A review of the data clearly shows the superior response experienced by the HALDOL patients with respect to their nausea and vomiting. In the HALDOL group, 83 (90%) of the 92 patients but only 43 (51%) of the 85 patients in the placebo group experienced "marked" to "moderate" therapeutic responses. The difference between the two groups was significant ($P < .01$) in favor of HALDOL.

The vital signs obtained initially and at the end of the 2-hour observation period shows a significant ($P < .05$) change in the body temperature of the HALDOL group when compared to the placebo group. The initial temperature (99.2°) decreased to a final temperature of 98.8°. This difference, however, is not considered to be clinically significant. There was no significant difference in any other vital signs.

Side effects were reported by two patients in the HALDOL group. One had blurred vision and the other reported drowsiness. One placebo patient was reported to have an increased pulse during the study. One patient in the placebo group continued to have nausea and vomiting to a degree requiring immediate treatment. He was considered a treatment failure and dropped from the evaluation. The patient was then administered 1.0 mg of uncoded parenteral HALDOL and exhibited a marked therapeutic response.

In summary, the data in this combined analysis indicates that HALDOL at an intramuscular dose of 1.0 mg was more effective than placebo in controlling the episodes of vomiting and

the severity of nausea ($P < .05$ and in some instances $P < .01$) that occur following gastrointestinal disorders. The global evaluation also clearly reveals the superiority ($P < .01$) of HALDOL in this comparison.

(2) HALDOL - 2.0 mg

1. Leslie, R.E., M.D. (18)
A double-blind evaluation of the antiemetic properties of HALDOL in nonhospitalized patients with nausea and vomiting as a result of gastrointestinal disorders.

Sixty-five patients who required antiemetic treatment for moderate to severe vomiting with nausea were entered into the study. One patient was excluded from analysis since his nausea and vomiting was due to other than gastrointestinal etiology (Meniere's disease). Seven patients were studied twice, but only their first evaluations were included in the analysis.

The characteristics of the remaining 64 patients are shown in Table LXV. Either HALDOL 2.0 mg or placebo was administered intramuscularly as a single dose within four hours of an episode of vomiting.

Table LXV
Patient Characteristics

Drug Group	Age		Sex		Weight		Total Patients
	Mean	Range	Male	Female	Mean	Range	
HALDOL	59.2	18-85	15	16	172.3	123-300	31
Placebo	55.7	19-81	11	22	176.9	125-350	33

Patients were evaluated for 12 hours post-drug administration The episodes of vomiting were recorded initially and every two hours for the first four hours and every four hours thereafter up to 12 hours. These data are presented in Table LXVI.

A review of the data in Table LXVI shows that there were fewer episodes of vomiting in the HALDOL-treated group than in the placebo group. The difference between the two treatments was significant ($P < .01$ at the first 2-hour evaluation, $P < .05$ at the remaining evaluations) in favor of HALDOL. The data are presented graphically in Figure 15.

Figure 15

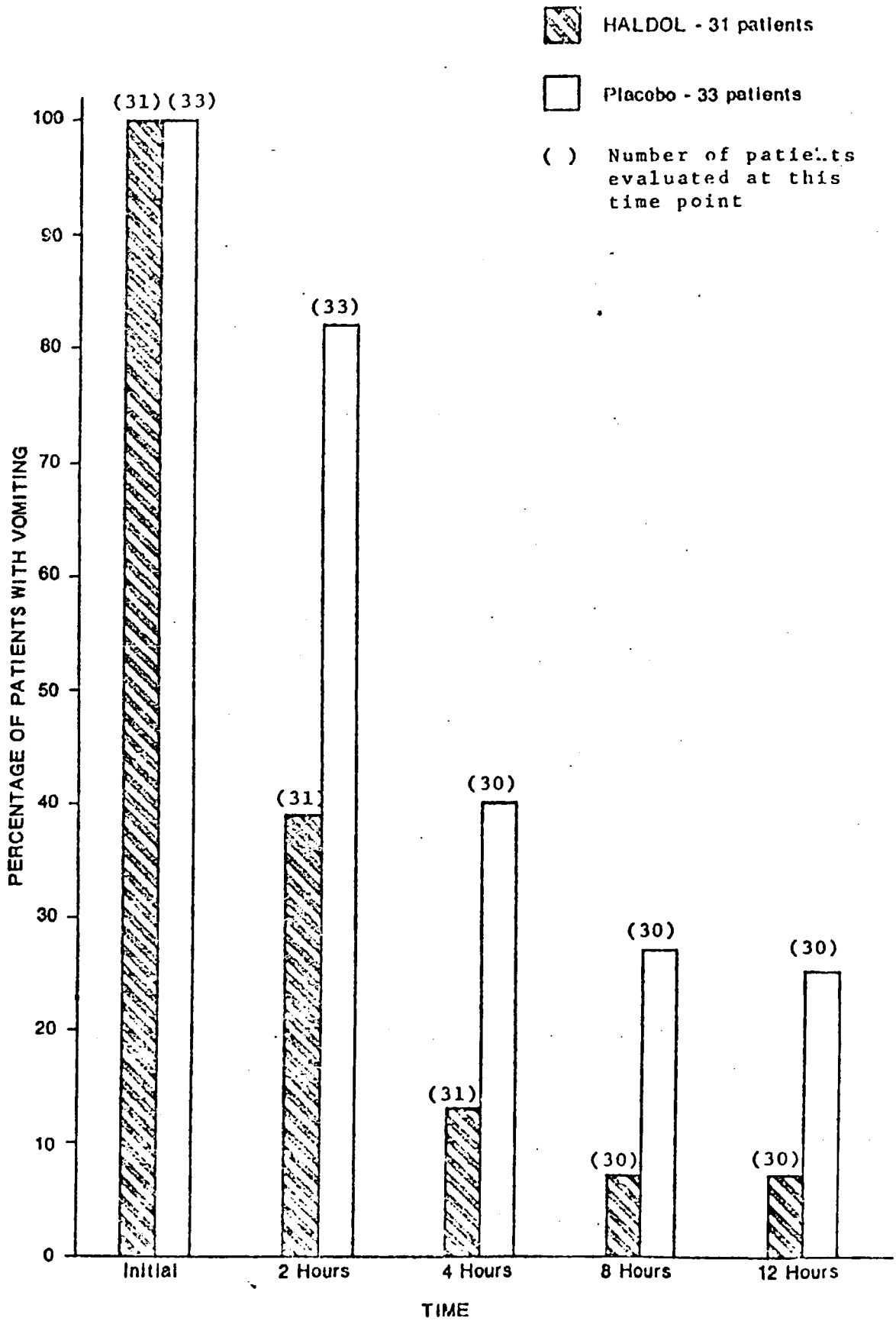

HALDOL - 31 patients
Placebo - 33 patients
( ) Number of patients evaluated at this time point
PERCENTAGE OF PATIENTS WITH VOMITING
100
90
80
70
60
50
40
30
20
10
0
(31) (33)
(31)
(33)
(31)
(30)
(30)
(30)
(30)
(30)
Initial
2 Hours
4 Hours
8 Hours
12 Hours
TIME

Table LXVI
Episodes of Vomiting

Time of Observation	Drug Group	Frequency						Total Pts.
		0	1	2	3	4	5	
Initially (Pre-Study Drug)	HALDOL	0	0	9	19	2	1	31
	Placebo	0	0	6	20	7	0	33
During First 2-Hour Post-Study Drug	HALDOL†	19	12	0	0	0	0	31
	Placebo	6	17	10	0	0	0	33
During 2-Hour to 4-Hour Period	HALDOL*	27	3	1	0	0	0	31
	Placebo	18	12	0	0	0	0	30
During 4-Hour to 8-Hour Period	HALDOL*	28	2	0	0	0	0	30
	Placebo	22	7	1	0	0	0	30
During 8-Hour to 12-Hour Period	HALDOL*	28	2	0	0	0	0	30
	Placebo	21	7	2	0	0	0	30

*Statistically significantly fewer episodes of vomiting during this particular period ($P < .05$, Rank "t" Test)
†$P < .01$

The incidence of vomiting in the HALDOL drug group was significantly ($P < .01$) less than in the placebo group over the 12-hour observation period; 17 (55%) of the 31 HALDOL patients, but only three (9%) of the 33 placebo patients were free of vomiting. This difference between the two treatments is statistically significant ($P < .01$) in favor of HALDOL.

The occurrence of nausea after treatment is presented in Table LXVII.

Table LXVII
Occurrence of Nausea

Time of Observation	Drug Group	Severity† of Nausea				Total Pts.
		0 †	1	2	3	
Initially (Pre-Study Drug)	HALDOL	0	0	29	2	31
	Placebo	0	1	27	5	33
During First 2-Hour Post-Study Drug	HALDOL*	4	22	5	0	31
	Placebo	4	13	12	4	33
During 2-Hour to 4-Hour Period	HALDOL**	13	16	1	1	31
	Placebo	3	22	5	0	30
During 4-Hour to 8-Hour Period	HALDOL**	23	6	1	0	30
	Placebo	4	23	3	0	30
During 8-Hour to 12-Hour Period	HALDOL**	23	7	0	0	30
	Placebo	10	17	3	0	30

†0=None, 1=Mild, 2=Moderate, and 3=Marked
*Statistically significantly less nausea among the HALDOL patient ($P < .05$, Rank "t" Test; ** = $P < .01$)

There were fewer occurrences of nausea among the HALDOL-treated patients than among the placebo patients at each evaluation point. The difference in the severity of nausea between the two treatments is significant ($P < .05$) favoring HALDOL during the first 2-hour evaluation period and $P < .01$ during the remaining evaluation points. The data are presented graphically in Figure 16.

The investigator's global or overall evaluation at the end of therapy is presented in Table LXVIII.

Table LXVIII
Global Evaluation

Drug Group	Evaluation				Total Patients
	Marked	Moderate	Minimal	Unchanged	
HALDOL	21	7	2	1	31
Placebo	5	10	13	5	33

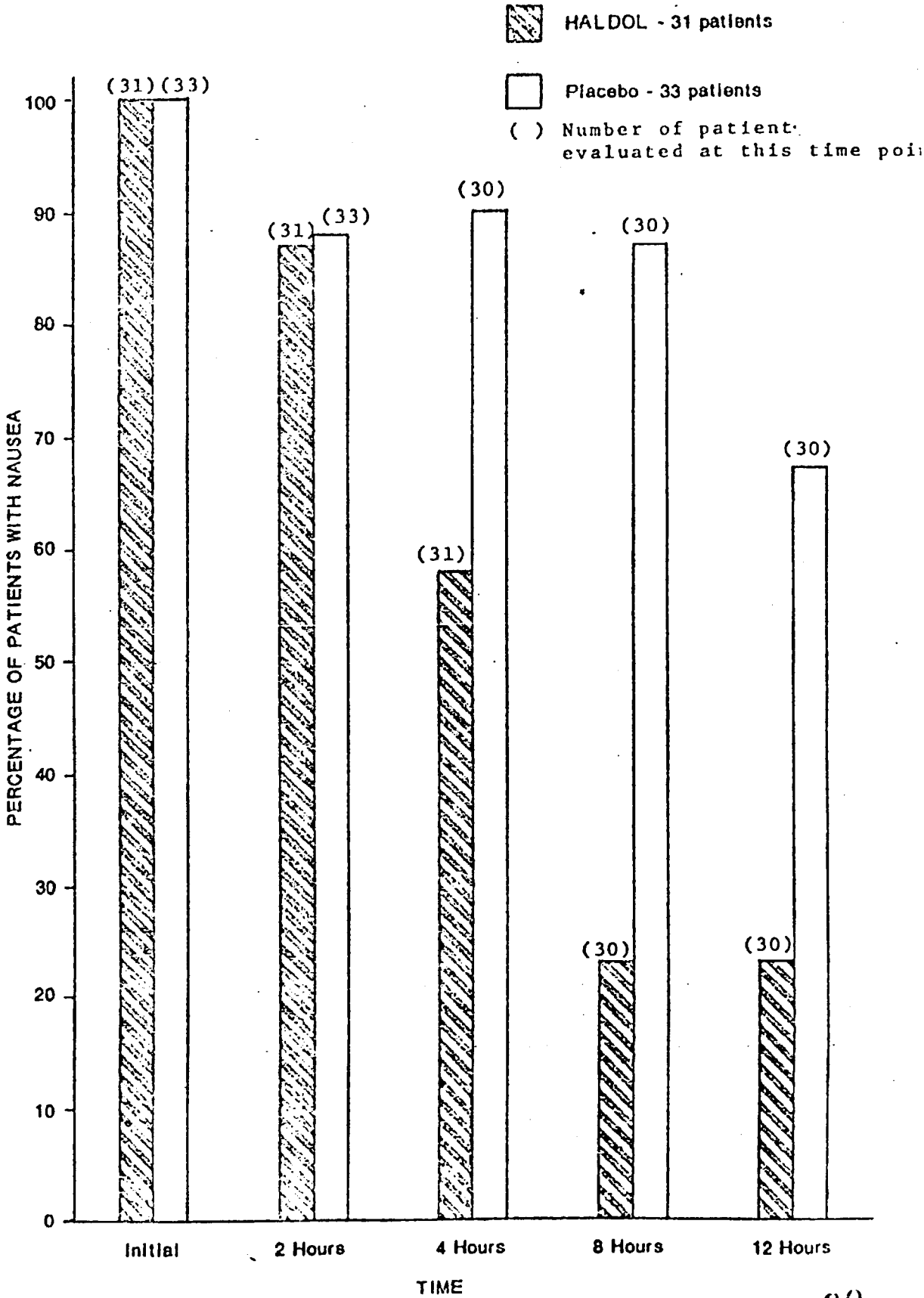
An analysis of the data clearly shows the superior response experienced by the patients treated with HALDOL. The statistical difference between the therapeutic responses to the two treatments is significant ($P < .01$) in favor of HALDOL.

The vital signs obtained initially and 2 hours after drug administration demonstrated no significant difference between the two treatment groups.

No side effects were reported by patients in either drug group during the course of the study.

In summary, the intramuscular injection of 2.0 mg of HALDOL was safe and significantly ($P < .05$ and in some instances $P < .01$) more effective than was placebo in controlling nausea and vomiting as a result of gastrointestinal disorders.

Figure 16


HALDOL - 31 patients
Placebo - 33 patients
( ) Number of patients evaluated at this time poi
PERCENTAGE OF PATIENTS WITH NAUSEA
0
10
20
30
40
50
60
70
80
90
100
(31) (33)
(31) (33)
(31) (30)
(30) (30)
(30) (30)
Initial
2 Hours
4 Hours
8 Hours
12 Hours
TIME

2. Everett, S.F., M.D. (19)
A double-blind evaluation of the antiemetic properties of HALDOL in hospitalized and nonhospitalized patients with nausea and vomiting as a result of gastrointestinal disorders.

Twenty-eight patients who required antiemetic treatment for moderate to severe vomiting with nausea were entered into the study. Eight patients were excluded from analysis for the following reasons: 6-had nausea and vomiting due to causes other than gastrointestinal etiology; 1-had received a known antiemetic agent concomitantly; 1-had insufficient evaluation following the administration of the study drug.

The characteristics of the remaining 20 patients are shown in Table LXIX. Each patient received either HALDOL 2.0 mg or placebo administered intramuscularly as a single dose within four hours of an episode of vomiting.

Table LXIX
Patient Characteristics

Drug Group	Age		Sex		Weight		Total Patient
	Mean	Range	Male	Female	Mean	Range	
HALDOL	50.3	20-86	3	7	138.0	109-176	10
Placebo	54.0	21-86	5	5	150.6	123-181	10

Patients were evaluated for 12 hours post-drug administration. The episodes of vomiting were recorded initially and every two hours for the first four hours and every four hours thereafter up to 12 hours. These data are presented in Table LXX.

Table LXX
Episodes of Vomiting

Time of Observation	Drug Group	Frequency						Total Patients
		0	1	2	3	4	≥ 5	
Initially (Pre-Study Drug)	HALDOL	0	2	2	2	0	4	10
	Placebo	0	2	4	1	0	3	10
During First 2-Hour Post-Study Drug	HALDOL*	10	0	0	0	0	0	10
	Placebo	5	1	3	1	0	0	10
During 2-Hour to 4-Hour Period	HALDOL	10	0	0	0	0	0	10
	Placebo	7	0	2	1	0	0	10
During 4-Hour to 8-Hour Period	HALDOL	9	0	1	0	0	0	10
	Placebo	7	3	0	0	0	0	10
During 8-Hour to 12-Hour Period	HALDOL	9	0	1	0	0	0	10
	Placebo	7	1	2	0	0	0	10

*Statistically significantly fewer episodes of vomiting during this period ($P < .05$, Rank "t" Test).

A review of the data in Table LXX shows that the episodes of vomiting were significantly less among the HALDOL-treated patients ($P < .05$, 2-hour evaluation point) than among the patients given placebo.

The incidence of vomiting in the HALDOL group was significantly ($P < .05$) less than in the placebo group over the 12-hour evaluation period. During the 12-hour observation period, nine (90%) of the ten HALDOL patients, but only four (40%) of the ten placebo patients were free of vomiting. This difference between the two treatments is statistically significant ($P < .05$) in favor of HALDOL.

The occurrence of nausea after treatment is presented in Table LXXI.

Table LXXI
Occurrence of Nausea

Time of Observation	Drug Group	Severity+ of Nausea				Total Patients
		0+	1	2	3	
Initially (Pre-Study Drug)	HALDOL	0	1	5	4	10
	Placebo	0	1	6	3	10
During First 2-Hour Post-Study Drug	HALDOL	3	4	1	1	9
	Placebo	3	4	2	1	10
During 2-Hour to 4-Hour Period	HALDOL	3	4	0	2	9
	Placebo	3	6	0	1	10
During 4-Hour to 8-Hour Period	HALDOL	3	3	3	0	9
	Placebo	5	3	1	1	10
During 8-Hour to 12-Hour Period	HALDOL	5	1	3	0	9
	Placebo	6	2	1	1	10

+0=None, 1=Mild, 2=Moderate, and 3=Marked

A review of the data in Table LXXI shows that the severity of nausea experienced by the patients treated with HALDOL was similar to that experienced by the patients given placebo.

The investigator's global or overall evaluation at the end of the study is presented in Table LXXII.

Table LXXII
Global Evaluation

Drug Group	Evaluation				Total Patients
	Marked	Moderate	Minimal	Unchanged	
HALDOL	5	4	1	0	10
Placebo	3	2	1	4	10

A review of the data shows that 90% of the HALDOL-treated patients experienced a marked to moderate therapeutic response; whereas, only 50% of the placebo-treated patients experienced a similar response. This difference approaches significance ($P < .10$) in favor of HALDOL.

The vital signs obtained initially and 2 hours after drug administration demonstrated no significant difference between the two treatment groups.

No side effects were reported by any patient in the HALDOL group; one placebo patient reported dry mouth during the course of the study.

In summary, the intramuscular injection of 2.0 mg of HALDOL was safe and significantly ($P < .05$) more effective than was placebo in controlling the vomiting that occurred in patients with gastrointestinal disorders.

3. Combined Analysis of Two Investigators (Leslie, R. & Everett, S.) (20)
A double-blind evaluation of the antiemetic properties of HALDOL in hospitalized and nonhospitalized patients with nausea and vomiting as a result of gastrointestinal disorders.

The above-named investigators used the same protocol and case report form to study the intramuscular administration of HALDOL at a dose of 2.0 mg in the therapeutic treatment of nausea and vomiting as a result of gastrointestinal disorders. Because of these factors, the studies have been combined to provide a larger sample for statistical purposes.

Ninety-three patients who required antiemetic treatment for moderate to severe vomiting with nausea were entered into the study. Nine patients were excluded from analysis for the following reasons: 7-had nausea and vomiting due to causes other than gastrointestinal etiology; 1-had received a known antiemetic concomitantly; 1-had insufficient evaluation following administration of study drug.

The final analysis included 41 patients in the HALDOL group and 43 in the placebo group. The patient population used is shown in Table LXXIII.

Table LXXIII
Patient Population

Investigator's Name	Number of Patients			
	Excluded		Included	
	HALDOL	Placebo	HALDOL	Placebo
R. Leslie, M.D.	1	0	31	33
S. Everett, M.D.	3	5	10	10
Total	4	5	41	43

The characteristics of the remaining 84 patients are shown in Table LXXIV. Each patient received either HALDOL 2.0 mg or placebo administered intramuscularly as a single dose within four hours of an episode of vomiting.

Table LXXIV
Patient Characteristics

Drug Group	Age		Sex		Weight		Total Patients
	Mean	Range	Male	Female	Mean	Range	
HALDOL	57.0	18-86	18	23	163.9	109-300	41
Placebo	55.3	19-86	16	27	170.8	123-350	43

Patients were evaluated for 12 hours post-drug administration. The episodes of vomiting were recorded initially and every two hours for the first four hours and every four hours thereafter up to 12 hours. These data are presented in Table LXXV.

Table LXXV
Episodes of Vomiting

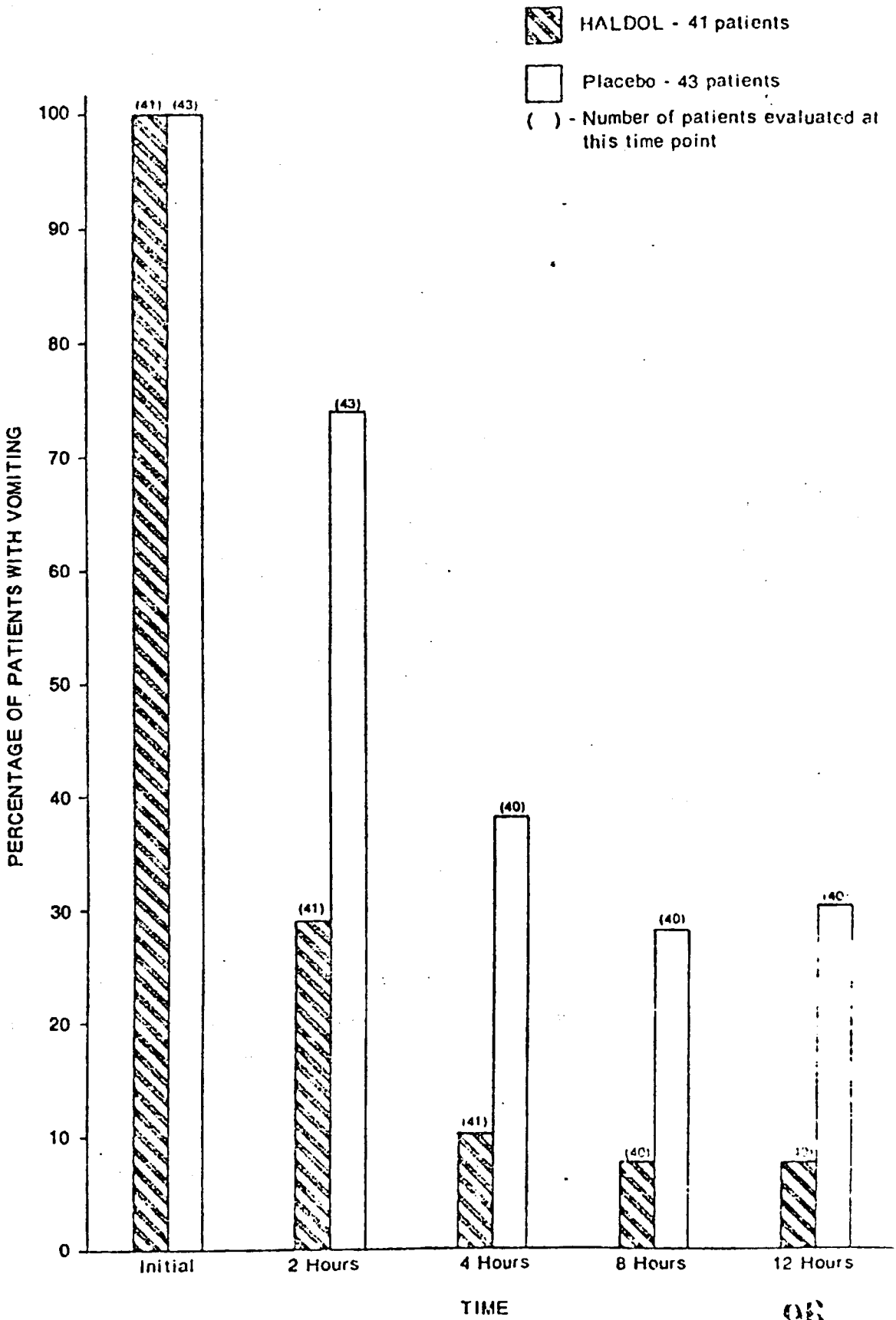
Time of Observation	Drug Group	Frequency						Total Patients
		0	1	2	3	4	≥ 5	
Initially (Pre-Study Drug)	HALDOL	0	2	11	21	2	5	41
	Placebo	0	2	10	21	7	3	43
During First 2-Hour Post-Study Drug	HALDOL**	29	12	0	0	0	0	41
	Placebo	11	18	13	1	0	0	43
During 2-Hour to 4-Hour Period	HALDOL**	37	3	1	0	0	0	41
	Placebo	25	12	2	1	0	0	40
During 4-Hour to 8-Hour Period	HALDOL*	37	2	1	0	0	0	40
	Placebo	29	10	1	0	0	0	40
During 8-Hour to 12-Hour Period	HALDOL*	37	2	1	0	0	0	40
	Placebo	28	8	4	0	0	0	40

*Statistically significantly fewer episodes of vomiting during this period ($P<0.05$, Rank "t" Test)
**$P<0.01$

A review of the data in Table LXXV shows that there were fewer episodes of vomiting among the patients treated with HALDOL than in those patients treated with placebo. The difference between the two treatments in the episodes of vomiting was significant ($P<.05$ and in some instances $P<.01$) in favor of HALDOL at each evaluation point. This data is presented graphically in Figure 17.

The incidence of vomiting in the HALDOL group was significantly ($P<.01$) less than in the placebo group over the 12-hour evaluation period. During the 12-hour observation period, 25

Figure 17


HALDOL - 41 patients
Placebo - 43 patients
( ) - Number of patients evaluated at this time point
PERCENTAGE OF PATIENTS WITH VOMITING
100
90
80
70
60
50
40
30
20
10
0
(41) (43)
(43)
(41)
(40)
(41)
(40)
(40)
Initial
2 Hours
4 Hours
8 Hours
12 Hours
TIME

(61%) of the 41 HALDOL patients but only seven (16%) of the 43 placebo patients were free of vomiting. This difference between the two treatments is statistically significant ($P < .01$) in favor of HALDOL.

The occurrence of nausea after treatment is presented in Table LXXVI.

Table LXXVI

Occurrence of Nausea

Time of Observation	Drug Group	Severity+ of Nausea				Total Patients
		0	1	2	3	
Initially (Pre-Study Drug)	HALDOL	0	1	34	6	41
	Placebo	0	2	33	8	43
During First 2-Hour Post-Study Drug	HALDOL*	7	26	6	1	40
	Placebo	7	17	14	5	43
During 2-Hour to 4-Hour Period	HALDOL*	16	20	1	3	40
	Placebo	6	28	5	1	40
During 4-Hour to 8-Hour Period	HALDOL**	26	9	4	0	39
	Placebo	9	26	4	1	40
During 8-Hour to 12-Hour Period	HALDOL**	28	8	3	0	39
	Placebo	16	19	4	1	40

+0=None, 1=Mild, 2=Moderate, and 3=Marked
*Statistically significantly less nausea among the HALDOL patients ($P < 0.05$, Rank "t" Test)
**$P < 0.01$

A review of the data indicates that the severity of nausea was lower among the patients treated with HALDOL than in the patients given placebo. The difference between the two treatments was significant ($P < .05$ and in some instances $P < .01$) in favor of HALDOL at each evaluation point. These data are graphically shown in Figure 18.

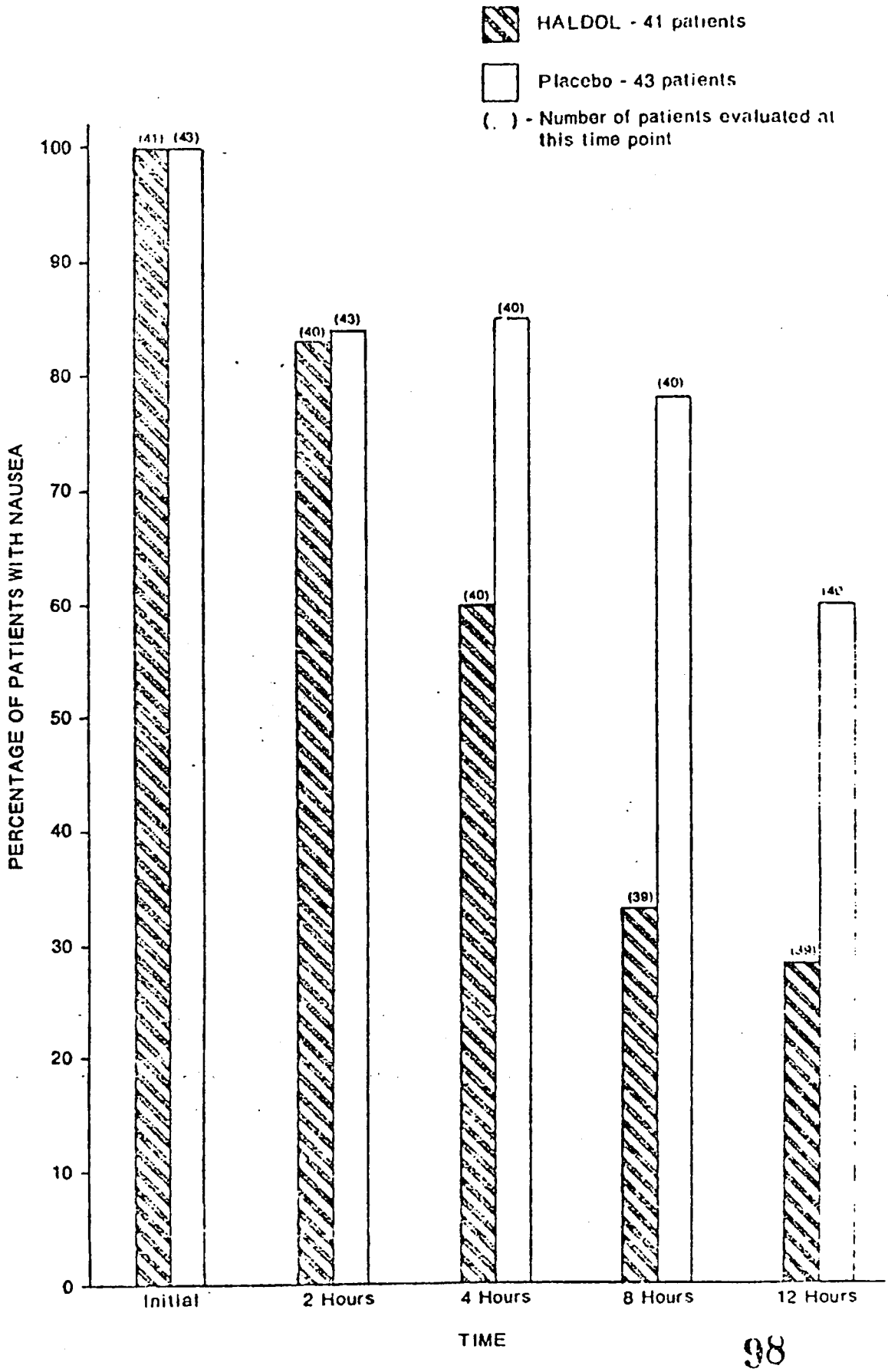
The investigators' global evaluations, which rated the patients' responses at the end of therapy, are shown in Table LXXVII

Table LXXVII

Global Evaluation

Drug Group	Final Evaluation					Total Patients
	Marked	Moderate	Minimal	Unchanged	Worse	
HALDOL	26	11	3	1	0	41
Placebo	8	12	14	9	0	43

Figure 18


HALDOL - 41 patients
Placebo - 43 patients
( ) - Number of patients evaluated at this time point
PERCENTAGE OF PATIENTS WITH NAUSEA
100
90
80
70
60
50
40
30
20
10
0
(41)
(43)
(40)
(43)
(40)
(40)
(40)
(39)
Initial
2 Hours
4 Hours
8 Hours
12 Hours
TIME