CHAPTER 4

RESULTS

Notice: for the following analysis and data presentation, p value < 0.05 (2-tailed) or p < 0.10 (1-tailed) is considered as being statistically significant; the continuous data are presented in the type of "mean ± SEM".

4.1   Patients Accounting

Consecutive 44 episodes of hepatic encephalopathy of stage 2 to 4 of 32 cirrhotic patients were initially enrolled in this study according to the eligibility criteria at the beginning of the trial between May, 1995 to March, 1996 in Zhong Shan Hospital, Shanghai, China.

Each episode of HE represented one piece of in-ward course from admission until the patient's discharge or death in the ward.

Among these 32 patients, 9 had been repeatedly enrolled for their second or third times of a subtotal of 12 repeated HE episodes out of total 44.

Because some results of the assistant tests were unavailable at the baseline or the initial enrollment, or, during the intensive observation period some fatal accidents occurs, finally, 14 out of 44 episodes of HE were consequently considered as being not eligible. The exclusive reasons for those 14 episodes included severe GI bleeding, unstable hemodynamic condition, renal failure, cerebral hemorrhage or end-stage of malignant diseases (hepatocellular carcinoma or renal carcinoma).

Table 4.1 Distribution of HE episodes and patients

	Trt Grp	Ctrl Grp	Total
Initially enrolled episodes	20	24	44
Initially enrolled patients	16	16	32
Finally exclusive episodes	6	8	14
Finally exclusive patients	3	4	7
Finally eligible patients	13	12	25
Finally "eligible" episodes	14	16	30

Trt = Treatment; Ctrl = Control; Grp = Group

Therefore (Table 4.1), **25 patients** (13 in treatment group and 12 in control group, respectively), all with their first episode of HE, were selected as the eligible samples for standard analysis of this trial at last.

As to the patients who had been repeatedly enrolled, the eligible but repeated episodes of HE will also be analyzed separately with their first episode of HE -- a pragmatic "cross-over" study.

Because of the short duration of intensive observation period (2.5 hours), no case dropped out of this study, and most of the patients were followed until their discharges or death in the ward, except the last case who hasn't been discharged but with quite good general conditions waiting for shunting or devascularizing operation for his portal hypertension when the investigators started analyzing the data.

The strong willingness of the patients' family members in making the patients awaken or normalize their mental condition greatly assisted the investigators to obtain the consents.

4.2   Analysis for the 25 Eligible Patients

4.2.1 Baseline Data

Table 4.2   Demographic and basic clinical data of
eligible patients

		Trt Grp n = 13	Ctrl Grp n = 12	p value
Age	(years)	52.23± 2.63	52.17±3.27	0.91*
Sex	(M / F)	10 / 3	9 / 3	1.00#
Etiology of Cirrhosis				0.50#
	Viral Hepatitis	9	11	
	Alcoholic	2	1	
	Biliary	1	0	
	Others	1[s]	0	
Cirrhotic Pathology	(Y/N)	10 / 3	7 / 5	0.41#
Duration of Cirrhosis	(years)	6.81±1.47	5.13±1.21	0.49*
Shunt-Operation	(Y/N)	5 / 8	2 / 10	0.38#
Previous HE History	(Y/N)	6 / 7	4 / 8	0.69#
Liver Cancer	(Y/N)	0 / 13	1 / 11	0.48#
Study Place				0.23#
	GI Ward	6	9	
	Emergency Ward	7	3	

* Student's t-test;   # Chi-squares test ;
[s] Budd-Chiari's Syndrome;   Y / N = yes / no
                              M /F = Male / Female

The demographic data and the background of liver diseases of these eligible patients are listed in Table 4.2. There is no significant difference between the two groups in age, sex, etiology of cirrhosis, duration of

cirrhosis, history of shunt-operation or history of previous HE. Male patients were much more than females in both groups (19:6), and the predominant cause of cirrhosis was viral hepatitis (80%), obtained from the case history and serum tests. About 43% cases were initially treated in the Emergency Room.

The present liver function and HE stage on the baseline are listed in Table 4.3. More than half (13/25) of the precipitating factors were esophageal varices hemorrhage. The duration of HE from the commencement of that HE episode to the point of enrollment was about averagely 12 to 15 hours. Nearly half of the patients (12/25, 48%) were in poor condition of liver function (Child-Pugh stage of C). Sixty-four percent of patients were in the HE stage of 2. These values were all comparable in the 2 groups.

Table 4.3   HE and liver function of eligible patients

	Trt Grp n = 13	Ctrl Grp n = 12	p value
HE Duration (hours)	15.46±1.88	12.58±2.97	0.58*
HE Stage at Enrollment			0.42#
Stage 2	7	9	
3	5	3	
4	1	0	
Precipitating Factors			0.15#
GI bleeding	5	8	
Protein overload	5	1	
Infection	2	0	
Trauma	0	1	
Unknown	1	2	
Child-Pugh Stage at Enter			0.21#
Stage A (1)	2	0	
B (2)	4	7	
C (3)	7	5	
Child-Pugh Raw Score	9.15±0.66	9.25±0.73	0.92*
Albumin (g/L)	31.00±1.03	30.25±1.69	0.70*
Total bilirubin (mmol/L)	57.27±10.68	67.73±15.41	0.58*
Prothrombin time (seconds)	14.31±0.86	13.92±0.53	0.71*
Prothrombin activity (%)	74.54±6.51	70.75±6.95	0.70*
Ascites			0.97#
Absent (Degree 1)	6	5	
Slight (Degree 2)	5	5	
Moderate (Degree 3)	2	2	
Ammonia (mmol/L)	55.23±5.50	58.53±18.09	0.67*
Hemoglobin (g/L)	94.15±5.38	97.17±6.37	0.72*

* Student's T-test;   # Chi-squares test

4.2.2   Therapeutic Results

According to the Operational Definition, the effectively improved patients after the proposed "treatment" were only found 3 in the flumazenil group (3/13, 23%).   All three who had effective flumazenil effect were initially in the 2nd clinical stage of HE. Though Fisher's exact test didn't show the significant difference of this result (1-tailed p value was 0.124, Table 4.4), the power of this test was only 56% (z_β=0.144).

The test of another therapeutic result of positive responder comparison (Table 4.5) achieved the significant "threshold" of comparing 2 proportions with the p value of 0.008 and also with a high power of 91.5% (z_β=1.378).   Eight cases (8/13, 61.5%) in flumazenil group showed the different degrees of positive response to the drug from the baseline stage of 2, 3 or 4,   while only one case (1/12, 8.3%) had the responsive reaction in the placebo group (stage 2 at the baseline).

These improvement of clinical stages of HE by flumazenil could be seen in patients (8/13) at any stage of the baseline (4/7 in stage 2, 3/5 in stage 3 and 1/1 in stage 4).

Table 4.4   Treatment results (1)

- **For patients who were effectively improved**

	Flumazenil	Placebo	Total
Non-effectiveness	10	12	22
Effectiveness	3	0	3
Total	13	12	25

Fisher's exact test: $p = 0.1243$ (one-tailed)

Power = 56%

Table 4.5   Treatment results (2)

- **For patients who positively responded**

	Flumazenil	Placebo	Total
Non positive responders	5	11	16
Positive responders	8	1	9
Total	13	12	25

Fisher's exact test: $p = 0.0079$ (one-tailed)

Power = 91.5%

Since initially the patients were in different stages of HE, subgroup analysis (Table 4.6) of the treatment outcomes according to the strata -- HE stages, is necessary. This result with the p value of 0.028 is consistent with the former Fisher's exact test, showing the significant difference of the positive response in the 2 groups.

Table 4.6   Subgroup analysis

- For "effective"-entity

HE Stage = 2	Flu	Pla	Subtotal	
Non-effectiveness	4	9	13	Fisher's exact
Effectiveness	3	0	3	(1-tailed)
Subtotal	7	9	16	p = 0.063

HE Stage = 3	Flu	Pla	Subtotal	
Non-effectiveness	5	3	8	
Effectiveness	0	0	0	
Subtotal	5	3	8	p NA

HE Stage = 4	Flu	Pla	Subtotal	
Non-effectiveness	1	0	1	
Effectiveness	0	0	0	
Subtotal	1	0	1	p NA

M-H Summary Chi-square = 2.20   p =0.138

- For "positive response"-entity

HE Stage = 2	Flu	Pla	Subtotal	
Non positive responders	3	8	11	Fisher's exact
Positive responders	4	1	5	(1-tailed)
Subtotal	7	9	16	p = 0.077

HE Stage = 3	Flu	Pla	Subtotal	
Non positive responders	2	3	5	Fisher's exact
Positive responders	3	0	3	(1-tailed)
Subtotal	5	3	8	p = 0.179

HE Stage = 4	Flu	Pla	Subtotal	
Non positive responders	0	0	0	
Positive responders	1	0	1	
Subtotal	1	0	1	p NA

M-H Summary Chi-square = 4.23   p value = 0.028

Flu = Flumazenil group   Pla = Placebo group
NA = non available (cannot compute)
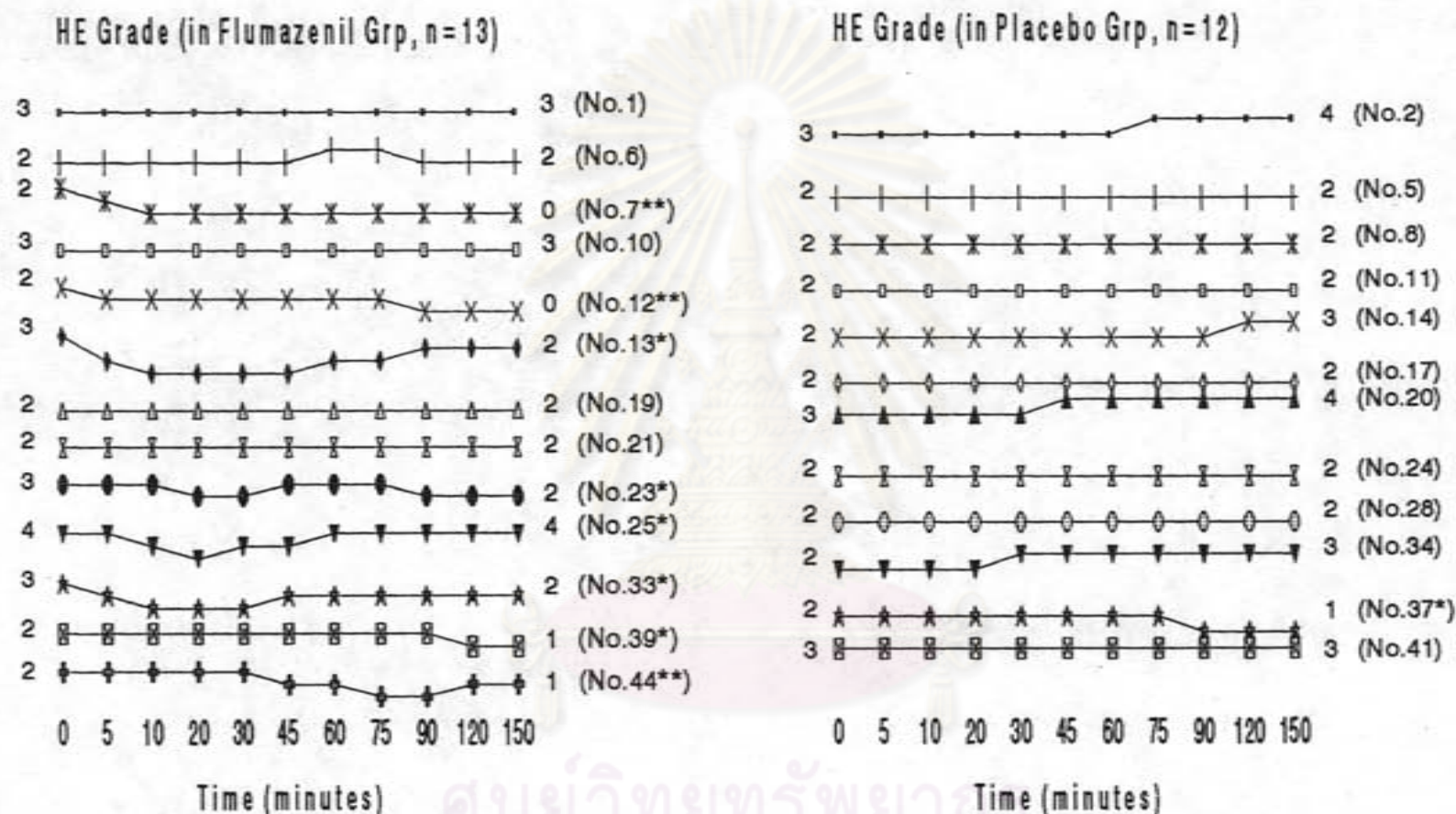
4.2.3 Clinical Patterns and Long-term Outcomes

The proportions and their changes of the different stages of HE in 2 groups at several timepoints of the trial, comparing with the initial stages, are pragmatically listed in Table 4.7. It was found that more than half of the responses to flumazenil (in the lower left part of the corresponding single table) initiated early within 10 minutes. However, there are several cases, 4 in the placebo and 1 in flumazenil group, entering into the upper right part, indicating that their stages were worsening in that period. Moreover, some patients, though they responded to the treatment at certain timepoints, however, they fell down to the previous or more severe stages at the following points (Figure 4.1).

These phenomena suggested that the changing patterns of the clinical stages of HE of these patients were not consistent or stable along with one-dimension route.

Table 4.7 Distribution of HE stage at different timepoints

Flumazenil group (n=13)

10 minutes after treatment

I*		0	1	2	3	4
n	1					
i	2	1	1	5		
t	3	1	1		3	
	4				1	

30 minutes after treatment

I		0	1	2	3	4
n	1					
i	2	1	1	5		
t	3	1	1	1	2	
	4				1	

60 minutes after treatment

I		0	1	2	3	4
n	1					
i	2	1	2	3	1	
t	3		1	1	3	
	4				1	

150 minutes after treatment

I		0	1	2	3	4
n	1					
i	2	2	2	3		
t	3			3	2	
	4				1	

Placebo group (n=12)

10 minutes after treatment

I		0	1	2	3	4
n	1					
i	2			9		
t	3				3	
	4					

30 minutes after treatment

I		0	1	2	3	4
n	1					
i	2			7	2	
t	3				3	
	4					

60 minutes after treatment

I		0	1	2	3	4
n	1					
i	2			7	2	
t	3				2	1
	4					

150 minutes after treatment

I		0	1	2	3	4
n	1					
i	2		1	6	2	
t	3				1	2
	4					

* Init = initial stage of HE

HE Grade (in Flumazenil Grp, n=13)

HE Grade (in Placebo Grp, n=12)

0 5 10 20 30 45 60 75 90 120 150

Time (minutes)

Figure 4.1 Changing patterns of HE stages of patients in both groups during intensive observation period

The "X-axis" indicates the timepoints after the commencement of the trial (0 - 150 minutes).

The labels in the left "Y-axis" indicate the HE stage of one patient (No. corresponding to the right) at the baseline (0 min).

The labels in the right "Y-axis" indicate the HE stage of that patient at the end (150th min) of the trial and his record No..

** = effectively improved and positively responded   * = positively responded

From Figure 4.1, in the treatment group, besides that the HE stages of 4 patients (No., 10, 19 and 21) didn't change and 2 patients (No. 7 and 12) steadily decreased their HE stages to the normal level, several pieces of 2-dimensional changing patterns could also be identified that some of the positive-responders (No. 13, 23, 25, 33 and 44) had their grades of HE increasing as compared to the previously decreased grades at certain timepoints in the intensive observation period (150 minutes). Of these 5 responders, none of the final stages was worse than that of the baseline (initial timepoint); moreover, 3 patients (No. 13, 23 and 40) were in the better stages at the end of the intensive observation period, and one patient (No. 44) was still considered as an effectively improved case.

On the other hand, in the control (placebo) group, 7 patients didn't show any changes in HE stage, and 4 patients (No. 2, 14, 20 and 34) had their grades of HE worsened, comparing with their baseline levels; only one patient (No. 37) appeared late-onset positive response (after 75 minutes).

More than half (5/8) of the positive responders in the treatment group improved clinically within 10 minutes. The maintenance time, though, varied widely,

from 20 minutes (No. 25) to no worsening at all (No. 7 and 12) during that 150 minutes and even after that period. Mostly the favorable pharmaceutical duration of flumazenil in this study was about 1 hour. If accounting the "residual" effect of this agent, the so-called "responsive" time duration was about 2 to 4 hours.

Focusing upon the flumazenil group, attempts have been tried to search for certain characteristics of the positive responders (8 cases), which were supposed to be different from those of non-responders (5 cases). However, none of these independent variables have been found to be statistically significant, such as age, sex, etiology of cirrhosis, duration of cirrhosis and HE, HE stage at baseline, Child-Pugh grades or scores and their components.

The changing patterns of the mental status of these patients during the following-up period are schematically presented in Figure 4.2 and 4.3 (only for their first 9 days after the trial). Three effectively-improved patients (No. 7, 12 and 44) maintained the HE stage in 0 or 1 during the following time in the ward. Two of them were discharged after 7 and 9 days. The remaining one (No. 44) was still in the ward waiting for the operation with quite good condition of physical and

HE Grade (in Flumazenil Group , n = 13)
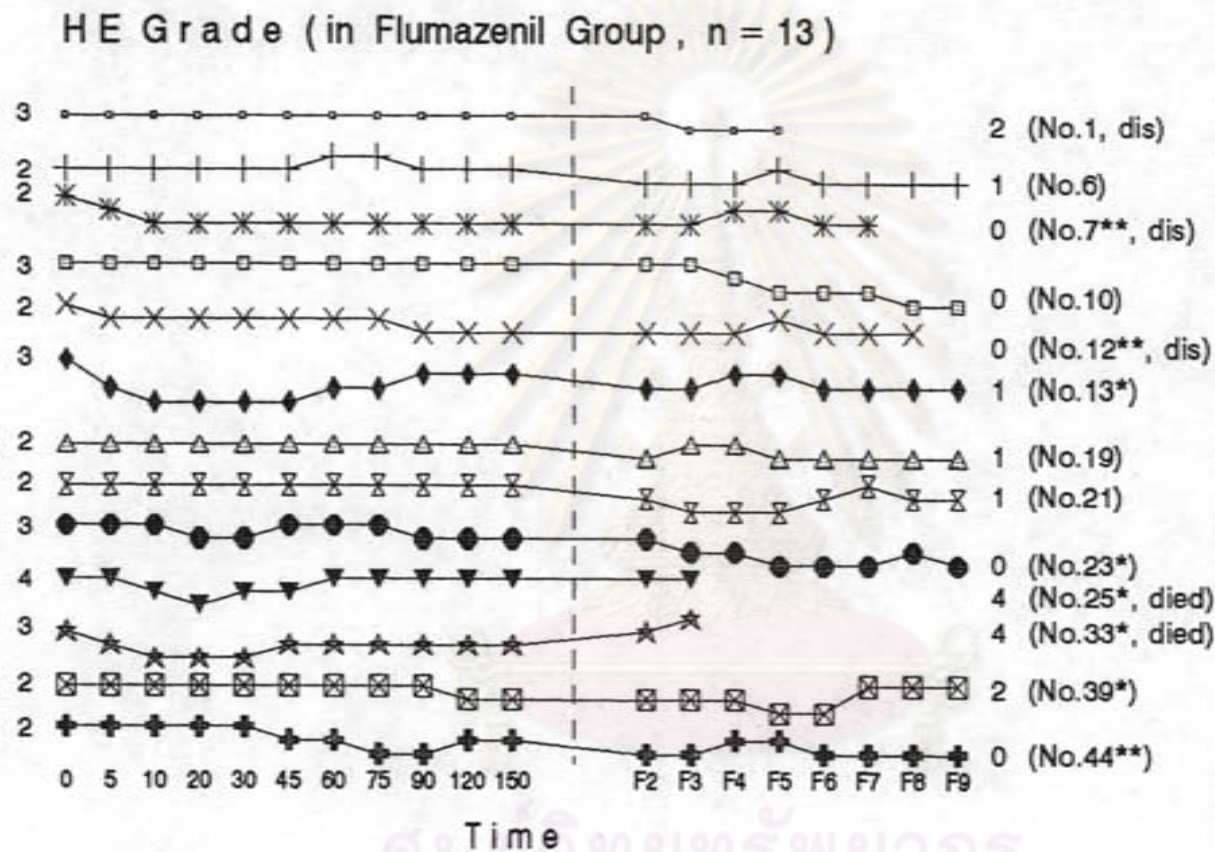
Figure 4.2   Changing patterns of HE stages of patients in the treatment group during the first 9 days after the trial

The "X-axis" indicates the timepoints after the commencement of the trial (0 - 150 minutes, and the following 2nd to 9th day <F2 - F9>).

The labels in the left "Y-axis" indicate the HE stage of one patient (No. corresponding to the right) at the baseline (0 min).

The labels in the right "Y-axis" indicate the HE stage of that patient at the 9th day or at the death or discharge day, and his recording No..

** = effectively improved and positively responded   * = positively responded

HE Grade (in Placebo Group, n = 12)
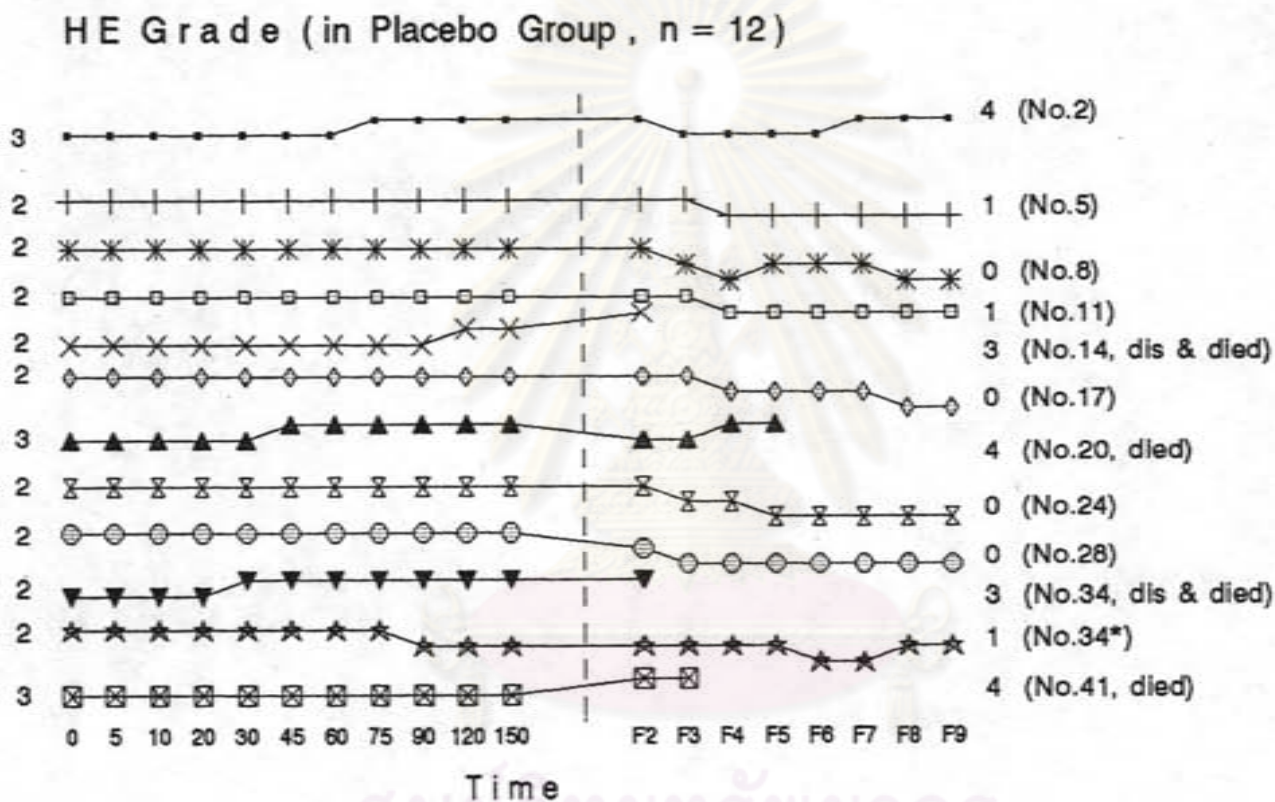
Time

Figure 4.3   Changing patterns of HE stages of patients in the control group during the first 9 days after the trial

The "X-axis" indicates the timepoints after the commencement of the trial (0 - 150 minutes, and the following 2nd to 9th day <F2 - F9>).

The labels in the left "Y-axis" indicate the HE stage of one patient (No. corresponding to the right) at the baseline (0 min).

The labels in the right "Y-axis" indicate the HE stage of that patient at the 9th day or at the death or discharge day, and his recording No..

** = effectively improved and positively responded   * = positively responded

mental status at the moment of analyzing the data recently. Except the 2 patients (No. 25 and 33) who died in the 3rd day after the trial and the 1st patient who were transferred to another hospital in the 6th day with the HE stage of 2, the other patients in this treatment group regained their mental normal function in the following 2nd to 5th day, half of those showed wavelike HE stages during their inward courses. There were no difference, comparing with the treatment group, in face, in the pattern of regaining the normal clinical HE stage in the control group, mostly in the 2nd to the 4th day, except No. 20 who died in the 5th day or No. 14 and 34 who appeared the worsen grade-changing in the following day of the trial and both were discharged at the HE stage of 3 by the strong requirement of their family. Telecommunication approved their passing away within one week after discharge. The only one positive responder (No. 37) in the control group, who showed a late-onset positive change after 75 minutes, was discharged 3 weeks later with normal mental condition.

In each treatment and control group, 3 patients died respectively in the ward. Those who died in the treatment group all had shown the positive responding reaction to flumazenil. Two died within 2 days of the trial because of severe liver function failure (No. 25)

and another episode of variceal bleeding (No. 33), their HE stages were in 3 and 4 after the trial. Another patient (No. 39) died 2 months later of an assumed cause of intracranial hemorrhage. As in control group, 3 patients (No. 41, 20 and 2) died in the 2nd, 4th and 8th day later with the causes of severe variceal bleeding or electrolytes-acid-base disturbance.

Death is the final unfavorable outcome. In this study, 6 patients died during their admission period. If taking account of 2 cases who died within one week after their "self-requiring" discharge, total 8 patients, 3 in the treatment group while 5 in the control group, should be considered as their death in the ward.

Attempts have been taken to search for the factors which could predict the final long-term outcome -- death. It was found that in the treatment group, there was no significant relation between the death and the positive response of flumazenil (p=0.231, Table 4.8).

Table 4.8   Death rate comparison in the treatment group

	Death ?		
	yes	no	Total
Positive responders	3	5	8
Non-positive responders	0	5	5
Total	3	10	13

Fisher's exact test   p = 0.231 (2-tailed)
Power = 28.8%

Comparing the whole treatment and control group, even the subgroups among these 2 groups (by HE stage or Child-Pugh grade, Table 4.9), statistically, there was not significant difference of the death rate, implying that flumazenil might not be able to change or decrease the risk of death of the patients who received this agent.

Table 4.9   Death rate and relative risks comparison between the 2 groups

	Death yes	Death no	R.R.	95% C.I. of R.R.	p value
For all patients in 2 groups					
Flumazenil group	3	10	0.55	0.17 - 1.83	0.411
Placebo group (ref.)	5	7	1.00		
◊ For patients in HE Stage 2					
Flumazenil group	1	6	0.64	0.07 - 5.73	1.000
Placebo group (ref.)	2	7	1.00		
◊ For patients in HE Stage 3 or 4					
Flumazenil group	2	4	0.33	0.11 - 1.03	0.167
Placebo group (ref.)	3	0	1.00		
♦ For patients in C-P Grade A or B					
Flumazenil group	0	6	NA	NA	1.000
Placebo group (ref.)	1	6			
♦ For patients in C-P Grade C					
Flumazenil group	3	4	0.54	0.20 - 1.40	0.293
Placebo group (ref.)	4	1	1.00		

R.R. = relative risk   ref. = reference level   C.I. = confidence interval
C-P Grade = child-Pugh Grade

Among the other independent variables at the baseline, the stage of HE and Child-Pugh Grade seemed to show the significance, in some sense (Tale 4.10). The other components of Child-Pugh Grade, such as albumin (p=0.57), bilirubin (p=0.97) and prothrombin time prolonged (p=0.97), did not have such significance individually.

Table 4.10   Relative risks for death of HE patients

		Death yes	Death no	R.R.	95% C.I. of R.R.	p value
♦ Flumazenil Group						
HE Stage	2 (ref.)	1	6	1.00		
	3 or 4	2	4	2.33	0.27 ~ 19.80	0.559
♦ Placebo Group						
HE Stage	2 (ref.)	2	7	1.00		
	3 or 4	3	0	4.50	1.33 ~ 15.28	0.045
Both Groups						
HE Stage	2 (ref.)	3	13	1.00		
	3 or 4	5	4	2.96	0.91 ~ 9.60	0.087
◊ Flumazenil Group						
C-P Grade	A or B (ref.)	0	6	1.00		
	C	3	4	NA	NA	0.192
◊ Placebo Group						
C-P Grade	A or B (ref.)	1	6	1.00		
	C	4	1	5.60	0.87 ~ 36.22	0.072
Both Groups						
C-P Grade	A or B (ref.)	1	12	1.00		
	C	7	5	7.58	1.09 ~ 52.92	0.011

R.R. = relative risk   ref. = reference level   C.I. = confidence interval
C-P Grade = Child-Pugh Grade

Table 4.11   Analysis of eligible repeated episodes

Serial No.	Crossed	Effective?		Positive?	
		Flumazenil	Placebo	Flumazenil	Placebo
6, 22*	Yes	-	-*	-	-*
7, 18*	Yes	+	+*	+	+*
13, 43*	Yes	-	-*	+	-*
8, 27*	No		- -*		- -*
10, 29*	No	- -*		- -*	

* = not the first episode of HE in this trial and not included in the standard analysis
\+ = effective or positive reaction to flumazenil or placebo
\- = no reaction to flumazenil or placebo

One patient, No. 7 (or No. 18 in the 2nd enrollment), not only had been improved effectively by flumazenil in the first allocation to the treatment group, but also showed effective improvement when in the second allocation to the control group. He was discharged with normal mental function twice.

The only discordant pair among the 3 was in Serial "13, 43" that flumazenil could induce positive response while placebo failed. There was no difference if the reaction was evaluated by the definition of "effectiveness". Obviously, such a small (3 pairs) of pragmatic cross-over trial could not be tested by certain

statistical tests, such as McNemar test to draw some inferences.

Those 2 patients who had been allocated in the same group both showed no change of HE stages during the twice enrollment, whatever the group they were in. They got well in the 2nd and 3rd day, but appeared wavelike changing pattern in the following days, and finally were discharged with normal brain function.

4.4   Analysis for the Un-eligible Patients

Seven un-repeated cases were finally excluded, though they had been enrolled initially at baseline. According to the eligibility criteria, they were suffering from another sudden episode of variceal bleeding (No. 3, 26 and 30), endstage of liver cancer (No. 4 and 36) or kidney cancer (No. 9) with anuria, or severe electrolyte disturbance (No. 31).

Comparing with the eligible patients (25 cases), these un-eligible ones (7 cases) exhibited no statistically significant difference in age, sex, primary liver diseases, history of shunting or history of HE. Neither has been found the difference of the present HE duration or precipitating factors of HE at the baseline. The principle clinical manifestation, disturbed mental

status and its stage, was still comparable between the eligible and un-eligible cases (p=0.446, Table 4.12). The distribution of hepatic carcinoma of the eligible patients (24 no/1 yes) and the un-eligible ones (5/2) was not distorted statistically, either (p=0.113). The significance existed in the index of liver function -- Child-Pugh Grade and Score. All the un-eligible patients were in Child-Pugh Grade C (p=0.047) and the raw scores were larger than the eligible (11.86 ± 0.70 vs. 9.20 ± 0.48, p=0.011). The components of Child-Pugh grade, except HE (p=0.446) and ascites (p=0.35), were also demonstrating the significance, such as albumin (p=0.016), total bilirubin (p=0.011), prothrombin time prolonged (0.0257) or prothrombin activity (p=0.027).

Table 4.12   Comparison of the characteristics and therapeutic outcomes of the eligible and the un-eligible patients

	Eligible	Un-eligible	p value
Group allocation (Flu / Pla)	13 /12	3 / 4	~ 1.000
HE stages (2 / 3 / 4)	16 / 8 / 1	3 / 3 / 1	0.466
Child-Pugh grades (A / B / C)	2 / 11 / 12	0 / 0 / 7	0.046
Child-Pugh raw scores	9.20±0.48	11.86±0.70	0.011
"Effectively improved" (Y / N)	3 / 22	1 /6	~ 1.000
"Positive response" (Y / N)	9 / 16	2 / 5	~ 1.000
Death (Y / N)	8 / 17	5 / 2	0.091

The therapeutic outcomes of un-eligible patients were showed in Table 4.12 and compared with the eligible. More death cases obviously was the characteristic, but no statistical significance (p=0.091) with power of 46%.

There were 3 patients who were excluded after the randomization because another sudden episode of severe variceal hemorrhage broke out respectively with an unstable hemodynemic state and emergent rescue therapies were conducted during the intensive observation period. These critical facts made the HE-stage evaluation very difficult or impossible in a formatted way as described before. Case No. 26 was allocated in the treatment group with the baseline HE stage of 2, while the other 2 in the control group with HE stages of 2 (No. 2) and 3 (No. 30). Only Case No. 3 died 5 days after the trial in the ward, the other 2 were discharged later with the regained mental status.

If they (No. 2, 26 and 30) were all considered as the failure cases (not effective nor positive responding) and collapsed into the formal eligible 25 patients, re-analysis of the data (Table 4.13) indicated that the statistical test results for the therapeutic outcomes defined as the effective or positive responders were not

altered, compared with the "standard" analysis (Table 4.4, 4.5 and 4.8).

Table 4.13 Re-analysis of the therapeutic results after including 3 patients who were previously excluded

	"Standard" analysis		Analysis including those who were excluded	
Allocation	Trt grp 13	Pla grp 12	Trt grp 14	Pla grp 14
⇒ Effective responders	3	0	3	0
p value	0.1243		0.1111	
power	56.0%		57.9%	
⇒ Positive responders	8	1	8	1
p value	0.0079		0.0063	
power	91.5%		92.0%	
⇒ Death	3	5	3	6
p value	0.4110		0.4197	
power	23.1%		22.2%	

Trt grp = Treatment group, Pla grp = Placebo group

4.5 PSE Index

A semi-quantified measure composing five weighted factors was supposed to evaluate the severity of HE. However, in this research, this Index hasn't been fully accomplished. No patient has been serially tested the

change of EEG. Blood ammonia concentrations were only checked at the baseline and the end of the intensive observation, and the following 2nd, 5th and 9th day. Some data were missing. There was no change of the ammonia level in this 150 minute period. While in the follow-up period, a trend (data not shown) could be found that ammonia level gradually decreased. For the HE patient in stage of 3 or 4, it is impossible to process psychometric test. Only the patients with stage 2 or lower could perform one of the components of PSE Index -- NCT. The time of accomplishing it varied, however, the shortening trend was consistent with the improvement of clinical stage (data not shown here). It was also difficult to test asterixis for the patient with uncooperative apathy or coma in stage of 3 or 4. For the patients who had been examined asterixis, there were little changes of the grade of asterixis during the intensive observation period. Therefore, the Index only remained the most important and heavy weighted component -- mental status, always available to make grade of HE. This situation made it impractical to process PSE Index as an assistant measure for HE, especially in fast-onset therapeutic trials.