MELSMON CLINICAL TRIAL ON INSUFFICIENT MILK SECRETION

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Abstract

Mother's milk has always been the best nutrition for newborn which stands true till today. But after giving birth, cases of low milk secretion has made us, the obstetrician, worried.

The Phenomenon of milk secretion in human being is complicated and involved various aspects, despite numerous research and theories, many things are still unexplained.

The contributing factors are mammary gland's development level, breast's shape, nipple's shape, the state of mothers nutrients, appetite, sleeping, mental and physical stress, the relation between baby's sucking force and nipple stimulation, etc.

Therefore to encounter the inadequate milk secretion many methods have been adopted.

In the year of Showa 31, Melsmon launched a product with the main ingredient as the substance extracted from placenta .It has been used to improve human's milk secretion.

Melsmon is an injection liquid, 1 ampoule (2ml) contain 100 mg of water soluble villous lymphocyte extracted from frozen fresh placenta by using a peculiar method .It is known to consist of all sorts of Amino Acid, Nucleic acid substances, mineral etc. It is also believed to contain other unknown effective substances.

Human Placenta is an organ where fetus can grow amazingly in only 10 months. Many research have been carried out on its effectiveness and usage since long ago .In Herbal medicine it is known as "Shikasha" (*placenta essence in Chinese*)(Listed in "Honzou Koumoku" (*compendium of materia medica*)" " and "Chinese Medicinal Dictionary") .

Recently more attention are given to placenta especially after γ Globulin which is believed to be the answer to immunization is being extracted.

Mammals including herbivore instinctively eat their placenta after it is delivered and it is found that it has contributed to the secretion of breast milk. Due to this placenta is believed to have the milk flow-promoting characteristic.

There are many literatures regarding Placenta extracts and milk secretion effect. It is effective when milk secretion is decreasing because it is physiologically activated. This is due to the secondary effect at the center which controls the hormon secretory function.

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As a matter of fact, Placenta based medicine Melsmon which has obtained approval from the Ministry of Health and Welfare, has been in the market since 25 years ago and has shown numerous clinical effect. It has no side effect and until today there is no claim of any problem due to its usage.

Acute and chronic toxicity test ,Teratogenic test and Anaphylaxis test on animal have also shown that it is safe .*1

What is required to be done after this is to clarify completely the application mechanism.

By checking the Melsmon clinical effect, it will also lead us to understand the application mechanism which will finally clarify the contributing factor for the phenomenon of milk secretion.

From this perspective we have conducted a inter-centric study to compare the effectiveness, safety and the usefulness of both Melsmon and Placebo in milk secretion.

This experiment was conducted for a period of 9 month, from March till November of 1980.

METHOD

1. Patients

The subject patients were mothers who had given birth at 8 hospitals as listed in **Table 1**. They were spiritually and physically stable.

But persons with the following conditions were excluded.

1) Person with adequate milk secretion
2) Person that has no intention to breast feed
3) Person with mammary gland problem
4) Person detected with heart, liver, kidney or others serious illness.
5) Person with premature or abnormal delivery.
6) Person that undergone caesarean.
7) Others who had been considered unsuitable by the in-charge Doctor.

2. Medication for the test

1) Type of medicine

M-1001 : Melsmon (1 ampule (2ml) contain 100 mg of water soluble villous lymphocyte)

M-1002 : Isotonic Sodium Chloride Solution (comparison medicine)

Table 1

Participating Institution (In Japanese alphabetical order)

Omiya Red Cross Hospital	Gynecology
Oomori Red Cross Hospital	Gynecology
Kanto Central Hospital	Gynecology
Social Insurance Central Hospital	Gynecology
Tokyo Sanraku Hospital	Gynecology
Tokyo Welfare Annuity Hospital	Gynecology
Capital Otsuka Hospital	Gynecology
Yamanashi Central Hospital	Gynecology

The above 2 medicines are inserted into same color, same shape and same amount ampoule with same label. 1 box is filled with 5 ampoule

2) Distribution of medicine

The distribution of medicine is carried out by controller .The same quantity of Melsmon and Placebo in each group of medicine is distributed to each institute.

3) Supply of medicine

The medicine is supplied according to the sequence no. of distributed medicine.

The medicine is supplied 1 ampoule once a day. It is injected under the patient skin continuously from day 1 to day 5.

4) Combined medicine

Unless it is necessary, combined medicine shall not be applied. In case it is necessary, the responsible doctor should record it accordingly.

3. Evaluation

1) Checking item before starting the test

Patients' height, weight, age, marriage, occupation, delivery condition, menstrual status, medical history, complication and general clinical test etc. are recorded.

2) Evaluation of delivery condition

Milk secretion condition table is filled up with milk amount (feeding amount + left over), Infant weight, infant health status and the progressing from day 0 to day 7.

3) Overall Evaluation

The effectiveness, the safety and the usefulness after third day of supply, (5-7 days after discharged) Are being checked via following methods:

*1 refer Foundation and Clinical Vol 12 .No 12 1978

(1) To determine the effectiveness test, milk secretion volume(feeding volume + left over) is the main criteria. It is being conducted after day 3, day 5 and day 7. It is combined with infant weight progress and condition of the lactation after 1 month. The rate is divided into 5 levels based on infant weight increase "Very effective" , "Effective", "Slightly effective" , "not effective" and "getting worse"

(2) Safety is judged by responsible doctor based on the following 4 levels "Totally no side effect" "Mild side effect and continue treatment", "Require appropriate treatment for the side effect" and "severe side effect and require stopping supply".

(3) Usefulness is judged by the responsible doctor by considering the efficacy and safety and is based on the following 5 levels, "very useful", "Useful", "Quite useful", "Hard to say" and "Not advisable".

4) Side Effect

The side effect is checked for every prescription. If there is any side effect, it shall be recorded (Occurring day and time, severity, treatment etc). If details were required it had to be recorded in remark column .The doctor then shall judge whether continuity of the test is appropriate.

Before and after 5 days of supply the infant is diagnosed for abnormalities and it is recorded.

5) General Clinical Test

Before prescription and after prescription (3 weeks after) red blood count, white blood count, hemoglobin, hematocrit value, GOT, GPT, bilirubin, urine sugar level, Urine protein, blood pressure and pulse are measured.

If any abnormality found after prescription investigation shall be carried out and to be recorded.

6) Stop prescription

During the test, if the symptoms worsen and the in-charge Doctor judge that the test shall not be continued the prescription would be stopped.

If it is stopped, the reason shall be recorded into the case card.

When prescription is stopped due severe side effect the in-charge Doctor shall immediately report to the Controller.

7) Drop out Guideline

Person with any of the following cases had to be dropped out;

(1) Supply has not reach 2/3 of standard dosage.

(2) The data recording is obviously insufficient

Table 2 No. of Illness cases and no. of exclusions

		Melsmon (%)	Placebo (%)	Total (%)	
No. of Illness case		80 (50.6)	78 (49.4)	158 (100)	
No .of Exclusions		13 (8.2)	10 (6.4)	23 (14.6)	χ_2= 0.148 N.S
Actual no. of Analysis		67 (42.4)	68 (43.0)	135 (85.4)	
Reason of Exclusion	Stop supply	11	9	20	
	Others *	2	1	3	

* It is excluded as per execution of cubes storage, phototherapy etc due to pneumonia

(3) Test was unable to continue due to severe side effect.

However side effect drop out cases shall be added into the safety list and symptom worsen drop out is to be added into usefulness list and are subjected to be evaluated.

(4) Others, person who has been decided to be dropped out in a meeting.

4. Guideline of analysis's exclusion

The following cases are excluded from the statistical analysis.

1) Non target (refer previous page ,topic 1)
2) When serious complication occurred.
3) Drop out cases (refer previous page ,3-7)

5 Statistical analysis

Melsmon group and Placebo group are analyzed and compared using χ2-Test, 2 x C segregation experiment method, exact-test of Fisher and U-test of Mann Whitney.

Result

1. No. Of illness case

There are total of 158 cases accumulated from 8 institutions (**Table 1**) and 23 cases are being excluded (**Table 2**) based on Regulation of exclusion from analysis (4), statistical analysis is being carried out on the remaining 135 cases.

There is no significant difference to show that Placebo group has more exclusion cases than Melsmon group in statistical analysis example.

Table 3 Patients age distribution

Age	Melsmon	Placebo	Total	
~19	0	1 (0.8)	1 (0.8)	
20~24	12 (8.9)	14 (10.4)	14 (10.4)	$\chi 2=3.147$
25~29	38 (28.1)	38 (28.1)	76 (56.2)	N.S
30~34	15 (11.1)	15 (11.1)	30 (22.2)	
35~	2 (1.5)	0	2 (1.5)	
Total	67 (49.6)	68 (50.4)	135 (100)	
Average	26.9 ± 0.38*	27.5 ± 0.37 *		

Unit: No of persons ( ) : % * S.E.

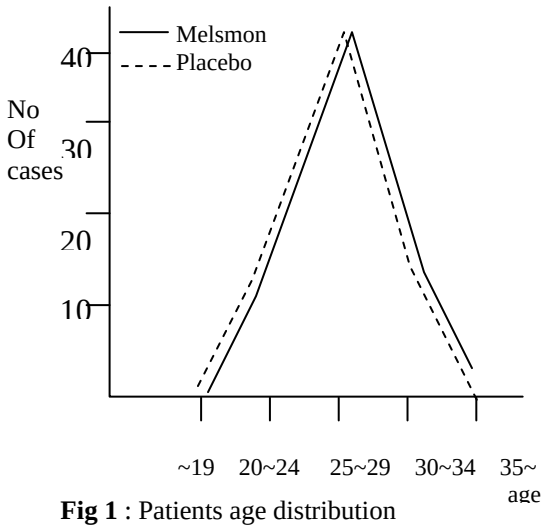

Fig 1 : Patients age distribution

Exclusion is 15% from the total of 158. This figure is normal for this kind of test and it is not considered as problematic issue.

Most of the excluded cases were due to excessive of milk secretion after 1st and 2nd day of confinement and it is not a special case.

2. Age Distribution

1) Age distribution

Age distribution is as shown in **Table 3**. There is no significant difference shown in between Melsmon group and Placebo group. Besides, there is no significant difference shown in the average age of both groups.

Among the 135 cases used for statistical analysis, age 97.7% comprise age 20~34 and from here 56.3% comprise age 25-29, which is more than half (other 2.3% are below 19 and above 35) .

Case of late first childbirth, age 30 above is 23.7 % and it is 11.2% above the general average. Age distribution is shown in Fig. 1

3. Evaluation Criteria

1) Effectiveness Evaluation

The effectiveness judgment of the medicine supplied by the in charged doctor is shown in **Table 4**. There are significant differences between Melsmon and Placebo group.

More patients from Melsmon group have judged "very effective " compare to patients from Placebo group.($\rho < 0.01$)

Melsmon group have rated "very effective" 17.9 % and " effective" 50.7% , total of 68.6% ,which is significantly different compared to Placebo group.($\rho < 0.01$)

(1) Effect of milk secretion in late first childbirth women

The effectiveness for women who had their first childbirth late (age 30) and believed to have little milk secretion is shown in **Table 5**.

Total of "very effective" and "Effective" for Melsmon group is 64.7%, much higher compared to Placebo group ($\chi 2=4.783$; $\chi 2$ (1, 0.05) = 3.84)

(2) Milk Secretion Volume

The changes of milk secretion volume in Melsmon group and Placebo group are shown in Fig 2.The daily average is shown in **Table 6**.

As shown in **Table 6**, between Melsmon group and Placebo group there is significant difference after 5th day of confinement. The difference is bigger after 7th day. ($\rho < 0.01$)

In **Table 7**, the volume of milk secretion has been divided for every 150ml, and the change is shown in **Fig 3**.

By categorizing the effectiveness to more than 300ml and 300 ml and less, after 7 days of confinement a significant difference can be seen between Melsmon and Placebo group. ($\chi 2=9.217$; $\chi 2$ (3, 0.05) = 7.81)

Table 4 Effectiveness in milk secretion

	Very Effective	Effective	Slightly Effective	Not Effective	Worse	Total
Melsmon	12 (17.9)	34 (50.7)	8 (12.0)	13 (19.4)	0	67 (100)
Placebo	1 (1.5)	14 (20.5)	27 (39.7)	26 (38.3)	0	68 (100)
Total	13	48	35	39	0	135

$\chi 2=32.285$; $\chi 2(4, 0.01) = 13.28$ Unit : no of person , ( ) :%

Table 5 Milk secretion effect on late first childbirth women

	Very Effective	Effective	Slightly Effective	Not Effective	Worse	Total
Melsmon	0	11 (64.7)	1 (5.9)	5 (29.4)	0	17 (100)
Placebo	0	3 (20.0)	5 (33.3)	7 (46.7)	0	15 (100)
Total	0	14	6	12	0	32

(Above 30 years old), Unit : no of person , ( ) :%

Table 6 Milk secretion amount (daily) Average

		No.of patient	Mean ± SD	t Test
Day 1	Melsmon	67	13.06 ± 36.63	t = 1.02
	Placebo	68	7.75 ± 22.10	N.S
Day 2	Melsmon	67	64.82 ± 81.45	t = 1.59
	Placebo	68	45.25 ± 59.36	N.S
Day 3	Melsmon	67	144.24 ± 118.69	t = 1.54
	Placebo	68	114.94 ± 101.07	N.S
Day 4	Melsmon	67	224.03 ± 160.19	t = 1.87
	Placebo	68	177.56 ± 126.15	N.S
Day 5	Melsmon	67	275.63 ± 159.15	t = 2.06
	Placebo	68	223.256 ± 135.47	$0.01< \rho <0.05$
Day 6	Melsmon	67	328.12 ± 190.09	t = 2.57
	Placebo	68	253.04 ± 146.57	$0.01< \rho <0.05$
Day 7	Melsmon	67	345.39 ± 190.22	t = 2.82
	Placebo	68	260.84 ± 156.71	$\rho <0.01$

2) Side effect and safety

During the prescription, illnesses that have been judged by the in-charged doctor as side effect is listed in **Table 8**. No significant difference is seen between Melsmon group and Placebo group.

And the illnesses in both cases are minor illness and they have not interrupted the continual of the prescription.

Furthermore, the side effects to the newborn from both Melsmon and Placebo groups were not detected at all.

From **Table 9**, it is observed that there were no case of "Stop Prescription due to side effect" and "specific treatment is required". The only case detected were "minor side effect continue prescription" and "No side effect". Therefore from safety aspect no differences were noted between Melsmon and Placebo group.

Table 7 Classification in terms of milk secretion amount

		Less than 150ml	150-300ml	300-450ml	Above 350ml	Total
Melsmon	Day 1	65 (97)	2 (3)	0 ( )	0 ( )	67
	Day 2	61 (91)	4 (6)	2 (3)	0 ( )	(100)
	Day 3	41 (61)	16 (24)	9 (13)	1 (1)	
	Day 4	28 (42)	22 (33)	9 (13)	8 (12)	
	Day 5	15 (22)	27 (40)	13 (19)	12 (18)	
	Day 6	11 (16)	22 (33)	15 (22)	19 (28)	
	Day 7	10 (15)	17 (25)	20 (30)	20 (30)	
Placebo	Day 1	68 (100)	0 ( )	0 ( )	0 ( )	68
	Day 2	62 (91)	6 (9)	0 ( )	0 ( )	(100)
	Day 3	46 (68)	18 (26)	4 (6)	0 ( )	
	Day 4	32 (47)	24 (35)	10 (15)	2 (3)	
	Day 5	25 (37)	24 (35)	15 (22)	4 (6)	
	Day 6	21 (31)	21 (31)	20 (29)	6 (9)	
	Day 7	20 (29)	22 (32)	18 (27)	8 (12)	

Divided to each 150ml , Unit : Person ,( ) : %

Table 8 Side effect symptoms

	Stomach problem	*Dry Mouth*	*Red and pain at inject-ed area*	*total*	
Melsmon	5	7	6	18(16)	2=0.234
Placebo	3	3	4	10 (9)	N.S
Total	8	10	10	28 (25)	

( ) : Person , Unit : cases

3) Usefulness

Usefulness is judge by the in-charged doctor due to the effectiveness and the safety of the medicine. It is shown in **Table 10**, significant difference can be seen between Melsmon and Placebo group. ($\rho <$ 0.01)

The total % of “Very useful” and “Useful” in Melsmon group is 68.7% and Placebo group is only 22.1% , huge difference is noted ($\rho <$0.01)

4) Clinical Inspection Value.

There is no difference found between Melsmon and Place clinically meaningful at various clinical values before and after prescription.

SUMMARY

Since the maternal feeding is rediscovered, many efforts have been put in breast care. But we need to admit that the awareness of breast feeding has not come to the satisfactory level.

Treatment is the best way to improve milk secretion; Melsmon which has been used to improve milk secretion is one of the interesting medications and has been considered beneficial.

It was from this viewpoint that this clinical test was conducted and the results shown in earlier section.

Previously there was no method to evaluate the effect on milk secretion but we have gone through all the difficulties and finally we think that we are able to evaluate it by measuring the volume of milk secretion.

The following factors are important in evaluating the milk secretion status, Tense level of the breast, Volume of milk secretion, Progress of infant weight and etc. The mechanism of milk secretion depend so much on psychological factor but the evaluation however has been successfully done by comparing the effect result on Melsmon group and Placebo group.

The effectiveness evaluation on milk secretion is shown in **Table 4**. The total rating of” Very effective” and “effective” for both Melsmon and Placebo are 68.6% and 22.0%, a big difference is noted .

Table 5 shows the effectiveness for women age 30 and above which are thought to have little milk secretion, The total rating of” Very effective” and “effective” for both Melsmon and Placebo are 64.7% and 20.0% , also noted to be a big difference.

Table 9 Safety Evaluation

	No Side Effect	Minor side effect, prescription continue	Side effect require specific treatment	Prescription stop due to side effect	Total
Melsmon	51	16	0	0	67
	(76.1)	(23.9)	( )	( )	(100)
Placebo	59	9	0	0	68
	(86.7)	(13.3)	( )	( )	(100)
Total	110	25	0	0	135

$\chi 2=2.535$N.S , Unit : person ( ) :%

Table 10 Evaluation for Usefulness

	Very useful	Useful	Quite useful	Not sure	Not recommended	Total
Melsmon	8	38	8	13	0	67
	(11.9)	(23.9)	(11.9)	(19.4)	( )	(100)
Placebo	1	14	27	26	0	68
	(1.5)	(20.6)	(39.7)	(38.2)	( )	(100
Total	9	52	35	39	0	135

$\chi 2=31.1645$; $\chi 2(4, 0.01) = 13.28$ Unit : no of person , ( ) :%

Statistic shows that percentage of women having late first childbirth is 11.2%, but this experiment has been carried out with higher percentage, 23.7%.

This test shows that Melsmon has more effect on milk secretion compared to Placebo in all range of age. The same effect also can be seen on women having late first childbirth.

Daily change of milk secretion volume is shown in **Table 6**. Difference between Melsmon and Placebo group can be seen beginning of day 5 and becomes more obvious after day 7.

The milk secretion volume is divided to every 150ml in **Fig 3**. Above 300 ml is considered effective, significant difference can be seen from the comparison data of Melsmon and Placebo group after 7 confinement days.

From the above result, Melsmon's effect can be seen after day 5 and the effect is greater after day 7.

Table 8 shows the number of side effect. Statistically no significant difference noted between Melsmon and Placebo group.

The symptoms in both cases were minor and no problem to continue the prescription .For the infant, no side effect was detected.

Due to above, Melsmon is considered highly safe. This also supported with the fact that it has been used as medication for 25 years and no claim of serious side effect reported.

The evaluation of the usefulness is shown in **Table 10**.The total rate of "very useful" and "useful" for Melsmon group is 68.7% and Placebo group is 22.1% , a significant difference between two groups , this is enough to show that Melsmon is clinically beneficial.

Based on all the above , we conclude that Melsmon is highly effective as a milk secretion medication , it has not shown any sign of side effect as found in other hormone medicine , it is considered highly safe and beneficial.

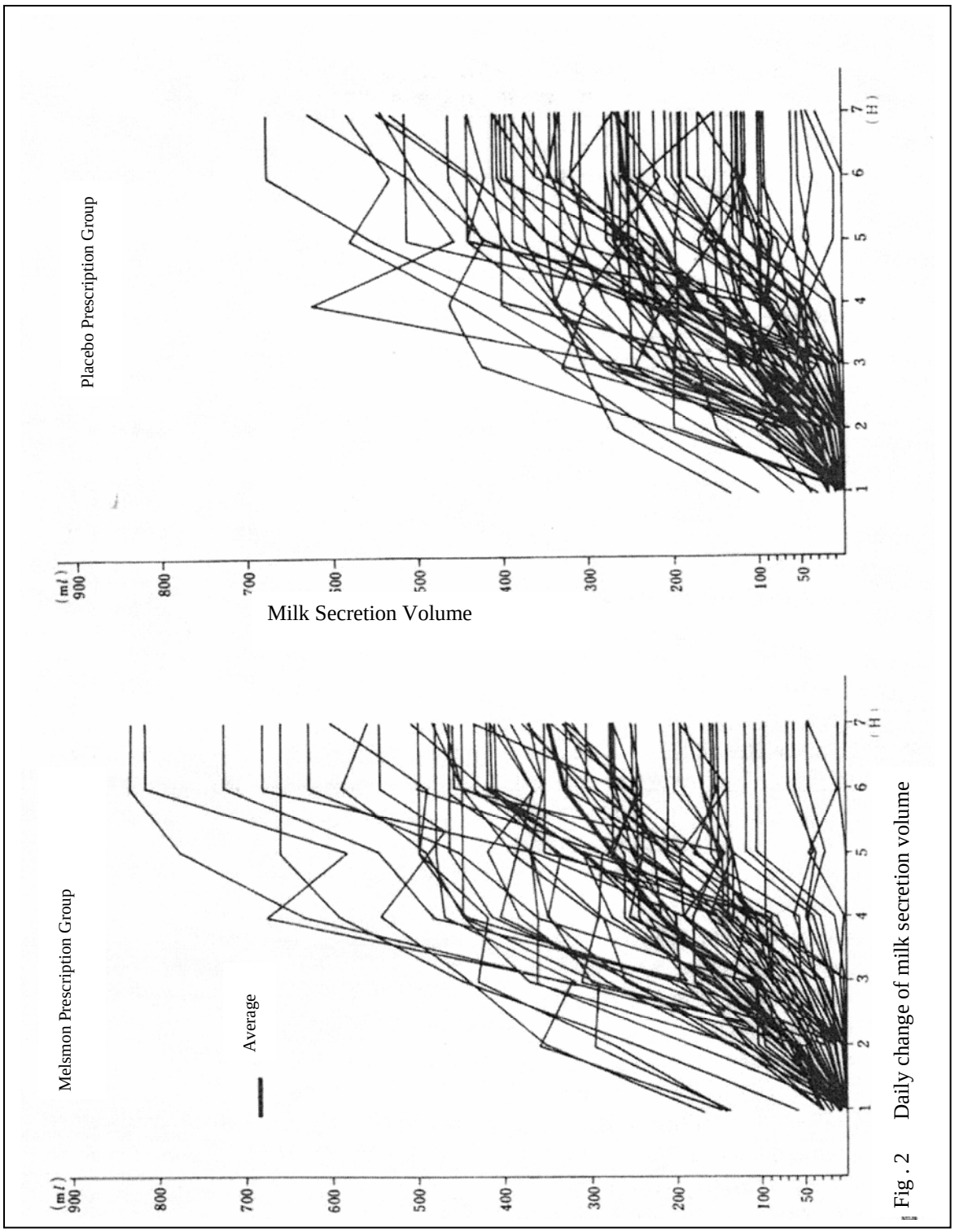

Fig . 2 Daily change of milk secretion volume

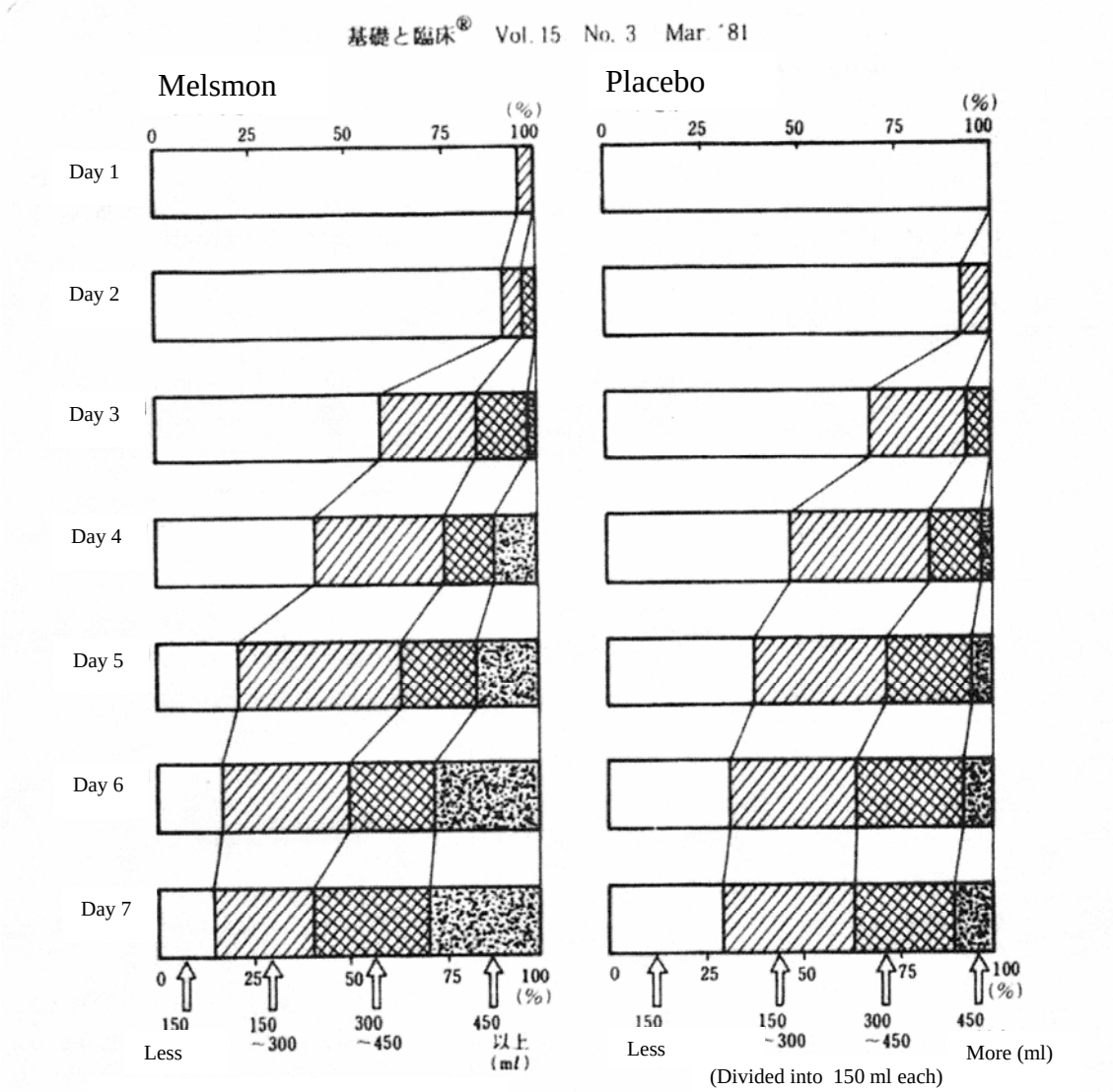

Fig 3 . Milk Secretion Volume (daily)

Conclusion

The effectiveness, safety and usefulness of Melsmon in insufficient milk secretion is checked through inter centric study by comparing it with Placebo's Isotonic Sodium Chloride Solution.

Total of 135 cases have been statistically analyzed and the following conclusions are obtained:

1) Result after mothers being given 1 ampoule /day continuously from day 1 till day 5 of confinement clearly shows that Melsmon is effective in promoting milk secretion.

2) Melsmon effect on milk secretion started to be seen from day 5 and is more significant after day 7.

3) Melsmon is also effective for mother who had their first childbirth at older age.

4) Side effect of Melsmon is minor, almost no different with Placebo; no special remark was noted therefore it is safe.

From the above, we conclude that Melsmon is an effective medication for milk secretion insufficiency with no major side effect, highly safe and very useful.

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