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Multicenter Study of General Anesthesia. II. Results

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A prospective, stratified, randomized clinical trial of the safety and efficacy of four general anesthetic agents (enflurane, fentanyl, halothane, and isoflurane) was conducted in 17,201 patients (study population). Patients were studied before, during, and after anesthesia for up to 7 days. Nineteen patients died (0.11%), and in seven of these (0.04%) the anesthetic may have been a contributing factor. The rates of death, myocardial infarction, and stroke in the study population were so low (less than 0.15%) that no conclusions regarding the relative rates of these outcomes among the four anesthetic agents could be reached. The rates of 16 of 66 types of adverse outcomes in the study population were significantly different among the four study agents. Most of these outcomes were minor. However, severe ventricular arrhythmia ($P < 10^{-6}$) was more common with halothane, severe hypertension ($P < 10^{-6}$) and severe bronchospasm ($P = 0.028$) were more common with fentanyl, and severe tachycardia ($P = 0.001$) was more common with isoflurane. Recovery from anesthesia during the first 30 min was slowest in those patients who received halothane ($P \leq 0.001$). In addition, patients who received fentanyl experienced less pain during the first hour in the recovery room ($P < 10^{-6}$). In conclusion, clinically important differences do exist for some outcomes among the four study agents. (Key words: Anesthetics, intravenous: fentanyl. Anesthetics, volatile: enflurane; halothane; isoflurane. Complication. Epidemiology: outcome; prospective study; randomization.)

DATA FROM PUBLISHED REPORTS do not indicate if specific general anesthetic agents contribute significantly to major perioperative complications. Retrospective studies have not resolved this issue because 1) no randomization of anesthetic agents was done, 2) data collection may not have been complete, and 3) inclusion/exclusion criteria for patient selection were not defined.[1–6] In the only large prospective study of which we are aware,[7] the allocation of anesthetics was not randomized and inclusion/exclusion criteria were not used.

We therefore conducted a prospective stratified randomized clinical trial of four commonly used general anesthetics: enflurane, fentanyl, halothane, and isoflurane. The aim of the study was to identify differences in safety and efficacy among the four study agents. Fifteen university-affiliated hospitals participated in this study of 17,201 patients (study population, *i.e.*, an intent to treat with the assigned agent existed). The study was designed to test the hypothesis that there are differences for outcomes (occurrence of potentially adverse events among the four study agents). We report our findings for 66 outcomes and the incidences of severe outcomes.

Methods

The design of the study has been described in detail in a companion paper.[8] Briefly, patients of either sex, 18 yr or older, who were able to provide informed consent, and who were scheduled for elective surgery with general anesthesia could participate. Patients were excluded if they were pregnant, receiving a monoamine oxidase inhibitor, known or suspected to be at risk for malignant hyperthermia, sensitive to any of the study agents, or if a hemoglobin or hematocrit value was not available within 1 month prior to the operation.

After being enrolled into the study, patients were assigned a standard preanesthetic medication at the discretion of the patient's anesthesiologist. The patients were then assigned randomly to receive one of the four study agents.

Prior to the commencement of the study the level of α was set at 0.01 and the power of the test ($1 - \beta$, in which β is the probability of accepting the null hypothesis when the alternative hypothesis is true) was set at 0.95 for comparisons of outcomes among the four study agents. For severe outcomes, recovery, and pain scores the level of both α and β was set at 0.05. For categorical data (binary form) chi-square analysis was carried out. Outcomes of all types were analyzed for the 15 hospitals, for preanesthetic medication strata, and for the four study agents. Data from the study population (intent to treat with the randomly assigned agent), protocol completions (treated only with the assigned agent), and protocol deviations (not treated only with the assigned agent) were analyzed separately but in the same way. Three anesthesiologists (Review and Audit Committee), independently and without knowledge of the anesthetic assigned, reviewed the complete records of all patients who died to determine if anesthetic management contributed to the death.

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TABLE 1. Number of Patients with Death, Myocardial Infarction (MI), and Stroke

	Enflurane	Fentanyl	Halothane	Isoflurane	Total	Overall Rate per 1,000	P*
Study population							
Number	4,311	4,296	4,249	4,345	17,201	—	—
Hospital death	5	8	1	5	19	1.11	0.160
Myocardial infarction	5	6	8	4	23	1.34	0.654
Stroke	1	1	2	3	7	0.41	0.672
Death, MI, stroke	10	13	10	10	43*	2.50	0.888
Protocol completions							
Number	4,150	3,697	4,018	4,158	16,023	—	—
Hospital death	5	8	1	5	19	1.19	0.113
Myocardial infarction	5	3	8	4	20	1.25	0.453
Stroke	1	1	2	3	7	0.44	0.704
Death, MI, stroke	10	10	10	10	40*	2.50	0.993

* Death, MI, and stroke are not the sum of the three outcomes; six patients had more than one of these outcomes.

Results

We enrolled 17,201 patients in the study (study population) of whom 16,023 successfully completed the protocol (protocol completions). The remaining 1,178 patients did not complete the protocol with only the assigned study agent (protocol deviations). There were more protocol deviations in patients assigned fentanyl (13.9%) than the other study agents (≤5.4%). In general, the differences in outcomes among the study agents were similar in the study population, protocol completions, and protocol deviations. Unless otherwise specified, we will refer in this communication only to the data from the study population.

Mortality rate in this relatively healthy population of patients (90.7% were ASA Physical Status 1 or 2) was 1.11 per 1,000. The rates of death, myocardial infarction, and stroke in the study population were so low (<0.15%) that no conclusions regarding the relative rates of these outcomes among the anesthetic agents could be reached (table 1). No patient classified as ASA Physical Status 1 died. Three of 7,131 patients classified as ASA Physical Status 2 (0.04%), nine of 1,519 patients classified as ASA Physical Status 3 (0.59%), and seven of 88 patients classified as ASA Physical Status 4 (7.95%) died (table 2). Evaluation of the data records for the 19 patients who died (Review and Audit Committee), indicated that anesthesia did not contribute to the death in 12 patients but could not be entirely discounted in seven patients (table 3). In no case was the anesthetic deemed to be the primary cause of death. Of the five patients who died during or immediately following anesthesia, three were considered to be possibly related to their anesthesia. Of the remaining 14 patients who died between the first and seventh postoperative day, only four deaths were possibly related to anesthesia and were mainly due to circulatory collapse occurring during or soon after anesthesia. Details of these patients are included in table 3.

Cardiovascular outcomes were most frequent with all four study agents (table 4). Tachycardia, bradycardia, hypotension, and hypertension were common and differed significantly among the study agents. Thus, tachycardia was more common with isoflurane, bradycardia and hypertension were more common with fentanyl, and hypotension was less common with fentanyl. Ventricular (6.3%) and nodal (1.9%) arrhythmias were infrequent but were most common with halothane. The majority (typically more than 95%) of episodes of outcomes were rated as minor (no or some therapy, and full recovery). There were no differences for these outcomes between those patients who received preanesthetic medication and those who did not.

Table 5 shows the number of patients with severe outcomes (significant therapy, with or without full recovery). Severe ventricular arrhythmia was more common with halothane and occurred in 1.6% of all patients receiving halothane. Severe tachycardia was more common with isoflurane and occurred in 1.3% of all patients receiving isoflurane. Severe hypertension and severe bronchospasm were more common with fentanyl and occurred in 2.0% and 0.3% of all patients receiving fentanyl. The number of patients with one or more severe outcomes of any type was least in patients who received enflurane (table 6).

The prevalences of five types of respiratory outcomes differed among the four study agents. Cough, laryngospasm, and secretions were more common with the in-

TABLE 2. Comparison of Death Rates

ASA Physical Status	Number of Patients	Deaths	This Study (%)	Vacanti *et al.*[19] (%)	Cohen *et al.*[25] (%)
1	8,460	0	0.00	0.07	0.07
2	7,131	3	0.04	0.24	0.20
3	1,519	9	0.59	1.43	1.15
4	88	7	7.95	7.46	7.66

TABLE 3. Summary of Deaths in Study Population

Patient Number	Study Drug	Age (yr)	Sex	ASA	Period	Cause of Death	Related to Anesthesia
1	I	52	FE	2	OR2	Hemorrhage	Possible
2	E	39	M	3	OR2	Cardiac arrest	No
3	F	47	M	4	RR1	Cardiac failure	Possible
4	E	63	M	4	RR1	Arrhythmia	Possible
5	E	74	M	3	RR3	Myocardial infarct	No
6	F	67	M	3	D1	Cardiac arrest	Possible
7	F	54	FE	3	D1	Hemorrhage	Possible
8	H	59	M	3	D1	Hemorrhage	Possible
9	I	62	M	2	D1	CVA/stroke	No
10	I	76	FE	2	D2	Liver failure	No
11	I	34	M	3	D2	Pulmonary embolus	No
12	F	83	FE	3	D2	Hemorrhage	No
13	E	65	M	4	D3	Cardiac arrest	Possible
14	F	76	FE	4	D3	Cardiac arrest	No
15	F	59	M	4	D3	Sepsis	No
16	F	82	FE	3	D6	Sepsis	No
17	E	70	M	4	D6	Cardiac failure	No
18	I	57	M	3	D6	Sepsis	No
19	F	69	FE	4	D7	Sepsis	No

E = enflurane; F = fentanyl; H = halothane; I = isoflurane; FE = female; M = male; OR2 = first hour of anesthesia/surgery; RR1 = first hour in recovery room; RR3 = over 2 h in recovery room; D1, D2, D3, D6, D7 = postanesthesia/surgery day; CVA = cerebrovascular accident.

halational agents than with fentanyl (table 7). By contrast, apnea and bronchospasm were more common with fentanyl.

Few of the other outcomes differed among the study agents. Nausea, vomiting, and muscle rigidity were more common and shivering was less common in patients who received fentanyl (table 8). The rates of severe episodes of these outcomes were not different among the study agents (table 5).

Fewer patients who received halothane were fully recovered at 15–30 min postoperatively (table 9). However, at 60 min there was no difference in the recovery among

TABLE 4. Number of Patients with Cardiovascular Outcomes

Outcome	Enflurane		Fentanyl		Halothane		Isoflurane		Total		P*
	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)	
Study population											
Arrhythmia											
Atrial	126	(2.9)	109	(2.5)	131	(3.1)	95	(2.2)	461	(2.7)	0.046
Nodal	86	(2.0)	62	(1.4)	124	(2.9)	55	(1.3)	327	(1.9)	$<10^{-6}$
Ventricular	257	(6.0)	160	(3.7)	463	(10.9)	197	(4.5)	1,077	(6.3)	$<10^{-6}$
Bradycardia	644	(14.9)	1,098	(25.6)	806	(19.0)	698	(16.1)	3,246	(18.9)	$<10^{-6}$
Tachycardia	1,738	(40.3)	1,517	(35.3)	1,724	(40.6)	1,990	(45.8)	6,969	(40.5)	$<10^{-6}$
Hypotension	1,419	(32.9)	1,154	(26.9)	1,346	(31.7)	1,356	(31.2)	5,275	(30.7)	$<10^{-6}$
Hypertension	1,154	(26.8)	1,350	(31.4)	956	(22.5)	1,242	(28.6)	4,702	(27.3)	$<10^{-6}$
Myocardial ischemia	22	(0.5)	26	(0.6)	15	(0.4)	28	(0.6)	91	(0.5)	0.251
Cardiac failure	20	(0.5)	25	(0.6)	14	(0.3)	15	(0.3)	74	(0.4)	0.245
Protocol completions											
Arrhythmia											
Atrial	124	(3.0)	85	(2.3)	118	(2.9)	89	(2.1)	416	(2.6)	0.028
Nodal	86	(2.1)	52	(1.4)	116	(2.9)	54	(1.3)	308	(1.9)	$<10^{-6}$
Ventricular	249	(6.0)	132	(3.6)	371	(9.2)	184	(4.4)	936	(5.8)	$<10^{-6}$
Bradycardia	612	(14.7)	930	(25.2)	772	(19.2)	667	(16.0)	2,981	(18.6)	$<10^{-6}$
Tachycardia	1,690	(40.7)	1,225	(33.1)	1,624	(40.4)	1,898	(45.6)	6,437	(40.2)	$<10^{-6}$
Hypotension	1,363	(32.8)	944	(25.5)	1,279	(31.8)	1,293	(31.1)	4,879	(30.5)	$<10^{-6}$
Hypertension	1,114	(26.8)	1,052	(28.5)	890	(22.2)	1,175	(28.3)	4,231	(26.4)	$<10^{-6}$
Myocardial ischemia	20	(0.5)	17	(0.5)	12	(0.3)	27	(0.6)	76	(0.5)	0.148
Cardiac failure	20	(0.5)	23	(0.6)	12	(0.3)	15	(0.4)	70	(0.4)	0.143

* Considered significant if $P \leq 0.01$.

TABLE 5. Number of Patients with Severe Outcomes

Outcome	Enflurane		Fentanyl		Halothane		Isoflurane		Total		P*
	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)	
Study population											
Arrhythmia											
Atrial	11	(0.3)	9	(0.2)	12	(0.3)	10	(0.2)	42	(0.2)	0.914
Nodal	3	(0.1)	1	(0.0)	5	(0.1)	1	(0.0)	10	(0.1)	0.211
Ventricular	11	(0.3)	15	(0.4)	69	(1.6)	12	(0.3)	107	(0.6)	$<10^{-6}$
Bradycardia	17	(0.4)	17	(0.4)	23	(0.5)	13	(0.3)	70	(0.4)	0.367
Tachycardia	24	(0.6)	42	(1.0)	30	(0.7)	57	(1.3)	153	(0.9)	0.001
Hypotension	48	(1.1)	48	(1.1)	45	(1.1)	50	(1.2)	191	(1.1)	0.983
Hypertension	23	(0.5)	84	(2.0)	28	(0.7)	37	(0.9)	172	(1.0)	$<10^{-6}$
Apnea	2	(0.1)	10	(0.2)	4	(0.1)	10	(0.2)	26	(0.2)	0.052
Cough	6	(0.1)	6	(0.1)	6	(0.1)	10	(0.2)	28	(0.2)	0.654
Laryngospasm	4	(0.1)	5	(0.1)	4	(0.1)	6	(0.1)	19	(0.1)	0.910
Bronchospasm	5	(0.1)	13	(0.3)	5	(0.1)	3	(0.1)	26	(0.2)	0.028
Secretions	3	(0.1)	2	(0.1)	3	(0.1)	3	(0.1)	11	(0.1)	0.965
Other CNS	4	(0.1)	10	(0.2)	3	(0.1)	5	(0.1)	22	(0.1)	0.154
Nausea	3	(0.1)	4	(0.1)	6	(0.1)	4	(0.1)	17	(0.1)	0.758
Vomiting	8	(0.2)	5	(0.1)	5	(0.1)	3	(0.1)	21	(0.1)	0.485
Shivering	1	(0.0)	1	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)	0.573
Muscle rigidity	1	(0.0)	5	(0.1)	1	(0.0)	1	(0.0)	8	(0.1)	0.111
Protocol completions											
Arrhythmia											
Atrial	11	(0.3)	8	(0.2)	6	(0.1)	8	(0.2)	33	(0.2)	0.708
Nodal	3	(0.1)	1	(0.0)	2	(0.0)	1	(0.0)	7	(0.0)	0.703
Ventricular	10	(0.2)	13	(0.4)	34	(0.8)	10	(0.2)	67	(0.4)	<0.001
Bradycardia	15	(0.4)	14	(0.4)	21	(0.5)	12	(0.3)	62	(0.4)	0.386
Tachycardia	17	(0.4)	22	(0.6)	25	(0.6)	40	(1.0)	104	(0.7)	0.017
Hypotension	44	(1.1)	35	(0.9)	40	(1.0)	43	(1.0)	162	(1.0)	0.963
Hypertension	20	(0.5)	40	(1.1)	25	(0.6)	35	(0.8)	120	(0.8)	0.013
Apnea	1	(0.0)	9	(0.2)	4	(0.1)	9	(0.2)	23	(0.1)	0.032
Cough	4	(0.1)	2	(0.1)	4	(0.1)	10	(0.2)	20	(0.1)	0.093
Laryngospasm	4	(0.1)	4	(0.1)	4	(0.1)	5	(0.1)	17	(0.1)	0.988
Bronchospasm	5	(0.1)	4	(0.1)	3	(0.1)	2	(0.0)	14	(0.1)	0.679
Secretions	3	(0.1)	2	(0.1)	2	(0.0)	3	(0.1)	10	(0.1)	0.965
Other CNS	4	(0.1)	2	(0.1)	3	(0.1)	5	(0.1)	14	(0.1)	0.778
Nausea	3	(0.1)	2	(0.1)	6	(0.1)	4	(0.1)	15	(0.1)	0.541
Vomiting	8	(0.2)	2	(0.1)	5	(0.1)	3	(0.1)	18	(0.1)	0.245
Shivering	0	(0.0)	1	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)	0.343
Muscle rigidity	1	(0.0)	3	(0.1)	1	(0.0)	1	(0.0)	6	(0.0)	0.484

* Considered significant if $P \leq 0.05$. Severe outcomes in the protocol deviations are not shown because these were too infrequent for a meaningful statistical analysis. Absolute values for protocol deviations can be obtained by subtraction of protocol completions from the study population. For example, there were six patients with atrial arrhythmias with halothane in the protocol deviations (12 − 6 = 6).

the study agents. In addition, fewer patients given fentanyl had severe pain in the recovery room than did patients given other anesthetics (table 10).

Discussion

Most of the patients in this study (90.7%) were healthy ASA Physical Status 1 or 2; therefore, the incidences of death, myocardial infarction, and stroke were low. It may appear from table 1 that fewer deaths occurred in the patients receiving halothane compared with the other three anesthetic agents. However, too few deaths occurred to be able to draw any valid statistical conclusions because of insufficient sample size. If anesthesia-related mortality is assumed to be 0.028%,[1-3,9-17] if α is 0.05 and the power is 0.95, more than 231,000 patients would have to be

TABLE 6. Number of Patients with Severe Outcomes in the Study Population

Outcome	Enflurane		Fentanyl		Halothane		Isoflurane		Total		P*
	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)	
One or more severe outcomes	174	(4.0)	277	(6.5)	249	(5.9)	225	(5.2)	925	(5.4)	$<10^{-5}$

* Considered significant if $P \leq 0.05$.

TABLE 7. Number of Patients with Respiratory Outcomes

Outcome	Enflurane		Fentanyl		Halothane		Isoflurane		Total		P*
	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)	
Study population											
Apnea	45	(1.0)	104	(2.4)	37	(0.9)	45	(1.0)	231	(1.3)	$<10^{-6}$
Cough	677	(15.7)	473	(11.0)	622	(14.6)	647	(14.9)	2,419	(14.1)	$<10^{-6}$
Laryngospasm	66	(1.5)	41	(1.0)	75	(1.8)	79	(1.8)	261	(1.5)	0.004
Bronchospasm	42	(1.0)	61	(1.4)	33	(0.8)	34	(0.8)	170	(1.0)	0.007
Secretions	172	(4.0)	106	(2.5)	167	(3.9)	171	(3.9)	616	(3.6)	0.001
Sore throat	286	(6.6)	277	(6.4)	279	(6.6)	271	(6.2)	1,113	(6.5)	0.885
Protocol completions											
Apnea	41	(1.0)	91	(2.5)	36	(0.9)	42	(1.0)	210	(1.3)	<0.001
Cough	656	(15.8)	391	(10.6)	586	(14.6)	617	(14.8)	2,250	(14.0)	<0.001
Laryngospasm	65	(1.6)	34	(0.9)	72	(1.8)	78	(1.9)	249	(1.6)	<0.003
Bronchospasm	41	(1.0)	29	(0.8)	29	(0.7)	31	(0.7)	130	(0.8)	0.519
Secretions	164	(4.0)	85	(2.3)	160	(4.0)	166	(4.0)	575	(3.6)	<0.001
Sore throat	279	(6.7)	234	(6.3)	268	(6.7)	249	(6.0)	1,030	(6.4)	0.496

Respiratory outcomes are not shown for protocol deviations, because there were no differences among the study agents.

* Considered significant if $P \leq 0.01$.

studied to detect a 50% increase in the incidence of death with one anesthetic agent and more than 1 million patients to detect a 50% reduction with one agent. Using the same α and power, and assuming a rate of 0.13%,[5] more than 111,000 and 232,000 patients, respectively, would be required to detect a 50% increase or decrease in the rate of myocardial infarction with one agent.[18]

In the university hospitals participating in this study, we had expected the inclusion of more high-risk patients (ASA Physical Status 3 and 4). However, it is apparent that many healthy patients seek care at university centers for elective surgery, and the investigators were more likely to permit inclusion of healthy patients into the study.

It is of interest to note that the rate of death in our study population for ASA Physical Status 1, 2, and 3 (table 2) was less than in two other studies.[19,20] The reason for this difference is not apparent.

For the 66 outcomes examined, valid conclusions can be drawn with our sample size. For most outcomes there was no significant difference among the four anesthetic

TABLE 8. Number of Patients with Neurologic, Gastrointestinal, Renal, and Miscellaneous Outcomes

Outcome	Enflurane		Fentanyl		Halothane		Isoflurane		Total		P*
	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)	
Study population											
Nervous system											
Headache	159	(3.7)	151	(3.5)	178	(4.2)	150	(3.5)	638	(3.7)	0.261
GI system											
Nausea	824	(19.1)	1,079	(25.1)	778	(18.3)	802	(18.5)	3,483	(20.2)	$<10^{-6}$
Vomiting	512	(11.9)	791	(18.4)	536	(12.6)	500	(11.5)	2,339	(13.6)	$<10^{-6}$
Renal system											
Anuria, oliguria, failure	45	(1.0)	35	(0.8)	25	(0.6)	38	(0.9)	143	(0.8)	0.138
Miscellaneous											
Shivering	348	(8.1)	190	(4.4)	337	(7.9)	329	(7.6)	1,204	(7.0)	$<10^{-6}$
Muscle rigidity	19	(0.4)	39	(0.9)	14	(0.3)	15	(0.3)	87	(0.5)	0.003
Protocol completions											
Nervous system											
Headache	151	(3.6)	116	(3.1)	167	(4.2)	141	(3.4)	575	(3.6)	0.093
GI system											
Nausea	782	(18.8)	933	(25.2)	729	(18.1)	757	(18.2)	3,201	(20.0)	<0.001
Vomiting	485	(11.7)	683	(18.5)	501	(12.5)	474	(11.4)	2,143	(13.4)	<0.001
Renal system											
Anuria, oliguria, failure	45	(1.1)	29	(0.8)	20	(0.5)	36	(0.9)	130	(0.8)	0.030
Miscellaneous											
Shivering	328	(7.9)	152	(4.1)	317	(7.9)	316	(7.6)	1,113	(6.9)	<0.001
Muscle rigidity	19	(0.5)	30	(0.8)	13	(0.3)	14	(0.3)	76	(0.5)	0.006

Outcomes are not shown for the protocol deviations because there were no differences among study agents.

* Considered significant if $P \leq 0.01$.

TABLE 9. Recovery of Patients in the Study Population

Study Population	Enflurane (n = 4,311)	Fentanyl (n = 4,296)	Halothane (n = 4,249)	Isoflurane (n = 4,345)	Total (n = 17,201)	P*
15 min						
R	2,689	2,866	2,389	2,563	10,507	$<10^{-6}$
NR	1,489	1,287	1,739	1,668	6,183	
(M)	(133)	(143)	(121)	(114)	(511)	
30 min						
R	3,383	3,393	3,242	3,382	13,400	<0.001
NR	652	627	757	727	2,763	
(M)	(276)	(276)	(250)	(236)	(1,038)	
60 min						
R	2,622	2,602	2,594	2,640	10,458	0.820
NR	277	296	294	289	1,156	
(M)	(1,412)	(1,398)	(1,361)	(1,416)	(5,587)	
90 min						
R	1,150	1,149	1,140	1,221	4,660	0.101
NR	108	135	125	106	474	
(M)	(3,053)	(3,012)	(2,984)	(3,018)	(12,067)	
Discharge						
R	4,001	3,985	3,959	4,067	16,012	0.958
NR	150	150	143	145	588	
(M)	(160)	(161)	(147)	(133)	(601)	

Recovery scores were calculated using five criteria[10] with maximum (fully recovered) score equal to 10 and minimum score (not recorded) equal to zero.

R = recovery score of 9 or 10; NR = recovery score of 8 or less; (M) = patients not admitted to recovery room (directly to ICU or ward) or discharged from recovery room.

* Considered significant if $P \leq 0.05$.

agents, and when they occurred, the outcomes were mainly rated as minor. However, the incidence of severe ventricular arrhythmia was significantly higher with halothane than with the other three agents. Also, the incidence of severe tachycardia was highest with isoflurane, and severe hypertension and severe bronchospasm occurred most frequently with fentanyl. The significant differences in severe outcomes among the four study agents are not surprising. It has been thought for some time that ventricular arrhythmia is more likely with halothane;[20] similarly, tachycardia has been reported in healthy young patients[21] with isoflurane. However, severe bronchospasm

TABLE 10. Pain Scores of Patients in the Study Population

Study Population	Enflurane (n = 4,311)	Fentanyl (n = 4,296)	Halothane (n = 4,249)	Isoflurane (n = 4,345)	Total (n = 17,201)	P*
15 min						
C	2,922	3,288	2,900	2,976	12,086	$<10^{-6}$
SP	1,242	854	1,220	1,246	4,562	
(M)	(147)	(154)	(129)	(123)	(553)	
30 min						
C	2,933	3,264	2,980	2,962	12,139	$<10^{-6}$
SP	1,092	744	1,015	1,134	3,985	
(M)	(286)	(288)	(254)	(249)	(1,077)	
60 min						
C	2,229	2,415	2,277	2,253	9,174	$<10^{-6}$
SP	653	470	598	661	2,382	
(M)	(1,429)	(1,411)	(1,374)	(1,431)	(5,645)	
90 min						
C	1,015	1,068	1,059	1,080	4,222	0.266
SP	228	207	203	240	878	
(M)	(3,068)	(3,021)	(2,987)	(3,025)	(12,101)	
Discharge						
C	3,557	3,662	3,550	3,574	14,343	$<10^{-6}$
SP	554	427	503	599	2,083	
(M)	(200)	(207)	(196)	(172)	(775)	

Pain scores were recorded as follows: no pain = 1, little pain = 2, a lot of pain = 3, unbearable pain = 4.

C = comfortable, pain score of 1 or 2; SP = severe pain, pain score of 3 or 4; (M) = patients not admitted to recovery room (directly to ICU or ward) or discharged from recovery room.

* Considered significant if $P \leq 0.05$.

with fentanyl has not been described before. This response, however, has been reported with other opioids, such as morphine, which is associated with release of histamine, whereas fentanyl is not.[22]

We conclude that in the vast majority of healthy patients any differences in outcomes that do exist among the four study anesthetics are not of clinical importance. However, we cannot exclude the possibility that certain diseases and medications may present a contraindication to the use of one or more of the four study agents. Our data also suggest that providing general anesthesia without an inhalational vapor is somewhat more difficult than with a vapor because significantly more patients were withdrawn from the fentanyl group than the other groups. No patient was assigned to receive fentanyl and a volatile anesthetic. Although, this combination is common in clinical practice, our study was designed to find differences among anesthetic agents (of which there were four in widespread use at the time the study was designed) and not among anesthetic techniques (of which there were many). Combining fentanyl with a volatile anesthetic would have confounded the identification of agent-specific outcomes or would have necessitated the inclusion of at least three additional groups. The required number of patients needed for study would have doubled, and such a large study was not feasible.

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