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Multicenter Study of General Anesthesia. I. Design and Patient Demography

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A prospective randomized clinical trial of enflurane, fentanyl, halothane, and isoflurane is described. The 17,201 patients were stratified into two groups (preanesthetic medication and no preanesthetic medication) and were randomized to one of four study agents: enflurane, fentanyl, halothane, and isoflurane. Fifteen university-affiliated hospitals in the United States and Canada participated. All patients were first assessed preoperatively. Data were collected during anesthesia, in the immediate recovery period, and for up to 7 days after anesthesia/surgery. The mean age of the patients was 43 yr, the mean height 167 cm, and the mean weight 68 kg. Sixty-five percent of patients were female. In this study 90.7% of patients were classified as ASA Physical Status 1 or 2, and 34.7% of patients smoked. It is concluded that pooling of data across institutions was valid and does allow determination of the efficacy and relative safety of the four study agents. (Key words: Anesthetics, intravenous: fentanyl. Anesthetics, volatile: enflurane; halothane; isoflurane. Complications. Epidemiology: outcome; prospective study; randomization; stratification.)

THE APPROPRIATE SELECTION of a general anesthetic for a particular procedure on a patient with a given disease state requires detailed information on the risk of certain outcomes and clinical events. Unfortunately, there are few data available to enable the anesthesiologist to decide which is the safest and most effective anesthetic in an individual patient.

We considered originally to test two hypotheses: 1) that there are no significant differences in the incidence of death, myocardial infarction, and stroke with use of enflurane, fentanyl, halothane, or isoflurane, and 2) that there are differences for adverse outcomes (*e.g.*, arrhythmia, hypotension, vomiting) with these anesthetics. Calculation of the required sample size based on death rates of 0.028% for elective procedures[1] and of 0.13% for myocardial infarction[2] showed that to detect a twofold difference between the anesthetic agents, 231,000 and 111,000 patients, respectively, would have to be studied. We decided that available resources did not permit us to test the first hypothesis because of the large sample size required. However, it was possible to test the second hypothesis. This also required a fairly large sample size, necessitating that the study be multi-institutional. This study was restricted to university-affiliated hospitals with large clinical bases. A number of university centers were approached, and of these 15 agreed to participate (Appendix).

Methods

ORGANIZATION

The Policy Committee (Dr. J. B. Forrest, Chairman, with Drs. M. K. Cahalan, W. J. Levy, K. Rehder, L. Strunin, B. Brown, D. Steward, and C. H. Goldsmith) was responsible for the design and coordination of the study and for the review of the analyzed data. The Investigator Group (all principal and associate investigators) was responsible for data collection in the study and for ensuring compliance with the protocol in their institutions. The Review and Audit Committee (Drs. Brown and Steward, nonvoting members of the Policy Committee) reviewed independently and blinded to study agent the patient data for each death to judge any possible association with anesthesia. The members of this latter committee also had unrestricted access to the data and had the right to recommend discontinuation of the study at any time for ethical or medical reasons. The study was coordinated by the chairman of the Policy Committee. The data were analyzed at McMaster University Departments of Anesthesia and Clinical Epidemiology and Biostatistics. Planning for this study began in April 1982 with funding approval in September 1983. Patient enrollment was from January 1984 to September 1985. Audit and verification of data was completed in July 1986.

DESIGN OF STUDY

The study was designed as a randomized clinical trial of enflurane, fentanyl, halothane, and isoflurane.

Sample size estimate. Sample size depends on several factors, the desired power, the α-level, the estimated base rate of the outcome of interest (null hypothesis), and the

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profile of rates when the null hypothesis is not true but the alternative hypothesis is true.

The data received at the data management center were reviewed in cohorts of 1,000 patients with regard to the validity of randomization and overall outcome rates without breaking the randomization code. Only the data management center personnel had access to this information. Data from the first 4,000 patients were used to recalculate the sample size required to determine statistical significance for outcomes. This was estimated to be 16,000 patients. Therefore, it was decided to study 17,000 patients to allow for withdrawals and missing data. Study accrual ceased when 17,451 patients had been entered (September 1985). Alpha (the probability of rejecting the null hypotheses when it is true) 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 the comparisons among the four study agents because these levels were considered to be appropriately stringent.

Inclusion and exclusion criteria. Patients of either sex, 18 yr of age or older, scheduled for elective surgery requiring general anesthesia, able to provide informed consent, and for whom any of the study agents was suitable, could participate. Patients who were receiving monoamine oxidase inhibitor therapy, were known or suspected to be at risk of malignant hyperthermia, or had any evidence of sensitivity to the study agents, or were pregnant, or in whom the hemoglobin or hematocrit value had not been determined within 1 month prior to the operation were excluded.

Method of patient recruitment. Any patient who met the inclusion/exclusion criteria could be selected according to the judgment of the investigator; thus, the study population may not represent the surgical patient population in the participating institutions. If there was any concern about the suitability of any one of the four study agents for a patient, that patient was considered to be ineligible. The protocol for the study was approved at each hospital by its institutional review board. Confidentiality of patient information was ensured by restricting the use of patient identification numbers to the participating hospitals, and another randomization code number was used thereafter. No patient names or hospital identification numbers were transmitted to the data management center at McMaster University. Master cross reference log books were kept by each principal investigator for each patient enrolled in the study. This provided a means of retrieval of original patient health records when requested by the data management center. The process of patient selection and data flow is shown in figure 1.

Stratification and randomization. The patients were first stratified into two groups: preanesthetic medication or no preanesthetic medication. The attending anesthesiologist on personal preference decided whether the patient

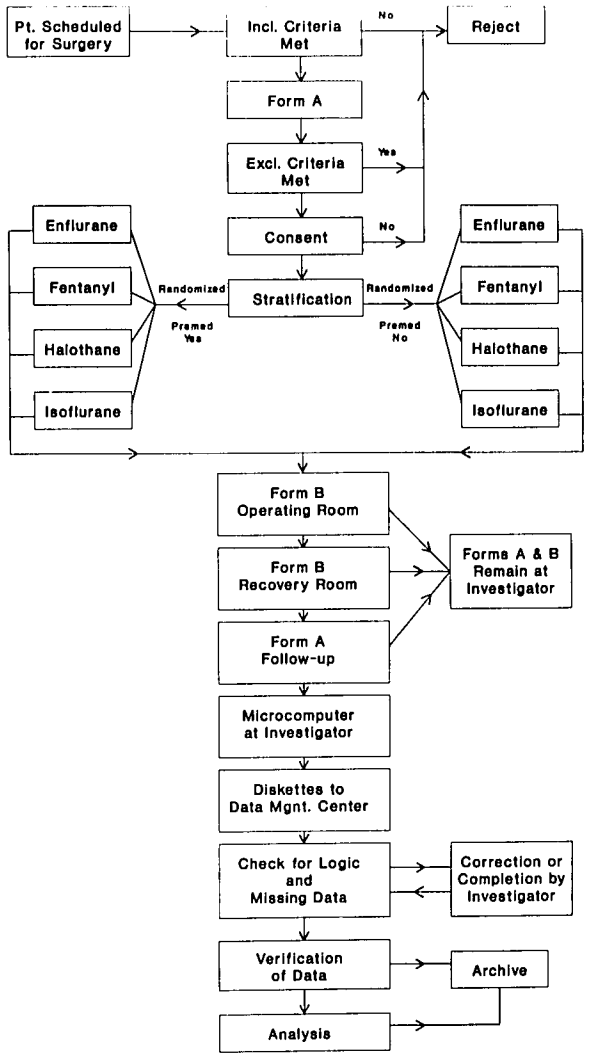

FIG. 1. This flow chart shows the process of patient selection, stratification, randomization, data acquisition, transferral of data to the data management center, verification, audit steps, analysis, and archive.

should receive preanesthetic medication. For both strata each center was provided with sealed envelopes, which were arranged in a specific sequence by the data center and contained the study agent assignments to be used. Thus, this study was a stratified randomized clinical trial with randomization in each stratum at each hospital. To ensure a balanced allocation to the four study agents, the trial randomization was in blocks of eight or 16 with a 1:1:1:1 allocation ratio. The investigators in the hospitals were kept unaware of this blocking structure, to prevent bias in selecting patients for the trial.

Anesthesia. The primary anesthetic was the assigned agent. Anesthetic adjuvant medications could be used as indicated with dosage and time of administration being recorded (Appendix, form B). After the data forms had been printed the muscle relaxants atracurium and vecuronium became available, and after modification of the

protocol were allowed to be used; the Entrypoint® program was modified appropriately. Preanesthetic medication, if selected by the attending anesthesiologist, consisted of either diazepam (5–10 mg) by mouth or morphine (5–15 mg) intramuscularly with or without atropine (0.4–0.6 mg) or glycopyrrolate (0.4 mg). In the majority of patients (97%) induction of anesthesia was by intravenous (iv) injection of sodium thiopental (2–7 mg/kg); in 551 patients an inhalation induction was performed with the assigned volatile study agent. For maintenance of anesthesia the assigned study agents were administered in the following doses: fentanyl 1–250 $\mu g \cdot kg^{-1} \cdot h^{-1}$, enflurane, halothane, or isoflurane, up to 2.5%. Nitrous oxide was administered to 96% of patients. If a neuromuscular blocking drug was chosen, the anesthesiologist could select among succinylcholine (1–1.5 mg/kg), pancuronium (0.06–0.1 mg/kg), *d*-tubocurarine (0.3–0.6 mg/kg), atracurium (0.2–0.5 mg/kg), and vecuronium (0.05–0.1 mg/kg). Neuromuscular blockade was reversed with appropriate doses of neostigmine or pyridostigmine with atropine or glycopyrrolate. Naloxone, during or after anesthesia, was permitted to treat patients with respiratory depression.

Data collection. Two data collection forms were used (forms A and B, Appendix). Page 1 of form A was completed during the preanesthetic interview of each patient and documented the physical status. If the patient refused to participate in the study or was unsuitable, the reason for this decision was entered. If a patient agreed to participate, he or she was stratified to preanesthetic medication or no preanesthetic medication and then randomized to one of the four study agents (fig. 1). Form B was completed during the operation and while the patient was in the recovery room. Page 2 of forms A and B were completed at the appropriate times for up to 7 days postoperatively or hospital discharge if this occurred sooner. If a patient was withdrawn from the study after randomization had occurred, the time of withdrawal and the reasons were noted on page 1 of form B. Data collection from this patient was continued as if the patient had not been withdrawn.

Original data forms were reviewed for completeness by each principal investigator before the data were entered into a microcomputer with Entrypoint® software. Logic checks were included. Double copies of all data were made on diskettes, and one set was mailed to the data management center for entry into the mainframe computer. If inconsistent or missing data were detected by logic and range checks at the data management center, the principal investigator at the appropriate hospital was instructed to correct or complete the data. Access to the data was restricted to data management center personnel and members of the policy committee.

Outcomes. All episodes of outcomes were entered on pages 1 and 2 of form B by using the outcome codes (1–66), a related subcode (1–6), a severity rating (1–5), and a treatment subcode (1–7) (page 2, form B). Outcomes were recorded during induction, maintenance, immediate recovery from anesthesia, and for up to 7 days thereafter. Space was provided for recording additional information of outcomes. All outcome criteria were defined in the protocol manual provided to all principal investigators prior to the study. Hypotension, hypertension, tachycardia, and bradycardia were defined as deviations of more than 20% of the value measured immediately before induction of anesthesia. The diagnosis of myocardial infarction required at all centers appropriate ECG and enzymatic evidence (CPK). Myocardial ischemia was diagnosed intraoperatively by ECG changes; postoperatively, pain and ECG changes were required.

The recovery from anesthesia and the degree of postoperative pain were documented (page 2, form B) for each patient. Preanesthesia and postanesthesia questionnaires and a patient rating of the quality of the anesthetic experience were also recorded on day 7 or on discharge if this occurred sooner (form A). The documentation of physical status of patients, preexisting disease, and current medications (page 1, form A) provided a profile of the patients studied as well as a means of analyzing risk factors for outcomes.

Data analysis. The data disks from each clinical center were read into a HP3000 computer with the data management software Powerhouse at the data management center. Analysis files were created with Powerhouse and passed to the statistical analysis packages: BMDP, SPSS, Minitab running on either a VAX 750 or VAX 8530 as appropriate.

All variables and outcomes were analyzed using the design of the study, *i.e.*, hospital stratum and anesthetic agent, to determine if these factors had any effect on that variable or outcome. Likewise, interactions of the anesthetic agent with hospital and stratum were investigated with either logistic or multiple regression techniques prior to the presentation of findings grouped over hospital and stratum. Basically, the balanced allocation of patients to anesthetic agent within hospital and stratum means that these interactions were negligible.

The hypothesis of equality of rates of allocation to the four study anesthetics was tested from a variety of viewpoints. In each case a simple chi-square test for homogeneity of rates was computed. These chi-squares have 3 degrees of freedom and *P* values were computed as two-tailed probabilities. However, in the interest of economy, only *P* values are reported. No adjustment was made for the analyses of multiple outcomes; however, the six comparisons of the anesthetic agents in pairs were used for adjustment of multiple comparisons between the agents within an outcome. The quoting of *P* values allows the interested reader to calculate an adjusted level of significance; *P* values are reported to three decimal places to

TABLE 1. Randomization of Patients

	Enflurane		Fentanyl		Halothane		Isoflurane		Total	
	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)
Study population	4,311	(25.1)	4,296	(25.0)	4,249	(24.7)	4,345	(25.3)	17,201	(100.0)
Protocol completions	4,150	(24.1)	3,697	(21.5)	4,018	(23.4)	4,158	(24.2)	16,023	(93.2)
Protocol deviations	161	(0.9)	599	(3.5)	231	(1.3)	187	(1.0)	1,178	(6.8)

permit such calculation. Any adjustment for multiple comparisons is stated as a footnote to the table where it was used.

Results

A total of 17,451 patients were enrolled in the study. Subsequent review showed that 250 patients did not meet the inclusion/exclusion criteria, for several reasons, including pregnancy (126 patients) and age younger than 18 yr (42 patients). The data from these 250 patients are not reported here. Thus, the study population comprised 17,201 patients, of whom 16,023 patients completed anesthesia with the assigned study agent (protocol completions). The remaining 1,178 patients were classified as protocol deviations because they did not complete anesthesia with the assigned study agent and required substitution or addition of one of the other three study agents. The data from the study population, protocol completions, and protocol deviations were analyzed separately. Of the 1,178 patients with protocol deviations, the occurrence of an undesirable outcome was the reason cited in 977 patients (82.9%), inadequate depth of anesthesia was cited in 89 patients (7.6%), and in 112 the proscribed protocol was not adhered to.

Successful randomization in the study population is shown by the similar number of patients entered for the four study agents (table 1) and for the two preanesthetic medication strata (table 2). There was less than 0.6% variation in the study population among the four study agents, and for the preanesthetic medication strata the variation among the four study agents was less than 0.7%. Similarly, within each of the 15 participating hospitals there was an acceptable level of matching among each of the four study agents (table 3). The variation between the highest and lowest number of patients for each study agent was 10.9 ± 5.2 (mean ± SD) across all institutions. The number of patients who at some point during anesthesia were withdrawn from the study (protocol deviations) was greatest (13.9%) in the fentanyl group (table 1); it was only 5.4% or less for the other agents.

Although not controlled by the randomization, the physical characteristics of the patients were similar among the four study agents (table 4). Figure 2 shows the age distribution of patients by sex. Females predominated (65%) and the majority of them were 40 yr of age or younger. Also, the ASA Physical Status was well matched among the four study agents at each risk level (table 5). The patients in this study were generally healthy (90.7% were ASA Physical Status 1 or 2), and approximately half the patients had no recorded preexisting disease (table 6). Diseases of the cardiovascular system occurred in 23% of the patients in the study population. Diseases of other systems varied from 4% to 12%. The 716 patients with hepatic diseases were unequally distributed among the four study agents in the study population ($P = 0.014$) and in the protocol completions ($P = 0.009$) with fewer patients receiving halothane compared with the three other agents. A similar imbalance occurred in the protocol deviations in the 313 patients with cardiovascular disease ($P = 0.005$) where a greater number received fentanyl. The number of patients in each group taking medication was similar (table 7). Although 23% of the patients had cardiovascular disease, only 14% were taking cardiac drugs, 11% of patients had respiratory disease, but only 4% were taking respiratory medication.

The most common procedures were musculoskeletal, gynecologic, and abdominal operations, accounting for 60% of the 21,864 procedures (table 8). Patients had up to four procedures. Only in the abdominal procedure group was there a difference among the four study agents ($P = 0.001$) with fewer patients receiving halothane.

Discussion

Prospective randomized clinical trials are the most rigorous means of investigating the safety and efficacy of drugs. However, this approach has not been used in the

TABLE 2. Stratification of Patients

	Enflurane		Fentanyl		Halothane		Isoflurane		Total	
Premedication	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)
Yes	2,594	(25.2)	2,568	(25.0)	2,530	(24.6)	2,600	(25.3)	10,292	(59.8)
No	1,717	(24.9)	1,728	(25.0)	1,719	(24.9)	1,745	(25.3)	6,909	(40.2)

TABLE 3. Patients Entered by Each Hospital

Hospital	Enflurane	Fentanyl	Halothane	Isoflurane	Total
1	648	652	644	655	2,599
2	544	538	523	543	2,148
3	448	449	451	452	1,800
4	431	423	429	433	1,716
5	356	367	365	376	1,464
6	366	359	359	367	1,451
7	339	353	337	352	1,381
8	301	298	290	300	1,189
9	272	267	267	271	1,077
10	233	238	230	233	934
11	143	137	139	146	565
12	77	66	73	76	292
13	62	62	61	58	243
14	53	54	55	49	211
15	38	33	26	34	131
Total	4,311	4,296	4,249	4,345	17,201

To maintain confidentiality the hospital listing does not correspond to the sequence of hospital listing in the Appendix.

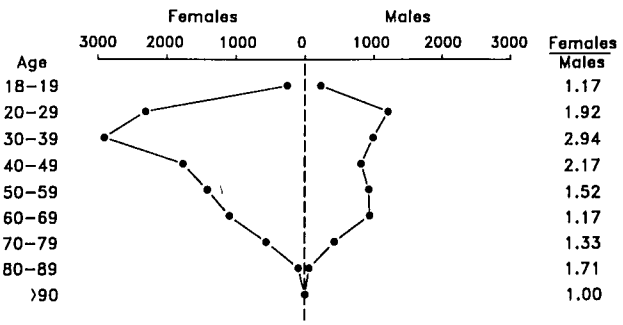

FIG. 2. The number of females and male patients is shown for each decade.

study of anesthetic morbidity or mortality. The present study is the first large prospective randomized clinical trial of general anesthetics.

Other large studies[1–4] used retrospective data collection. These studies provided useful information on overall morbidity rates. However, in the retrospective studies bias cannot be controlled. Furthermore, inclusion and exclusion criteria were not applied prior to the allocation of the anesthetic agent, and completeness of the data recording was not assured. For instance, the Manitoba Health Sciences Project[5–8] collected data using a standardized form on over 100,000 patients, but the allocation of the anesthetic agents was not randomized, there was no detailed written protocol describing the anesthetic management, and no inclusion and exclusion criteria were used. In the French National Survey[9] almost 200,000 patients were studied prospectively, but again there was no randomization of allocation of anesthetic agents, no inclusion and exclusion criteria were used, and the data collection relied on voluntary submission of a standardized questionnaire.

We report here the design, conduct, and data analysis of the first large prospective stratified, randomized clinical trial of anesthetic agents. The strengths of the present study are as follows: 1) a detailed written protocol was agreed upon by all investigators prior to data collection; 2) inclusion and exclusion criteria common to all participating centers were used; 3) patients were stratified to receive a standard preanesthetic medication or no preanesthetic medication; 4) allocation to the four study agents was by randomization; 5) administration of the anesthetic drugs and other permitted drugs was prospectively defined in the protocol manual (design control); 6) standardized data collection was used by all centers using

TABLE 4. Physical Characteristics of Patients

	Enflurane		Fentanyl		Halothane		Isoflurane	
	No.	(%)	No.	(%)	No.	(%)	No.	(%)
Study population								
Age (yr)	43		43		43		43	
Height (cm)	167		167		167		167	
Weight (kg)	68		69		68		68	
Females	2,801	(65.0)	2,789	(65.0)	2,759	(65.0)	2,828	(65.1)
Smokers	1,528	(35.4)	1,507	(35.1)	1,453	(34.2)	1,477	(34.0)
Protocol completions								
Age (yr)	43		43		43		43	
Height (cm)	167		167		167		167	
Weight (kg)	68		68		68		68	
Females	2,697	(65.0)	2,427	(65.6)	2,601	(64.7)	2,701	(62.2)
Smokers	1,462	(35.2)	1,290	(34.9)	1,362	(33.9)	1,413	(34.0)
Protocol deviations								
Age (yr)	44		46		44		43	
Height (cm)	166		168		166		167	
Weight (kg)	68		73		69		70	
Females	104	(64.6)	362	(60.4)	158	(68.4)	127	(67.9)
Smokers	66	(41.0)	219	(36.6)	94	(40.7)	64	(34.2)

Age, height and weight are mean values.

TABLE 5. Physical Status

ASA	Enflurane		Fentanyl		Halothane		Isoflurane		Total	
	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)
Study population										
1	2,113	(49.0)	2,105	(49.0)	2,119	(49.9)	2,123	(48.9)	8,460	(49.2)
2	1,784	(41.4)	1,769	(41.2)	1,778	(41.8)	1,800	(41.4)	7,131	(41.5)
3	380	(8.8)	397	(9.2)	340	(8.0)	402	(9.3)	1,519	(8.8)
4	32	(0.7)	25	(0.6)	12	(0.3)	19	(0.4)	88	(0.5)
Total	4,309*	(100.0)	4,296	(100.0)	4,249	(100.0)	4,344†	(100.0)	17,198‡	(100.0)
Protocol completions										
1	2,029	(47.1)	1,858	(43.2)	1,997	(47.0)	2,026	(46.6)	7,910	(46.0)
2	1,721	(39.9)	1,500	(34.9)	1,691	(39.8)	1,735	(39.9)	6,647	(38.6)
3	369	(8.6)	318	(7.4)	319	(7.5)	379	(8.7)	1,385	(8.1)
4	31	(0.7)	21	(0.5)	11	(0.3)	18	(0.4)	81	(0.5)
Total	4,150	(96.3)	3,697	(86.1)	4,018	(94.6)	4,158	(95.7)	16,023	(93.2)
Protocol deviations										
1	84	(1.9)	247	(5.7)	122	(2.9)	97	(2.2)	550	(3.2)
2	63	(1.5)	269	(6.3)	87	(2.0)	65	(1.5)	484	(2.8)
3	11	(0.3)	79	(1.8)	21	(0.5)	23	(0.5)	134	(0.8)
4	1	(0.02)	4	(0.09)	1	(0.02)	1	(0.02)	7	(0.04)
Total	159*	(3.7)	599	(13.9)	231	(5.4)	186†	(4.3)	1,175‡	(6.8)

* Information not available for two patients.
† Information not available for one patient.
‡ Information not available for three patients.

preprinted data forms; 7) standardized data management was used by all centers; and 8) central data analysis, using an agreed upon methodology, was employed. Finally, incomplete or inconsistent data reported to the data management center were corrected after logic and range audits and after verification by the source hospital.

TABLE 6. Number of Patients with Preexisting Diseases

Disease	Enflurane	Fentanyl	Halothane	Isoflurane	Total
Study population					
No disease	2,177	2,188	2,140	2,180	8,685
CVS	951	999	967	983	3,900
Respiratory	518	478	486	465	1,947
GI	512	509	491	542	2,054
Endocrine	428	406	410	406	1,650
CNS	386	342	380	368	1,476
Renal	326	338	309	322	1,295
Hepatic	184	178	145	209	716*
Protocol completions					
No disease	2,100	1,934	2,031	2,095	8,160
CVS	914	813	916	944	3,587
Respiratory	492	389	452	439	1,772
GI	490	405	453	510	1,858
Endocrine	414	325	382	387	1,508
CNS	372	288	365	355	1,380
Renal	308	288	288	302	1,186
Hepatic	175	151	136	203	665†
Protocol deviations					
No disease	77	254	109	85	525
CVS	37	186	51	39	313‡
Respiratory	26	89	34	26	175
GI	22	104	38	32	196
Endocrine	14	81	28	19	142
CNS	14	54	15	13	96
Renal	18	50	21	20	109
Hepatic	9	27	9	6	51

* $P = 0.014$.
† $P = 0.009$.
‡ $P = 0.005$.

However, there were also some weaknesses in the present study. The weaknesses include the following: 1) the available resources did not permit complete training of the investigators and staff and adequate monitoring of investigator performance; 2) there was the opportunity for investigators to violate the randomization of study agent allocation; and 3) we relied on the investigators to record all events as specified by the protocol. Finally, errors in data entry are inevitable in such a large and complex study. Despite the strictly defined inclusion and exclusion criteria, 250 patients were entered into the study, even though they did not meet the inclusion/exclusion criteria.

Two other potential problems also existed. First, although common in clinical practice, the combination of study agents would have required a large sample size. We restricted the study to the use of single anesthetic agents in an attempt to identify drug-specific outcomes and risks relevant to clinical practice. Second, we used in the post-

TABLE 7. Number of Patients Taking Medication

	Enflurane	Fentanyl	Halothane	Isoflurane	Total
Study population					
Cardiac	634	644	589	621	2,488
Respiratory	164	143	172	141	620
Others	752	745	700	734	2,931
Protocol completions					
Cardiac	607	526	554	591	2,278
Respiratory	156	114	156	134	560
Others	722	621	660	705	2,708
Protocol deviations					
Cardiac	27	118	35	30	210
Respiratory	8	29	16	7	60
Others	30	124	40	29	223

TABLE 8. Surgical and Diagnostic Procedures: Study Population

Procedure	Enflurane (n = 4,311)	Fentanyl (n = 4,296)	Halothane (n = 4,249)	Isoflurane (n = 4,345)	Total (n = 17,201)	*P*
Musculoskeletal	1,355	1,261	1,318	1,324	5,258	0.177
Gynecology	1,218	1,215	1,199	1,244	4,876	0.972
Abdominal	726	794	656	703	2,879	0.001
Diagnostic	661	636	660	653	2,610	0.792
EENT/endocrine	463	477	468	518	1,926	0.337
Head/neck	345	347	370	386	1,448	0.348
Urologic	272	308	307	291	1,178	0.289
Neurologic	206	245	226	224	901	0.282
Cardiovascular	150	133	139	135	557	0.722
Thoracic	55	69	46	61	231	0.186
No procedure	17	24	31	9	81	0.003

operative period chest pain and ECG changes in the diagnosis of myocardial ischemia. It is possible that the perioperative use of opioids may have obscured the detection of some cases of myocardial ischemia and other painful outcomes.

Despite these problems, our study provides useful and unique new information. We achieved a high level of compliance with the protocol, as evidenced by the successful randomization, which resulted in a similar number of patients receiving each of the four study agents. Although not guaranteed by the study design (not stratified except for preanesthetic medication), in general there was also a similar distribution of study agents within each of the physical characteristics of the patients, ASA Physical Status, preexisting diseases, types of medications, and surgical procedures (tables 5–8).

The randomization process was designed to permit analysis of all data within each hospital and to determine if there was any hospital interaction. We found an acceptable matching among the four study agents within each hospital; therefore, we concluded that pooling of data for data analysis was valid. In other words, unbiased estimates of treatment effects were possible by collapsing of data without controlling for other factors in the analysis. Furthermore, the design of the study minimized introduction of bias, which may have obscured differences in the relative safety and efficacy of the four study agents.

The internal validity (balanced number of patients with each study agent in each institution) of the study was ensured by the balanced randomized allocation of the four study agents. External validity was ensured by implementation of identical inclusion and exclusion criteria at each hospital. Therefore, to the extent that the patients included in this study represent a certain patient population, the results can be extended to such populations. Thus, comparison among the four study agents is valid not only for the participating hospitals but in general for similar groups of patients.

Although not part of the stratified randomization, the subgroups of disease categories generally were evenly matched across groups. Exceptions were that fewer patients with hepatic disease were entered in the halothane group and more patients with cardiovascular disease assigned fentanyl had protocol deviations. Possible explanations of the former include chance occurrence, disregard by the investigator for proper randomization, and inappropriate exclusion after randomization. The fact that more patients with cardiovascular disease assigned to fentanyl had protocol deviations is difficult to explain. The larger overall number of patients assigned to fentanyl who had protocol deviations may reflect undesirable outcomes or inadequate depth of anesthesia more than drug-specific complications. This conclusion is based on a review of all outcomes, changes in hemodynamic variables, and comments received from the participating anesthesiologists.

In conclusion, this large randomized clinical trial involving 17,201 patients achieved satisfactory matching of the number of patients with each of the four study agents in each of the participating university-affiliated hospitals. We believe that pooling of data was valid. This data base of controlled and complete data is a valuable resource for examination of relative safety and efficacy related to each of the four study agents. The companion paper[10] describes the effect of the selection of anesthetic on the occurrence of outcomes (*e.g.*, arrhythmia, hypotension, vomiting).

The authors wish to thank Drs. B. Brown and D. Steward for their invaluable advice and support and K. P. Offord for the critical review of the manuscript. The active involvement of numerous anesthesiologists and technical and nursing assistants at each participating institution was essential to the successful completion of this study. The authors are deeply indebted to these individuals.

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APPENDIX

Participating University-Affiliated Hospitals

Eye and Ear Hospital
Pittsburgh, Pennsylvania

Foothills Provincial General Hospital
Calgary, Alberta, Canada

Froedtert Memorial Lutheran Hospital
Milwaukee, Wisconsin

Magee Women's Hospital
Pittsburgh, Pennsylvania

McMaster University Medical Centre
Hamilton, Ontario, Canada

Milwaukee County Medical Complex
Milwaukee, Wisconsin

University of California, San Francisco Medical Center
San Francisco, California

Montefiore Hospital
Pittsburgh, Pennsylvania

Presbyterian University Hospital
Pittsburgh, Pennsylvania

Rochester Methodist Hospital
Rochester, Minnesota

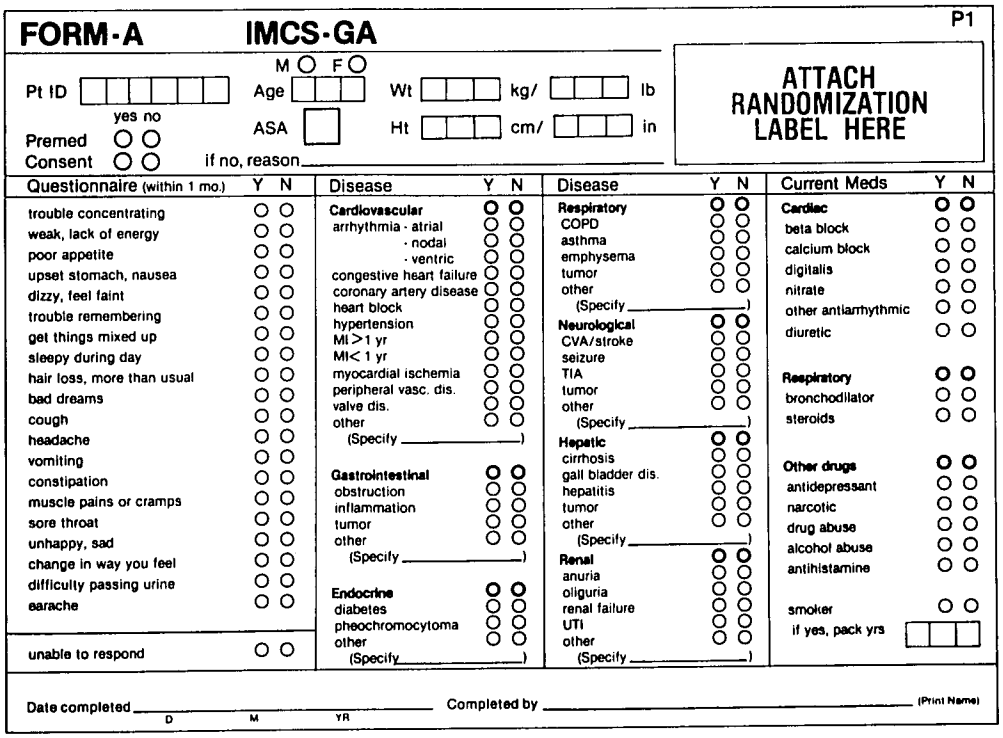
St. Joseph's Hospital
Hamilton, Ontario, Canada

Saint Marys Hospital
Rochester, Minnesota

University of Pennsylvania
Philadelphia, Pennsylvania

Veteran's Administration Hospital
Pittsburgh, Pennsylvania

Wood Veteran's Administration Medical Center
Milwaukee, Wisconsin



FORM-A IMCS-GA P1

Pt ID | M ○ F ○ | Age | Wt kg/ lb | Ht cm/ in | ATTACH RANDOMIZATION LABEL HERE

Premed ○ ○ yes no
Consent ○ ○ if no, reason

Questionnaire (within 1 mo.)	Y	N
trouble concentrating	○	○
weak, lack of energy	○	○
poor appetite	○	○
upset stomach, nausea	○	○
dizzy, feel faint	○	○
trouble remembering	○	○
get things mixed up	○	○
sleepy during day	○	○
hair loss, more than usual	○	○
bad dreams	○	○
cough	○	○
headache	○	○
vomiting	○	○
constipation	○	○
muscle pains or cramps	○	○
sore throat	○	○
unhappy, sad	○	○
change in way you feel	○	○
difficulty passing urine	○	○
earache	○	○
unable to respond	○	○

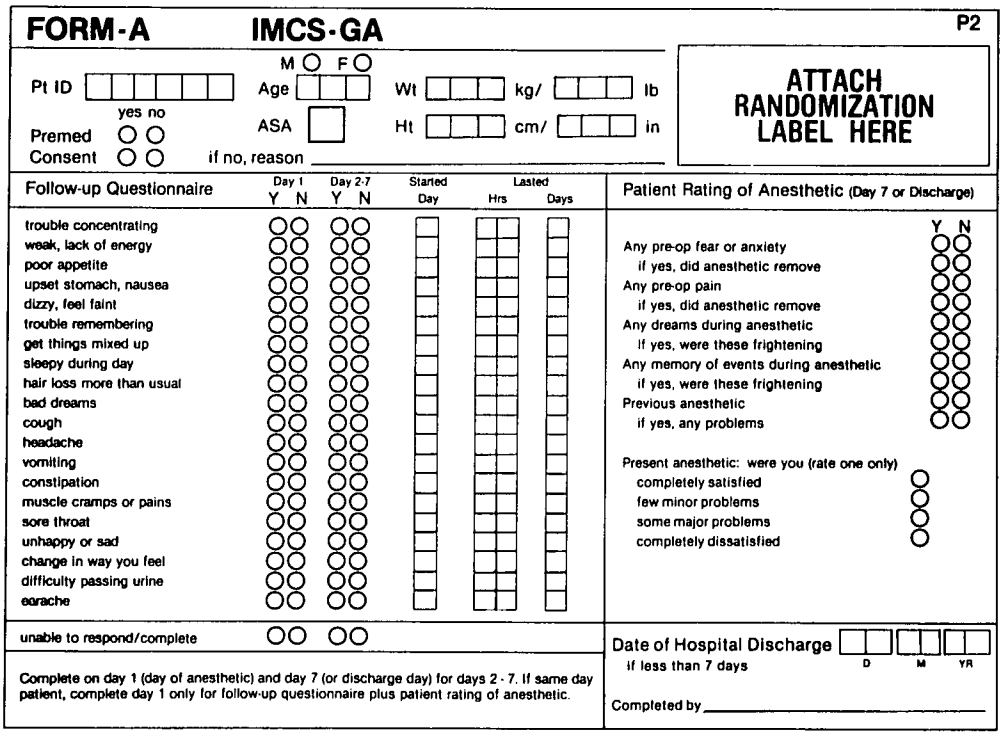
Disease	Y	N
Cardiovascular	○	○
arrhythmia · atrial	○	○
· nodal	○	○
· ventric	○	○
congestive heart failure	○	○
coronary artery disease	○	○
heart block	○	○
hypertension	○	○
MI>1 yr	○	○
MI< 1 yr	○	○
myocardial ischemia	○	○
peripheral vasc. dis.	○	○
valve dis.	○	○
other	○	○
(Specify ____)		
Gastrointestinal	○	○
obstruction	○	○
inflammation	○	○
tumor	○	○
other	○	○
(Specify ____)		
Endocrine	○	○
diabetes	○	○
pheochromocytoma	○	○
other	○	○
(Specify ____)		

Disease	Y	N
Respiratory	○	○
COPD	○	○
asthma	○	○
emphysema	○	○
tumor	○	○
other	○	○
(Specify ____)		
Neurological	○	○
CVA/stroke	○	○
seizure	○	○
TIA	○	○
tumor	○	○
other	○	○
(Specify ____)		
Hepatic	○	○
cirrhosis	○	○
gall bladder dis.	○	○
hepatitis	○	○
tumor	○	○
other	○	○
(Specify ____)		
Renal	○	○
anuria	○	○
oliguria	○	○
renal failure	○	○
UTI	○	○
other	○	○
(Specify ____)		

Current Meds	Y	N
Cardiac	○	○
beta block	○	○
calcium block	○	○
digitalis	○	○
nitrate	○	○
other antiarrhythmic	○	○
diuretic	○	○
Respiratory	○	○
bronchodilator	○	○
steroids	○	○
Other drugs	○	○
antidepressant	○	○
narcotic	○	○
drug abuse	○	○
alcohol abuse	○	○
antihistamine	○	○
smoker	○	○
if yes, pack yrs		

Date completed ____ (D M YR) Completed by ____ (Print Name)

FIG. 1A. Form A, page 1. This form was completed during the preanesthetic interview of the patient for assessment of physical status, presence of disease, and current medication. The questionnaire in the left-hand column was completed within 1 month after the anesthetic.



FORM-A IMCS-GA P2

Pt ID ☐☐☐☐☐☐ M ○ F ○ Age ☐☐☐ Wt ☐☐☐ kg/ ☐☐☐ lb

Premed yes ○ no ○ ASA ☐ Ht ☐☐☐ cm/ ☐☐☐ in

Consent yes ○ no ○ if no, reason _____

ATTACH RANDOMIZATION LABEL HERE

Follow-up Questionnaire	Day 1 Y	Day 1 N	Day 2-7 Y	Day 2-7 N	Started Day	Lasted Hrs	Lasted Days
trouble concentrating	○	○	○	○	☐	☐☐	☐☐
weak, lack of energy	○	○	○	○	☐	☐☐	☐☐
poor appetite	○	○	○	○	☐	☐☐	☐☐
upset stomach, nausea	○	○	○	○	☐	☐☐	☐☐
dizzy, feel faint	○	○	○	○	☐	☐☐	☐☐
trouble remembering	○	○	○	○	☐	☐☐	☐☐
get things mixed up	○	○	○	○	☐	☐☐	☐☐
sleepy during day	○	○	○	○	☐	☐☐	☐☐
hair loss more than usual	○	○	○	○	☐	☐☐	☐☐
bad dreams	○	○	○	○	☐	☐☐	☐☐
cough	○	○	○	○	☐	☐☐	☐☐
headache	○	○	○	○	☐	☐☐	☐☐
vomiting	○	○	○	○	☐	☐☐	☐☐
constipation	○	○	○	○	☐	☐☐	☐☐
muscle cramps or pains	○	○	○	○	☐	☐☐	☐☐
sore throat	○	○	○	○	☐	☐☐	☐☐
unhappy or sad	○	○	○	○	☐	☐☐	☐☐
change in way you feel	○	○	○	○	☐	☐☐	☐☐
difficulty passing urine	○	○	○	○	☐	☐☐	☐☐
earache	○	○	○	○	☐	☐☐	☐☐
unable to respond/complete	○	○	○	○			

Complete on day 1 (day of anesthetic) and day 7 (or discharge day) for days 2 - 7. If same day patient, complete day 1 only for follow-up questionnaire plus patient rating of anesthetic.

Patient Rating of Anesthetic (Day 7 or Discharge)

	Y	N
Any pre-op fear or anxiety	○	○
if yes, did anesthetic remove	○	○
Any pre-op pain	○	○
if yes, did anesthetic remove	○	○
Any dreams during anesthetic	○	○
If yes, were these frightening	○	○
Any memory of events during anesthetic	○	○
if yes, were these frightening	○	○
Previous anesthetic	○	○
if yes, any problems	○	○

Present anesthetic: were you (rate one only)

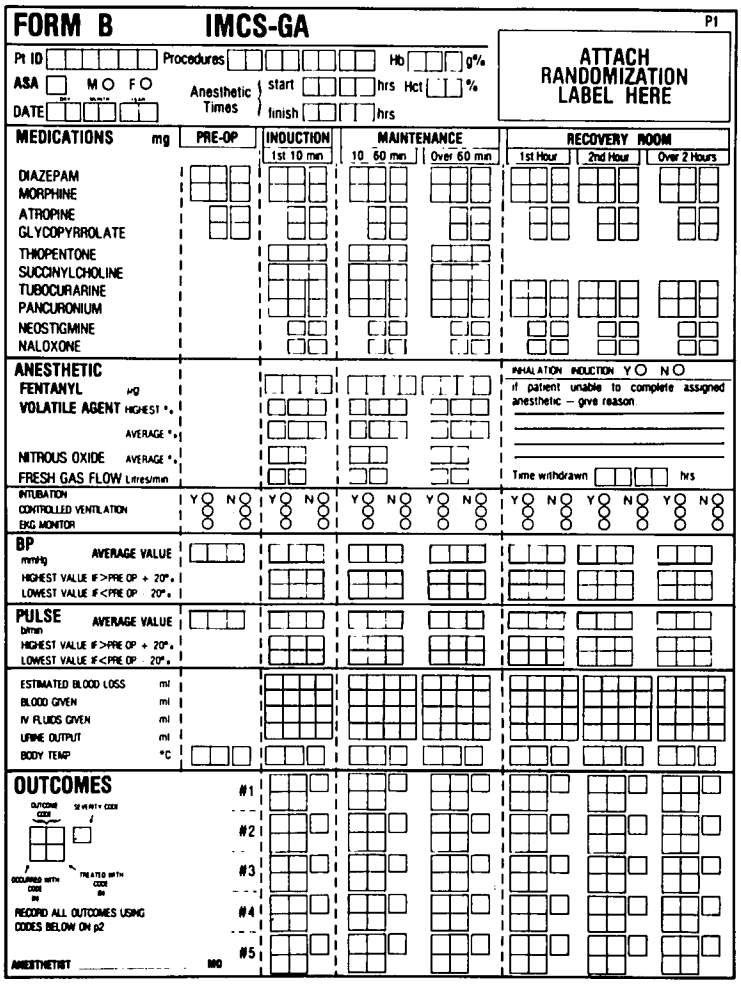
- completely satisfied ○
- few minor problems ○
- some major problems ○
- completely dissatisfied ○

Date of Hospital Discharge ☐☐ D ☐☐ M ☐☐ YR

if less than 7 days

Completed by _____

FIG. 2A. Form A, page 2. The follow-up questionnaire and the patient rating of the experience were completed between day 1 and day 7 or discharge from the hospital.



FORM B IMCS-GA P1

Pt ID ☐☐☐☐☐☐ Procedures ☐☐☐☐☐ Hb ☐☐ g%

ASA ☐ M ○ F ○ Anesthetic Times start ☐☐ hrs Hct ☐☐ %

DATE ☐☐ ☐☐ ☐☐ finish ☐☐ hrs

ATTACH RANDOMIZATION LABEL HERE

MEDICATIONS mg	PRE-OP	INDUCTION 1st 10 mn	MAINTENANCE 10 - 60 mn	MAINTENANCE Over 60 mn	RECOVERY ROOM 1st Hour	RECOVERY ROOM 2nd Hour	RECOVERY ROOM Over 2 Hours
DIAZEPAM	☐☐	☐☐	☐☐	☐☐	☐☐	☐☐	☐☐
MORPHINE	☐☐	☐☐	☐☐	☐☐	☐☐	☐☐	☐☐
ATROPINE	☐☐	☐☐	☐☐	☐☐	☐☐	☐☐	☐☐
GLYCOPYRROLATE	☐☐	☐☐	☐☐	☐☐	☐☐	☐☐	☐☐
THIOPENTONE		☐☐	☐☐	☐☐			
SUCCINYLCHOLINE		☐☐	☐☐	☐☐			
TUBOCURARINE		☐☐	☐☐	☐☐	☐☐	☐☐	☐☐
PANCURONIUM		☐☐	☐☐	☐☐	☐☐	☐☐	☐☐
NEOSTIGMINE		☐☐	☐☐	☐☐	☐☐	☐☐	☐☐
NALOXONE		☐☐	☐☐	☐☐	☐☐	☐☐	☐☐

ANESTHETIC

FENTANYL μg

VOLATILE AGENT HIGHEST %

AVERAGE %

NITROUS OXIDE AVERAGE %

FRESH GAS FLOW Litres/min

INHALATION INDUCTION Y ○ N ○

if patient unable to complete assigned anesthetic – give reason

Time withdrawn ☐☐ hrs

	PRE-OP	INDUCTION	MAINTENANCE 10 - 60 mn	MAINTENANCE Over 60 mn	RECOVERY ROOM 1st Hour	RECOVERY ROOM 2nd Hour	RECOVERY ROOM Over 2 Hours
INTUBATION	Y ○ N ○	Y ○ N ○	Y ○ N ○	Y ○ N ○	Y ○ N ○	Y ○ N ○	Y ○ N ○
CONTROLLED VENTILATION	○ ○	○ ○	○ ○	○ ○	○ ○	○ ○	○ ○
EKG MONITOR	○ ○	○ ○	○ ○	○ ○	○ ○	○ ○	○ ○

BP mmHg AVERAGE VALUE ☐☐

HIGHEST VALUE IF > PRE OP + 20% ☐☐☐

LOWEST VALUE IF < PRE OP - 20% ☐☐☐

PULSE AVERAGE VALUE ☐☐

b/min

HIGHEST VALUE IF > PRE OP + 20% ☐☐☐

LOWEST VALUE IF < PRE OP - 20% ☐☐☐

ESTIMATED BLOOD LOSS ml	☐☐☐	☐☐☐	☐☐☐	☐☐☐	☐☐☐	☐☐☐	☐☐☐
BLOOD GIVEN ml	☐☐☐	☐☐☐	☐☐☐	☐☐☐	☐☐☐	☐☐☐	☐☐☐
IV FLUIDS GIVEN ml	☐☐☐	☐☐☐	☐☐☐	☐☐☐	☐☐☐	☐☐☐	☐☐☐
URINE OUTPUT ml	☐☐☐	☐☐☐	☐☐☐	☐☐☐	☐☐☐	☐☐☐	☐☐☐
BODY TEMP °C	☐☐	☐☐	☐☐	☐☐	☐☐	☐☐	☐☐

OUTCOMES

OUTCOME CODE ☐ SEVERITY CODE ☐

OCCURRED WITH CODE ☐ TREATED WITH CODE ☐

RECORD ALL OUTCOMES USING CODES BELOW ON p2

#1 ☐☐☐☐☐☐

#2 ☐☐☐☐☐☐

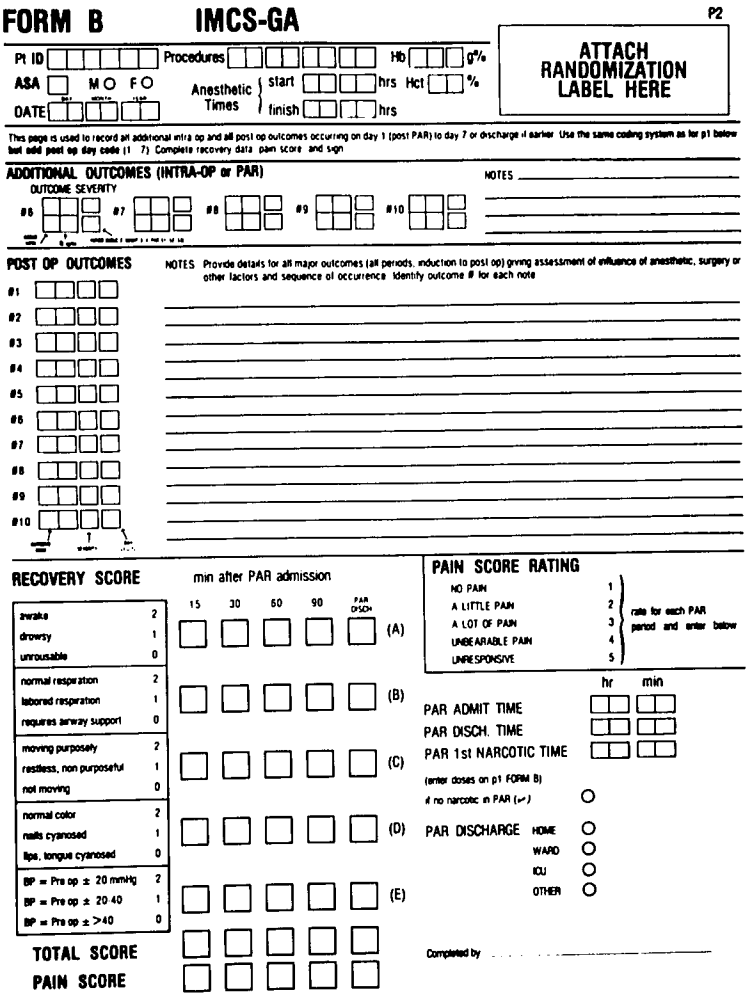
#3 ☐☐☐☐☐☐

#4 ☐☐☐☐☐☐

#5 ☐☐☐☐☐☐

ANESTHETIST _____ MD

FIG. 3A. Form B, page 1. This form was completed while the patient was in the operating room or recovery room.



FORM B IMCS-GA P2

Pt ID Procedures Hb g%

ASA M O F O Anesthetic Times start hrs Hct %

DATE finish hrs

ATTACH RANDOMIZATION LABEL HERE

This page is used to record all additional intra op and all post op outcomes occurring on day 1 (post PAR) to day 7 or discharge if earlier. Use the same coding system as for p1 below but add post op day code (1 7). Complete recovery data, pain score, and sign

ADDITIONAL OUTCOMES (INTRA-OP or PAR)

OUTCOME SEVERITY

#6 #7 #8 #9 #10

NOTES

POST OP OUTCOMES

NOTES: Provide details for all major outcomes (all periods, induction to post op) giving assessment of influence of anesthetic, surgery or other factors and sequence of occurrence. Identify outcome # for each note

#1
#2
#3
#4
#5
#6
#7
#8
#9
#10

RECOVERY SCORE

min after PAR admission

		15	30	60	90	PAR DISCH
awake	2					
drowsy	1					
unrousable	0					(A)
normal respiration	2					
labored respiration	1					
requires airway support	0					(B)
moving purposely	2					
restless, non purposeful	1					
not moving	0					(C)
normal color	2					
nails cyanosed	1					
lips, tongue cyanosed	0					(D)
BP = Pre op ± 20 mmHg	2					
BP = Pre op ± 20 40	1					
BP = Pre op ± >40	0					(E)
TOTAL SCORE						
PAIN SCORE						

PAIN SCORE RATING

NO PAIN	1	rate for each PAR period and enter below
A LITTLE PAIN	2	
A LOT OF PAIN	3	
UNBEARABLE PAIN	4	
UNRESPONSIVE	5	

	hr	min
PAR ADMIT TIME		
PAR DISCH. TIME		
PAR 1st NARCOTIC TIME		

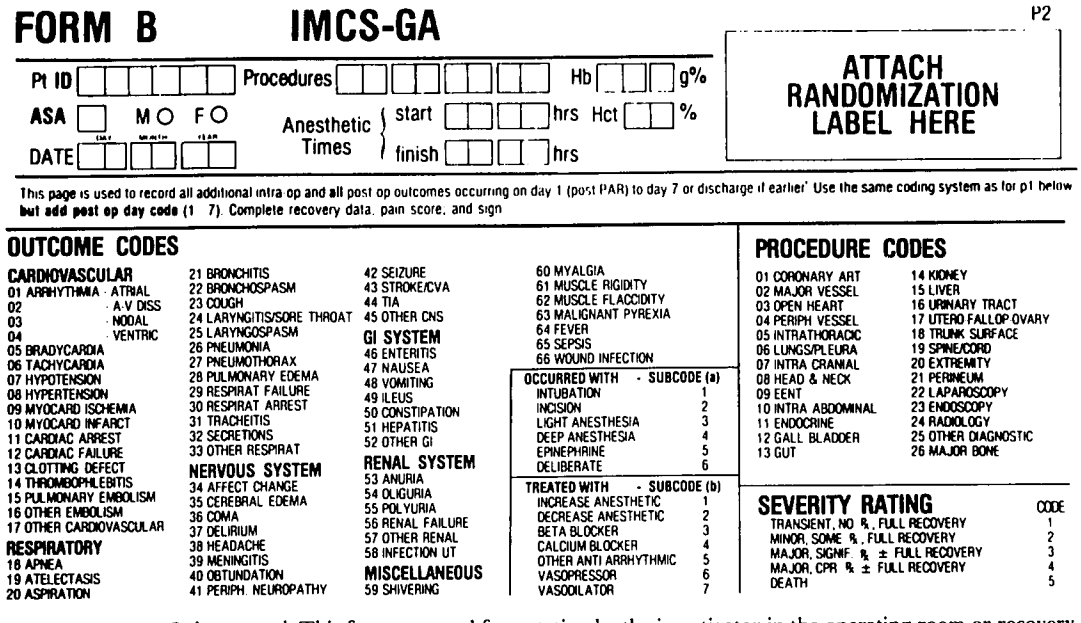
(enter doses on p1 FORM B)

if no narcotic in PAR (↵) ○

PAR DISCHARGE HOME ○ WARD ○ ICU ○ OTHER ○

Completed by _____

FIG. 4A. Form B, page 2, *upper panel:* Outcomes were recorded using coded notations from the outcome list.



FORM B IMCS-GA P2

Pt ID Procedures Hb g%

ASA M O F O Anesthetic Times start hrs Hct %

DATE finish hrs

ATTACH RANDOMIZATION LABEL HERE

This page is used to record all additional intra op and all post op outcomes occurring on day 1 (post PAR) to day 7 or discharge if earlier. Use the same coding system as for p1 below but add post op day code (1 7). Complete recovery data, pain score, and sign

OUTCOME CODES

CARDIOVASCULAR
01 ARRHYTHMIA · ATRIAL
02 · A-V DISS
03 · NODAL
04 · VENTRIC
05 BRADYCARDIA
06 TACHYCARDIA
07 HYPOTENSION
08 HYPERTENSION
09 MYOCARD ISCHEMIA
10 MYOCARD INFARCT
11 CARDIAC ARREST
12 CARDIAC FAILURE
13 CLOTTING DEFECT
14 THROMBOPHLEBITIS
15 PULMONARY EMBOLISM
16 OTHER EMBOLISM
17 OTHER CARDIOVASCULAR

RESPIRATORY
18 APNEA
19 ATELECTASIS
20 ASPIRATION
21 BRONCHITIS
22 BRONCHOSPASM
23 COUGH
24 LARYNGITIS/SORE THROAT
25 LARYNGOSPASM
26 PNEUMONIA
27 PNEUMOTHORAX
28 PULMONARY EDEMA
29 RESPIRAT FAILURE
30 RESPIRAT ARREST
31 TRACHEITIS
32 SECRETIONS
33 OTHER RESPIRAT

NERVOUS SYSTEM
34 AFFECT CHANGE
35 CEREBRAL EDEMA
36 COMA
37 DELIRIUM
38 HEADACHE
39 MENINGITIS
40 OBTUNDATION
41 PERIPH. NEUROPATHY
42 SEIZURE
43 STROKE/CVA
44 TIA
45 OTHER CNS

GI SYSTEM
46 ENTERITIS
47 NAUSEA
48 VOMITING
49 ILEUS
50 CONSTIPATION
51 HEPATITIS
52 OTHER GI

RENAL SYSTEM
53 ANURIA
54 OLIGURIA
55 POLYURIA
56 RENAL FAILURE
57 OTHER RENAL
58 INFECTION UT

MISCELLANEOUS
59 SHIVERING
60 MYALGIA
61 MUSCLE RIGIDITY
62 MUSCLE FLACCIDITY
63 MALIGNANT PYREXIA
64 FEVER
65 SEPSIS
66 WOUND INFECTION

OCCURRED WITH - SUBCODE (a)	
INTUBATION	1
INCISION	2
LIGHT ANESTHESIA	3
DEEP ANESTHESIA	4
EPINEPHRINE	5
DELIBERATE	6

TREATED WITH - SUBCODE (b)	
INCREASE ANESTHETIC	1
DECREASE ANESTHETIC	2
BETA BLOCKER	3
CALCIUM BLOCKER	4
OTHER ANTI ARRHYTHMIC	5
VASOPRESSOR	6
VASODILATOR	7

PROCEDURE CODES

01 CORONARY ART
02 MAJOR VESSEL
03 OPEN HEART
04 PERIPH VESSEL
05 INTRATHORACIC
06 LUNGS/PLEURA
07 INTRA CRANIAL
08 HEAD & NECK
09 EENT
10 INTRA ABDOMINAL
11 ENDOCRINE
12 GALL BLADDER
13 GUT
14 KIDNEY
15 LIVER
16 URINARY TRACT
17 UTERO FALLOP OVARY
18 TRUNK SURFACE
19 SPINE/CORD
20 EXTREMITY
21 PERINEUM
22 LAPAROSCOPY
23 ENDOSCOPY
24 RADIOLOGY
25 OTHER DIAGNOSTIC
26 MAJOR BONE

SEVERITY RATING

	CODE
TRANSIENT, NO ℞, FULL RECOVERY	1
MINOR, SOME ℞, FULL RECOVERY	2
MAJOR, SIGNIF. ℞ ± FULL RECOVERY	3
MAJOR, CPR ℞ ± FULL RECOVERY	4
DEATH	5

FIG. 5A. Form B, page 2, *lower panel:* This form was used for notation by the investigator in the operating room or recovery room and postoperatively for all outcomes occurring between day 1 (day of anesthesia) and day 7 or discharge from the hospital.