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A COMPARISON OF ETHER ANESTHESIA WITH THIOPENTAL—NITROUS OXIDE—SUCCINYLCHOLINE FOR UPPER ABDOMINAL SURGERY

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In 1954 Beecher and Todd reported a high anesthesia death rate associated with the use of muscle relaxants.¹ From their original clinical data it was not possible to determine the explanation for this observation. The present study represents an effort to obtain comparative information on some of the risks of general anesthesia with and without use of a relaxant. In order to minimize the effects of variations in clinical material and operation we have chosen a limited surgical population: patients scheduled for elective upper abdominal surgery. Anesthesia with nitrous oxide, oxygen and ether was compared with a technique using thiopental, nitrous oxide, oxygen and succinylcholine. In the evaluation of results, special attention was paid to hypotension during and following anesthesia, and to post-operative circulatory and respiratory complications. Particular attention was also given to surgical complications in order to examine the possibility that the superior operative conditions assumed to accompany use of muscle re-

laxants might lead to a lower incidence of surgical complications and surgical deaths.

METHODS

All patients scheduled for elective * gastrectomy, cholecystectomy or common duct exploration were included. During the period of study, February 1955 to August 1958, 693 patients fell within this group. Surgery and anesthesia were performed by residents in training; the two anesthetic techniques were assigned, without selection, on the basis of the patient's unit number (odd or even). † Any patient who presented a contraindication to either technique was omitted entirely. Only 7 patients were excluded from the study, 5 severe asthmatics and two pregnant women. An additional 12 patients were not included in the study because of errors in scheduling, or

* Operations scheduled before midnight for surgery the following day were considered to be "elective" to allow for the occasional changes in scheduling made in the evening. This arrangement allowed for an occasional "semi-emergency" procedure to be included.

† The patient's unit number was almost always assigned months or years in advance. The selection of anesthetic on the basis of random numbers would have been theoretically sounder, but unit number selection was chosen as practically simpler in a busy operating room and probably acceptable for the purposes of the current study. During the second half of the study patients with unit numbers ending in zero or nine were omitted from the study to provide upper abdominal procedures for instruction in other techniques.

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TABLE 1
THIOPENTAL AND SUCCINYLCHOLINE DOSAGE IN PATIENTS RECEIVING RELAXANT TECHNIQUE
Thiopental

Operation	Dose	0-500 Mg.		501-1,000 Mg.		1,001-1,500 Mg.		1,501 + Mg.	
	No. of Patients*	No. of Patients	Per Cent	No. of Patients	Per Cent	No. of Patients	Per Cent	No. of Patients	Per Cent
Cholecystectomy	92	12	13	40	43.5	33	35.9	7	7.6
Common duct exploration	96	14	14.6	43	44.7	31	32.3	8	8.4
Gastrectomy	124	14	11.3	41	33	51	41.2	18	14.5

Succinylcholine

Operation	Dose	0-500 Mg.		501-1,000 Mg.		1,001-1,500 Mg.		1,501 + Mg.	
	No. of Patients*	No. of Patients	Per Cent	No. of Patients	Per Cent	No. of Patients	Per Cent	No. of Patients	Per Cent
Cholecystectomy	92	30	32.6	47	51.1	14	15.2	1	1.1
Common duct exploration	95	19	20	48	50.6	19	20	9	9.4
Gastrectomy	113	13	10.7	55	48.9	30	26.7	15	13.7

* Information not available for approximately 10 per cent of patients.

in assignment of anesthetic. Thus a total of 19, or only 3 per cent of patients eligible for the study were lost. The assigned anesthetic technique could be changed at any time during the procedure when, in the estimation of the instructor in charge, this was essential to the patient's welfare. Only eight such occurred, six ether and two relaxant techniques.†

Premedication, in most instances, consisted of pentobarbital sodium, 50-100 mg. and atropine sulfate, 0.4-0.6 mg. given intramuscularly approximately one hour before induction of anesthesia. Twenty-eight patients in each group received meperidine, 50-100 mg. or morphine phosphate 6-10 mg. subcutaneously in place of, or in addition to, the barbiturate. (It was intended that no narcotic be given to any patient in this study. The occasional use of a narcotic was the result of oversight and was apparently entirely at random.) Seventeen patients received atropine sulfate alone.

† In five of these six ether cases, anesthesia was lightened and succinylcholine used because of hypotension. In the sixth, succinylcholine was used briefly because of inadequate relaxation. Anesthesia was changed to ether in the two relaxant cases because of excessive prolonged use of thiopental or of succinylcholine.

A Levine tube for gastric suction was inserted before the patient left the surgical ward.

Ether anesthesia was induced with nitrous oxide, 4 liters, and oxygen, one liter per minute in a semiclosed circuit with carbon dioxide absorption. After reaching surgical anesthesia (stage III, plane 1) the circuit was closed and anesthesia maintained on ether and oxygen. Endotracheal intubation with a cuffed endotracheal tube was performed in stage III, plane 2 or 3. Respirations were in almost all instances unassisted throughout surgery.

In the relaxant cases anesthesia was induced with thiopental sodium 2.5 per cent. When consciousness was lost oxygen 100 per cent was administered by mask. Intubation was accomplished following intravenous injection of succinylcholine 40-60 mg. Following intubation, anesthesia was maintained with nitrous oxide and oxygen at flow rates of 3 or 2 liters and one liter, respectively, and thiopental was added as required to maintain a light level of anesthesia; meperidine in increments of 10 to 25 mg. was used intravenously in 96 patients when thiopental in reasonable dosage failed to maintain adequate anesthesia. Relaxation was obtained with succinylcholine chloride in 0.2 per cent concentration admin-

TABLE 2
DISTRIBUTION OF CASES AND MORTALITY

	Ether Technique		Relaxant Technique	
	Cases	Deaths	Cases	Deaths
Cholecystectomy (benign disease of biliary tract)	98	2 (2%)	95	2 (2%)
Cholecystectomy (biliary tract malignancy)	2	1	1	0
Common duct exploration* (benign disease of biliary tract)	83	5 (6%)	99	7 (7%)
Common duct exploration* (biliary tract malignancy)	3	1	6	3
Gastroectomy (for benign ulcer)	94	5 (5%)	106	2 (2%)
Gastroectomy (for carcinoma)	23	7 (30%)	25	4 (16%)
Other procedures	29	4 (14%)	27	7 (26%)
No surgery†	1	—	1	—
Total cases	333	25 (7.5%)	360	25 (7%)

* Alone or in combination with cholecystectomy.

† Surgery cancelled because of difficulties with induction of anesthesia.

istered as an intravenous drip. Dosages of succinylcholine and of thiopental appear in table 1.

The larynx and trachea were anesthetized, at the time of intubation, with cocaine 4 per cent in half the patients in each group (on basis of next to last digit of unit number). The cocaine was administered as a spray in approximately 80 mg. dosage.

At completion of surgery the patient was taken to the recovery room to remain until conscious, and until vital signs were stable.

TABLE 3
CORRELATION OF ANESTHETIC AGENT WITH PULMONARY COMPLICATIONS

	Ether Technique	Relaxant Technique
Total cases*	318	355
Bronchitis	47 (15%)	55 (15%)
Atelectasis†	31 (10%)	56 (16%)
Pneumonia	7 (2.2%)	10 (2.8%)

* Patients who died or had second operation in immediate postoperative period not included.

† Alone or in combination with bronchitis or pneumonia.

RESULTS

Deaths [Table 2]. There was no difference in over-all hospital mortality between the two groups. Twenty-five § of the 360 patients who received the relaxant technique died (7 per cent), and 25 § of the 333 ether cases died (7.5 per cent). Anesthesia was considered the primary cause of death || in one patient in the relaxant group who suffered cardiac arrest in the recovery room after an apparent episode of hypoventilation and hypoxia. Anesthesia was considered a contributing cause of death in a second patient in the relaxant group who vomited and aspirated immediately postoperatively and died of bronchopneumonia on the fifth postoperative day. Anesthesia was considered a contributing cause of death in 4 patients who received ether. Two of these died with the clinical picture of cerebral thrombosis 24 and 36 hours following surgery. Severe hypotension had occurred in both. A third patient died 12 hours after ether anesthesia marked by severe, prolonged, operative and postoperative hypotension. A fourth patient who died of rapidly progressive tracheobronchitis and pneumonia was also classified as "anesthesia contributory." The majority of the remaining deaths was considered to have been primarily due to "patient's disease" and consisted largely of pneumonia, pulmonary emboli, pancreatitis, cardiac failure, and liver failure.

Nonfatal Complications. There were marked differences in the incidence of operative hypotension and of postoperative pulmonary complications between the two anesthetic groups. In other respects, the incidence of complications, both anesthetic and surgical, was practically identical.

Pulmonary complications # [Table 3]. The incidence of postoperative bronchitis was high (15 per cent) and the same in the ether and in

§ Deaths from all causes, same hospital admission as surgery in question.

|| Patients classified as to probable cause of death at the regular anesthetic service meeting at the time of occurrence.

The classification used by King² was followed. Bronchitis was considered present on the basis of cough, sputum, fever to 101-102 F. and coarse rales. The diagnosis of atelectasis was made by X-ray or on the basis of absent breath sounds cleared by coughing or bronchoscopy.

postoperative atelectasis as opposed to 25 of 291 (9 per cent) who did not receive a narcotic. In the relaxant group, atelectasis occurred in 9 of 28 (32 per cent) premedicated with a narcotic and in 24 of 104 (23 per cent) who received a narcotic as premedication or during surgery. Atelectasis occurred postoperatively in 33 of 224 (15 per cent) of relaxant patients who did not receive a narcotic before or during surgery.

The incidence of atelectasis rose with increasing duration of surgery under certain conditions (gastrectomy in males following ether; common duct exploration in males following thiopental, nitrous oxide, and succinylcholine) but the effect of length of surgery was not consistent. Within the relaxant group there was no difference in atelectasis between patients requiring large amounts of thiopental or succinylcholine and patients receiving small amounts during anesthesia and surgery.

Age of patient, smoking habits, and presence or absence of preoperative pulmonary disease (emphysema, bronchitis) did not have any clear-cut effect on postoperative atelectasis. Obesity was a factor only in the small group of massively obese patients undergoing gastrectomy. Atelectasis occurred in four of ten

such patients following gastrectomy under ether, and in four of eleven following the relaxant technique.

Hypotension [Table 7]. "Severe" and "moderate" hypotension occurred two and a half times as often during ether anesthesia as during anesthesia with thiopental, nitrous oxide, oxygen and succinylcholine. A fall in systolic blood pressure of 40 per cent or more below that measured immediately preoperatively was arbitrarily defined as "severe" hypotension and occurred in 15 per cent of ether cases and in 6 per cent of relaxant cases. A fall of 20 to 40 per cent ("moderate" hypotension) occurred in 31 per cent and 13 per cent respectively. Hypotension during abdominal exploration occurred three times as often during ether (16 per cent ether, 5 per cent relaxant). Severe postoperative hypotension occurred two and a half times as often following ether (5 per cent) as following the relaxant technique (2 per cent). Hypotension occurred during surgery more than twice as often in patients over 60 years of age as in those younger than 60. Women suffered hypotension approximately one and one-half times as often as men.

There was no difference in incidence of hypotension with nature of surgery (gastrectomy or biliary tract surgery). Surprisingly, there was no increased incidence of hypotension in patients with coronary heart disease, in hypertensives, or in patients receiving digitalis. Similarly, there was no correlation between operative hypotension and preoperative hemoglobin level** and only a suggestion of correlation with operative risk (standard classification of the American Society of Anesthesiologists).

A vasopressor, usually ephedrine sulfate, was used to correct hypotension in 58 of the ether patients (17%) and in 18 of the relaxant cases (5%). In five of the ether patients the use of ether was abandoned because of the severity of hypotension. On a single occasion severe hypotension during induction with thiopental, nitrous oxide, and succinylcholine necessitated cancellation of surgery.

** Severe anemia, when present, was corrected preoperatively, and therefore the comparison was between patients with mild anemia and patients with normal hemoglobin levels.

TABLE 6
CORRELATION OF POSTOPERATIVE PAIN
MEDICATION WITH OPERATION,
ANESTHETIC AND SEX

Does Narcotic for Pain, 1st 48 Hours Post- operatively		Ether Technique			Relaxant Technique		
		0-4	5-7	8+	0-4	5-7	8+
Cholecystectomy	M	9	1	1	5	3	0
	F	24	14	3	25	16	7
Common duct exploration	M	6	7	2	16	11	0
	F	17	17	5	24	9	3
Gastrectomy (for benign ulcer)	M	10	16	9	16	20	10
	F	11	4	2	6	9	1
Gastrectomy (for carcinoma)	M	6	3	1	2	8	0
	F	4	3	0	7	3	0
Other procedures	M	4	2	1	6	2	0
	F	7	4	0	3	6	1
Totals	M	35	29	14	45	44	10
	F	63	42	10	65	43	12

TABLE 7
HYPOTENSION DURING ANESTHESIA AND SURGERY

Age		Ether Technic			Relaxant Technic		
		Patients	"Moderate"* Hypotension	"Severe"* Hypotension	Patients	"Moderate" Hypotension	"Severe" Hypotension
20-39	M	17	2	0	16	2	0
	F	31	7	1	33	3	0
40-59	M	60	19	3	67	8	1
	F	63	21	7	59	6	4
60+	M	61	17	12	77	7	8
	F	99	37	28	108	22	8
Totals	M	138	38 (28%)	15 (11%)	160	17 (11%)	9 (6%)
	F	193	65 (34%)	35 (18%)	200	31 (16%)	12 (6%)

* "Moderate" hypotension arbitrarily designated as fall of 20-40 per cent below systolic blood pressure after premedication; "severe" hypotension designated as fall in systolic pressure greater than 40 per cent.

Miscellaneous. The possibility that the superior operating conditions associated with use of relaxants might shorten surgery was examined and did not materialize: average length of surgery was, if anything, slightly longer for operations using succinylcholine than for the same procedure with ether anesthesia. Similarly, the possibility that superior operating conditions provided by the relaxants might allow a more successful surgical procedure and, hence, a smoother and, perhaps, shorter postoperative course was examined. The duration of postoperative hospitalization was essentially the same for the two anesthetic techniques: slightly but again not much longer for the relaxant than for the ether cases.

DISCUSSION

It could not be anticipated that in a relatively small series of patients such as this death would occur often enough to allow meaningful comparisons between anesthetic agents. However, it was impressive that the over-all mortalities for ether and for the thiopental, nitrous oxide, succinylcholine technique were identical. The total mortality was high—2 per cent for cholecystectomy, 6.5 per cent for common duct exploration, 3.5 per cent for gastrectomy for benign ulcer, and 23 per cent for gastrectomy for carcinoma. These figures are at least in part a reflection of the advanced age of the patients: almost half were 60 years of age or

over. Three-quarters of the deaths occurred in patients over 60, two-thirds in patients over 70 years of age.

The incidence of death in which anesthesia was considered a contributing factor was also high, 1:115, when compared with the approximately 1:1,000 incidence of "anesthetic death" associated with general anesthesia in Beecher and Todd's series.¹ However, it must be remembered that the patients in the present study were selected as particularly likely to present a high incidence of anesthetic and surgical difficulties. The numbers of deaths in which anesthesia may have played a rôle are, of course, too small for any kind of statistical comparison.

Consideration of the circulatory and pulmonary complications reveals impressive differences between the two anesthetic groups. One might argue that hypotension is not in itself a complication, but it must be assumed that the severe hypotension not uncommonly observed with ether anesthesia is undesirable. One of the possible sequelae of severe hypotension, cardiac arrest, did not, in fact, occur during ether anesthesia in this study. A second catastrophe generally associated with hypotension, coronary occlusion with myocardial infarction, did occur in 4 patients following ether anesthesia and was demonstrated at postmortem examination. Two of these four patients also suffered cerebral vas-

cular thrombosis. In 3 of the 4 severe operative or immediate postoperative hypotension had occurred. Two patients dying after thiopental-nitrous-oxide-succinylcholine anesthesia were also found to have recent myocardial and cerebral infarction. (A third patient who died two days postoperatively was found to have a myocardial infarct, estimated by the pathologist as two weeks old.) Neither of these two patients had suffered hypotension during anesthesia; one of the two had moderate, brief hypotension in the recovery room. All 6 patients with myocardial infarction were over 60 years of age and all were women.

The dangers of acute hypoventilation associated with the use of muscle relaxants are well recognized, but the observation of increased postoperative atelectasis came as a surprise. It is possible that this reflects persistent residual effects of succinylcholine or, perhaps, the combined effect of the several different agents used in the relaxant technic. Bendixen has recently demonstrated³ that in the recovery phase following use of muscle relaxants there may be a marked reduction of ventilatory reserve, as reflected in the measurement of inspiratory force, and at a time when tidal and minute volume and alveolar carbon dioxide tension are normal. It is reasonable to speculate that inability to develop normal inspiratory force hinders the clearing of obstructing secretions and prevents the occasional deep breath apparently important in preventing alveolar collapse.

Thiopental, with well known respiratory depressant effects of its own, is logically suspected of contributing to any postoperative hypoventilation postulated as a cause of atelectasis. The lack of correlation between dose of thiopental and postoperative atelectasis suggests that this is not a major factor.

The correlation between atelectasis and the use of morphine or meperidine preoperatively, during surgery, or to control pain postoperatively was impressive. It cannot be determined from the present study whether this is a primary drug effect, or whether it is the presence of increased pain (reflected in the increased need for medication) which persuades the patient to limit respirations and cough, and hence sets the stage for atelectasis.

By similar reasoning, it might be argued that it is the same sort of patient who needs postoperative medication who also seems to need more anesthesia during surgery, and who accordingly is given morphine or meperidine preoperatively, or as an anesthetic supplement. It was of interest that the increase in atelectasis with increased postoperative narcotic occurred in men only, and, as a corollary, the increase in atelectasis in males over females occurred only in heavily medicated, but not in lightly medicated patients [table 5].

SUMMARY AND CONCLUSIONS

A controlled comparison of complications and deaths during and following anesthesia and surgery has been presented. The surgical procedures were cholecystectomy, common duct exploration, or gastrectomy. The anesthetic techniques compared were nitrous oxide, oxygen, and ether or thiopental, nitrous oxide, oxygen, and succinylcholine. Six hundred and ninety-three patients were studied. The improvement in operating conditions associated with use of the relaxant technique was not great enough to cause a detectable diminution in surgical complications, total mortality, length of surgery, or duration of hospitalization. On the basis of complications directly related to the anesthetic agent, it was not justified to state that one agent or technique was "better" or "worse" than the other. Rather, certain dangers associated with the use of each of the techniques have been identified. Specifically, it appeared that ether anesthesia for upper abdominal surgery offered an increased hazard of circulatory depression in the elderly and in women. On the other hand, the use of light general anesthesia, with succinylcholine for relaxation, appeared to involve, in addition to the obvious dangers of acute hypoventilation in the operative and immediate postoperative period, an increased incidence of the serious postoperative complication of atelectasis, greatest in men undergoing gastrectomy.

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STEROID ANESTHESIA Hydroxydion was used in 100 poor risk patients. A 5 per cent solution with 0.2 per cent procaine drip is injected at body temperature. It is combined with nitrous oxide, oxygen, meperidine and curare. Advantages are smooth induction and absence of circulatory and respiratory depression during anesthesia. No undesirable postanesthetic effects were observed. The only complications were two cases of mild thrombophlebitis. (Bergmann, H., and Vogl, W.: *Steroid Anesthesia and Surgery in Poor Risk Patients*, *Wiener-Medizinische-Wochenschrift* 109: 536 (June) 1959.)

FLUOTHANE In 2,000 cases, Fluothane was used as an adjuvant to nitrous oxide-oxygen anesthesia, chiefly with semiclosed or non-rebreathing systems. Standard premedication was usually used. Adequate atropinization was shown to be essential. The vaporizer was placed so that only new gases passed over it. The concentrations delivered must be accurately known with respect to the conditions under which Fluothane is used. Some types

of vaporizers must be modified for such use. Hypotension was not considered to be a major factor, and was not as evident as when meperidine was used as an adjunct instead of Fluothane. All relaxants were used with Fluothane without ill effects. The amount of succinylcholine required as a relaxant with Fluothane was less than with meperidine. Fluothane was used in all age groups; lower concentrations should be employed in the elderly. (MacWalter, D., and others: *Two Thousand Cases of Fluothane Anesthesia*, *Canad. M. A. J.* 80: 976 (June 15) 1959.)

STEROID ANESTHESIA There is smooth induction and absence of undesirable side effects, except a fall of blood pressure in some hypertensive patients. The agent is used as a basal anesthetic. No antagonist is known. Rapid intravenous injection of a concentrated solution at body temperature, followed by saline, reduces danger of phlebitis. (Frank, D., and others: *Studies Concerning Hydroxydion Anesthesia*, *Der Anaesthetist* 8: 97 (April) 1959.)