma alfentanil concentration required to control the hypertensive response to retropubic dissection (489 ± 135 ng·ml^{-1}) is consistent with the concentration required to maintain hemodynamic stability during intraabdominal surgery.[4,7]

Other investigators have reported that acute hypertensive episodes were associated with significant increases in plasma catecholamines, ADH, cortisol, and β-endorphin concentrations.[8–13] Although a high degree of variability existed among the patients, plasma catecholamine and ADH concentrations were significantly elevated within 5 min after retropubic dissection. The mean percentage increases in epinephrine, norepinephrine and ADH concentrations in response to retropubic dissection were 173 ± 205, 59 ± 48, and 1,287 ± 367%, respectively. It has been shown that cortisol concentrations increase 5–10

TABLE 3. Postoperative Recovery Times and Drug Therapies in the PACU

	Alfentanil	Trimethaphan	Isoflurane
Awakening (min)	3.0 ± 3.9	2.8 ± 3.3	3.8 ± 4.2
Spontaneous ventilation (min)	6.5 ± 5.8	3.1 ± 2.6	5.0 ± 3.9
Extubation (min)	10.3 ± 8.5	8.4 ± 15.3	8.1 ± 4.8
Orientation (min)	22.9 ± 15.5	19.6 ± 20.4	24.6 ± 19.1
Opioid antagonist (%)	35	4*	24
Antihypertensive therapy (%)	12	38*	48*
Antiemetic therapy (%)	15	27	21
PACU time (min)	138 ± 66	123 ± 34	118 ± 35
Morphine therapy (mg)			
PACU	6.7 ± 7.7	9.6 ± 6.6	8.6 ± 6.6
Ward (0–8 h postoperative)	18.0 ± 15.6	14.0 ± 10.8	14.4 ± 10.9
Hospital discharge (days)	8.9 ± 3.3	7.8 ± 3.2	9.5 ± 4.8

Mean values ± SD (or percentages).
PACU = postanesthesia care unit.
* Significantly different from alfentanil, $P < 0.05$.

min after the occurrence of acute hypertensive events and are mediated *via* adrenocorticotropic (ACTH) hormone release from the anterior pituitary.[14] Thus, stimulation of the hypothalamic–pituitary–adrenal axis would have been better assessed by measuring plasma adrenocorticotropic hormone or corticotropin-releasing factor. Plasma β-endorphin concentrations were unchanged, suggesting that either the sampling interval was too short or that the alfentanil administered as part of the standardized balanced anesthetic technique blunted the β-endorphin response. Cork *et al.*[15] found that fentanyl, but not halothane, blocked increases in β-endorphin concentrations during stressful intraoperative events. Thus, the anesthetic (or analgesic) drugs used to maintain hemodynamic stability may influence the release of endogenous stress hormones to differing degrees.

Rapid control of the hypertensive response to retropubic surgical dissection with alfentanil resulted in a return of the stress hormone concentrations to their preincision values. This finding is in agreement with other studies suggesting that supplemental opioid administration blocks the hypothalamic-pituitary-adrenal response to surgical stimulation.[16,17] However, Philbin *et al.* found that high plasma opioid concentrations did not reliably suppress catecholamine responses to laryngoscopy and sternotomy in patients undergoing coronary artery bypass graft procedures with either a fentanyl- or sufentanil-based anesthesia.[18] Given the high incidence of chronic hypertension in patients with coronary artery disease, it is not surprising that the hypertensive and neuroendocrine stress responses to laryngoscopy[19] were more difficult to attenuate with an opioid analgesic alone. In the subset of patients in our study with well-controlled hypertension (n = 33), we found a pattern of hemodynamic and endocrinologic changes that was consistent with the changes reported for our entire study population. However, MAP values at the end of the operation and at extubation were significantly higher (101 ± 26 *vs.* 94 ± 13 mmHg and 124 ± 17 *vs.* 113 ± 15 mmHg, respectively) in the hypertensive (*vs.* normotensive) group. Other factors that may have contributed to the apparent differences reported in these two studies include the surgical stimulus (sternotomy *vs.* retropubic dissection), opioid analgesic (fentanyl or sufentanil *vs.* alfentanil), and adjunctive anesthetic drugs (oxygen alone *vs.* nitrous oxide 67% in oxygen).

Although the adjunctive use of isoflurane provided rapid control of the hemodynamic response to retropubic dissection, norepinephrine and glucose concentrations remained elevated above their preincision values. Previous studies have also shown that administration of isoflurane has minimal effect on plasma norepinephrine concentrations and that its use is often associated with an elevation of blood glucose concentrations.[12,20] Trimethaphan therapy effectively controlled the blood pressure response and decreased plasma norepinephrine concentrations. However, the latter effect most likely represented a pharmacologic effect of trimethaphan's ganglionic blocking activity rather than a reduction in the stress response *per se.* Although the trimethaphan-treated patients clinically appeared to be adequately anesthetized, they exhibited neuroendocrinologic signs consistent with continued responsiveness to the surgical stimulus (table 2).

Despite differing patterns of neuroendocrine responses within each of the three treatment groups, the only significant difference between the groups was the increased ADH concentration after trimethaphan therapy (table 2). We also failed to find significant differences among the three treatment groups in recovery times, postoperative morbidity, opioid analgesic requirements, or duration of hospital stay. These data may reflect the fact that all patients were administered "analgesic" plasma alfentanil concentrations and amnestic concentrations of nitrous oxide intraoperatively as part of their balanced anesthetic technique. The acute increase in MAP was the only clinical manifestation of inadequate anesthesia that we observed. In all three groups, the increases in blood pressure were promptly treated, and no patient displayed subsequent signs of excessive autonomic activity (*e.g.*, sweating, tearing, or tachycardia). However, one must be cautious in applying these findings to other surgical situations involving different anesthetic drugs and/or surgical stimuli.

Most clinicians use autonomic responses to noxious stimuli (*e.g.*, acute increases in blood pressure and/or heart rate) as a measure of depth of anesthesia.[1] These acute intraoperative hemodynamic responses can be effectively treated with opioid analgesics, volatile agents, or vasodilating drugs. The lack of intergroup differences (except for the elevated ADH concentration after trimethaphan therapy) may be related in part to the marked variability among patients in their responses to the surgical stimuli and to the therapeutic maneuvers. The greater residual analgesia upon emergence from anesthesia in the alfentanil treatment group may have contributed to the decreased requirement for antihypertensive therapy in the PACU. In addition to controlling the response to stress during surgery, it may also be important to control the neuroendocrine response during the early postoperative period in patients with coronary artery disease.[21]

Are the elevations in plasma catecholamine and ADH concentrations that occurred during retropubic dissection of any clinical significance? Given that plasma ADH concentrations > 18 $pg \cdot ml^{-1}$ produce cardiac depression and concentrations > 25 $pg \cdot ml^{-1}$ may cause coronary artery constriction,[22,23] many of the patients in our study would have experienced ADH-induced cardiovascular effects during the retropubic dissection. In his review article, Share suggested that even lower concentrations of ADH

(> 10 pg · ml^{-1}) can produce pharmacologic effects on the peripheral vasculature.[24] In addition, all patients in our study manifested significant increases in plasma catecholamine concentrations after retropubic dissection. In patients with preexisting coronary artery disease, we would speculate that the presence of high concentrations of these vasoactive compounds could contribute to an increased incidence of perioperative myocardial ischemia. Future studies should examine the effects of elevated concentrations of stress hormones on end-organ function using more refined monitoring techniques.

In conclusion, despite differing patterns of hormonal responses during surgery, we failed to demonstrate any advantage with respect to improved perioperative outcome with any one of these three pharmacologically different adjunctive therapies. Analogous to the findings of other investigators,[25,26] surgical outcome after lower abdominal surgery was similar irrespective of whether an inhalation or iv drug was used to supplement balanced anesthesia. Postoperative outcome depends on a multitude of factors and is probably more influenced by the anesthetic and surgical skills of the individuals caring for the patient than the specific drugs used as part of a general anesthetic technique.

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