Post-Transfusion Hepatitis

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There have been many reports[1-5] concerning the incidence of hepatitis after blood transfusion in Japan. In the majority of the Japanese reports, the attack rate of post-transfusion hepatitis is roughly 5 to 10 per cent as detected by jaundice, 10 to 20 per cent by bromsulphthalein retention test and 30 to 60 per cent by serum transaminase level. Thus, the incidence of post-transfusion hepatitis in Japan is much more frequent than in foreign countries.[6-7]

Materials Examined

A pertinent questionaire was sent to each patient who had received blood transfusions in our hospital during the period of 1962–63 to obtain follow-up information concerning post-transfusion jaundice before july 10, 1964.

Excluding the patients who had obvious liver metastasis from gastric cancer, who had received operations of the liver, pancreas or spleen, and who had died within 6 months after the blood transfusions, the answers of 745 patients were studied.

The clinical pictures of 39 patients with post-transfusion icteric hepatitis hos-

pitalized in our clinic were observed.

A. Frequency of Post-Transfusion Hepatitis

Patients were classified by the following diseases and (a) neurosurgical disease, (b) non-malignant orthopedic disease, (c) non-malignant surgical disease not including abdomino-, chest- and neuro-surgical diseases, (d) non-malignant oto-rhinolayngological disease, (e) non-malignant abdomio-surgical disease not including gastric disease, (f) partially gastrectomized gastric ulcer, (g) non-malignant obstetric and gynecological disease, (h) non-malignant disease requiring cholecystectomy, (i) malignant oto-rhinolaryngological disease, (j) malignant surgical disease not including abdomino-, chest- and neuro-surgical diseases

Table 1. Frequency of Post-Transfusion Hepatitis and Transfused Blood Volume

Patients with:	Frequency of Jaundice		Transfused Blood Volume
(a) Neurosurgical disease	1/37	2.7%	701m/.
(b) Non-malignant orthopedic disease	9/137	6.5%	356m/.
(c) Non-malignant surgical disease not including abdomino-, chest- and neuro-surgical diseases	3/23	13.0%	522m/.
(d) Non-malignant oto-rhinolaryngological disease	0/11	0.0%	914m/.
Non-malignant extra-abdominal surgical diseases (a-d)	13/208	6.2%	465m/.
(e) Non-malignant abdomino-surgical disease not including gastric disease	9/63	14.3%	539m/.
(f) Gastric ulcer	11/68	16.2%	786m/.
Non-malignant abdomino-surgical diseases (e, f)	20/131	15.3%	667m/.
(g) Non-malignant obstetric and gynecological disease	9/155	5.8%	755m/.
(h) Cholecystectomy (non-malignant disease)	3/35	8.6%	598m/.
Non-malignant diseases (a-h)	55/539	10.2%	598m/.
(i) Malignant oto-rhinolaryngological disease	4/14	28.6%	890m/.
(j) Malignant surgical disease not including abdomino-, chest- and neuro-surgical diseases	5/24	20.8%	986m/.
(k) Malignant gynecological disease	7/103	6.8%	1490m/.
Malignant diseases not including gastric cancer (i-k)	16/141	11.3%	1345m/.
(l) Gastric cancer	14/75	18.7%	1053m/.
Malignant diseases (i-l)	30/216	13.9%	1243m/.
Obstetric and gynecological diseases (g, k)	16/258	6.2%	1132m/.
Summary with exception of obstetric and gynecological diseases	59/487	12.1%	655m/.
Total	75/745	10.0%	797m/.

(mostly mammary cancer), (k) malignant gynecological disease, and (l) totally or partially gastrectomized early gastric cancer without metastasis.

The incidence of post-transfusion hepatitis and averaged volume of transfused stock blood were summarized in Table 1.

Despite the fact that a large amount of blood was transfuged, icteric patients were not found among those who had received operations for oto-rhinolaryngological diseases, but the number of those patients was too small for accurate statistics. Attack rate of post-transfusion jaundice among the patients with neurosurgical disease (2.7 per cent) and orthopedic disease (6.5 per cent) was lower than that of non-malignant surgical disease with the exception of the patients with abdomino-, chest- and neuro-surgical diseases (13.0 per cent).

In summary, frequency of post-transfusion icteric hepatitis among the patients with extra-abdominal surgical diseases (a-d) was 6.2 per cent. On the other hand, incidence of jaundice among the patients with non-malignant abdominal surgical diseases (15.3 per cent, e-f) was higher than that of extra-abdominal surgical diseases.

Among the patients with non-malignant obstetric and gynecological diseases, frequency of jaundice was low (5.8 per cent) though most of them had received a laparatomy and a large amount of stock blood. The patients who had received cholecystectomies showed an unexpectedly low rate of post-transfusion jaundice (8.6 per cent).

Frequency of post-transfusion jaundice among the patients with malignant extra-abdominal surgical diseases (i, j), including malignant oto-rhinolaryngological disease (20.6 per cent) and malignant surgical disease not including abdomino-, chest- and neuro-surgical diseases (20.8 per cent), was the highest, but it was low among the patients with malignant gynecological diseases (6.8 per cent). Frequency of post-transfusion jaundice among the patients with gastric cancer was 18.7 per cent though metastasis of the liver could not be completely excluded. In summary, incidence of post-transfusion icteric hepatitis among patients with malignant diseases was 13.9 per cent, which was a little higher than that of non-malignant diseases (10.2 per cent).

Incidence of jaundice after blood transfusions among all the patients examined was 10.0 per cent.

It may be concluded that incidence of post-transfusion hepatitis is low among the patients with neurosurgical and orthopedic diseases, obstetric and gynecological diseases, and high among the patients with abdomino-surgical diseases and malignant general surgical diseases.

It suggests that a strict sterile operation technic for neurosurgical and orthopedic diseases may result in a low frequency of post-transfusion jaundice, and an invasion of intestinal virus into the portal system during the upper abdominal operation may result in a high frequency of jaundice. The low frequency of

jaundice after obstetric and gynecologic operation may be due to the fact that the operative procedure is limited to the lower abdomen.

B. Relationship between Post-Transfusion Hepatitis and Transfused Blood Volume: Sex- and Age-wise Distribution of Post-Transfusion Hepatitis

The statistics were gathered from all patients except those with obstetric and gynecological diseases, because the attack rate of post-transfusion jaundice among the patients with these diseases was low even though they had received a large amount of stock blood.

Frequency of hepatitis after blood transfusion in both sexes was nearly the same; viz., it was 11.8 per cent (transfused blood volume 626 m*l*.) in female and 12.2 per cent (transfused blood volume 875 m*l*.) in males.

As indicated in Table 2, frequency of post-transfusion hepatitis was low (6.6

Table 2. Relationship between Transfused Blood Volume and Frequency of Post-Transfusion Hepatitis (Excluding the patients with obstetric and gynecological diseases)

Transfused Blood Volume (m*l*.)	Frequency of Post-Transfusion Hepatitis	
0- 200	10/149	6.7%
- 400	16/125	12.8%
- 600	8/ 65	12.3%
- 800	6/ 30	20.0%
-1000	4/ 22	18.2%
-1400	5/ 38	13.2%
-2000	5/ 26	19.2%
Above 2000	4/ 21	19.0%

per cent) among the patients whose stock blood volume received was below 200 m*l*., moderate (12–13 per cent) between 200 to 600 m*l*., and high (18–20 per cent) with those above 600 m*l*.

As shown in Table 3, no jaundice was detected in the first decade or above the 7th decade. The highest frequency was revealed in the third decade. However, there remains some question as to the relationship between frequency of post-transfusion jaundice and transfused blood volume because the transfused blood volume was very small in the first decade.

C. Relationship between Frequency of Post-Transfusion Hepatitis and Pre-Transfusion Values of Clinico-Chemical Examination

Two groups of non-icteric (non-hepatitic) and icteric (hepatitic) patients with

Table 3. Age-Wise Distribution of Post-Transfusion Hepatitis and Transfused Blood Volume (Excluding the patients with obstetric and gynecological diseases)

Age	Frequency of Post Transfusion Hepatitis		Infused Blood Volume
0-10	0/ 24	0.0%	180ml
11-20	2/ 53	3.8%	462ml
21-30	5/ 57	8.8%	419ml
31-40	18/ 92	19.6%	662ml
41-50	13/104	14.1%	749ml
51-60	10/ 91	11.0%	868ml
61-70	7/ 67	9.0%	718ml
Above 71	0/ 16	0.0%	630ml

non-malignant diseases (a-g) were comapared in relation to the averaged values and incidence of abnormal values of clinico-chemical examination prior to blood transfusion.

As indicated in Table 4, hemoglobin concentration levels and hematocrit values in females of the icteric group revealed anemia. However, it may not have any relationship to post-transfusion hepatitis because of the fact that males of icteric group showed no anemia.

Serum transaminase activity was somewhat elevated and abnormal values were rather frequently detected in the icteric group, but the degree of elevation and frequency was too low to consider it as an essential factor in producing jaundice. Between the two groups there was no difference both in averaged values and rate of abnormalities of serum protein, albumin, globulin, cholinesterase activity, phenol turbidity test, cephalin-cholesterol flocculation test, urea and non-protein nitrogen.

Thus, it may be concluded that the incidence of post-transfusion hepatitis is not influenced by general physical condition and liver function prior to blood transfusion.

D. Incubation Period of Post-Transfusion Hepatitis

Averaged incubation period of post-transfusion hepatitis from the first transfusion to the appearance of jaundice was 10 ± 4 weeks (3–21 weeks) in our clinical patients and 10 ± 5 weeks (2–29 weeks) on questionaire.

E. Clinical Picture of Post-Transfusion Hepatitis (Comparison with Infectious Hepatitis)

It is common course of infectious hepatitis that the bilirubinemia will disappear within three months after the onset.[8] Thus, such cases of infectious hepa-

Table 4. Frequency of Post-Transfusion Hepatitis and Pre-Transfusion Values of Clinico-Chemical Examination

Examination	Normal Values	Non-Icteric Group (Non-Hepatitis)				Icteric Group (Hepatitis)			
		Numbers	Averaged Values	S. D.*	Incidence of Abnormal Values	Numbers	Averaged Values	S. D.*	Incidence of Abnormal Values
Hemoglobin (male)	14-18gm/dl	94	13.3	2.3	46.7%	22	13.2	2.3	62·1%
Hemoglobin (female)	12-16gm/dl	67	11.8	2.7		7	6.1	5.0	
Hematcrit (male)	40-54%	94	39.7	6.3	38.8%	22	40.4	6.9	39.4%
Hematcrit (female)	37-47%	67	36.3	5.8		5	26.0	10.1	
Serum Protein	6.5-8.0gm/dl	178	6.9	0.5	11.1%	30	6.9	0.6	10.0%
Serum Albumin	3.5-5.0gm/dl	176	3.6	0.2	29.1%	30	3.6	0.2	40.0%
Serum Globulin	2.5-4.0gm/dl	176	3.4	0.7	12.1%	30	3.3	0.6	6.7%
A/G	1.2-1.8	176	1.06	0.29	62.0%	30	1.09	0.12	50.0%
Serum Cholinesterase	0.75-1.10 △pH	170	0.78	0.18	30.2%	30	0.80	0.23	38.0%
CCF Test	0	172	0.4	0.7	26.3%	29	0.4	0.8	23.3%
Serum GPT	10u.	170	7	1	13.4%	29	12	2	23.1%
Serum Alkaline Phosphatase	1-4u.	171	3.2	1.4	10.1%	30	2.3	1.5	10.3%
Serum Total Cholesterol	130-200mg/dl	171	176	43	22.3%	29	170	34	23.1%
Phenol Turbidity Test	8-15u.	170	13	6	23.4%	29	8	5	18.5%
Serum NPN	20-30mg/dl	148	28	9	16.9%	27	27	5	25.9%
Serum Urea	8-15mg/dl	148	15	9	17.5%	27	14	4	21.2%

* S. D. $= \pm \sqrt{\frac{\Sigma (\bar{x}-x)^2}{n-1}}$

titis were made the control of post-transfusion hepatitis in the following observation.

In the patients who have had ordinary infectious hepatitis the prodromal symptom such as fever, chill, anorexia or general malaise had usually appeared distinctly prior to the onset of jaundice. The averaged interval period between the prodromal symptom and jaundice was 6 ± 3 days (1–11 days). On the contrary, the onset of the prodromal symptom was usually indefinite in post-transfusion hepatitis. Thus, the course of both types of hepatitis was expressed as the lapse of time from the onset of jaundice in the following observations.

The averaged values ($\pm$ standard error)* of clinico-chemical examination at each week (W) and month (M) were indicated in Fig. 1–10. The numbers of those examined (n) are shown in Table 5.

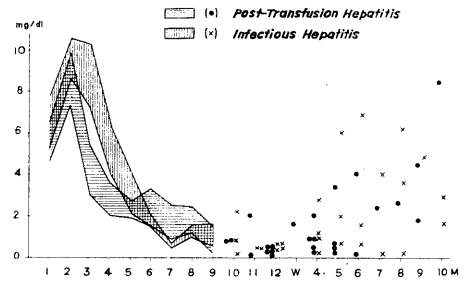

Fig. 1 Serum Bilirubin

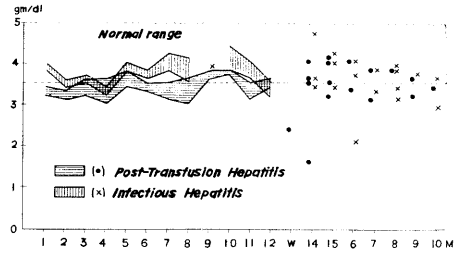

Fig. 2 Serum Albumin

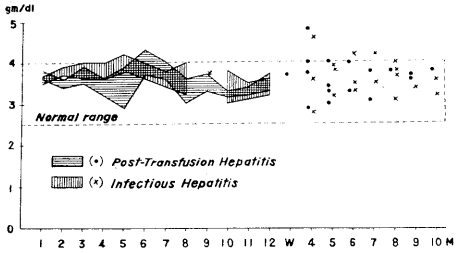

Fig. 3 Serum Globulin

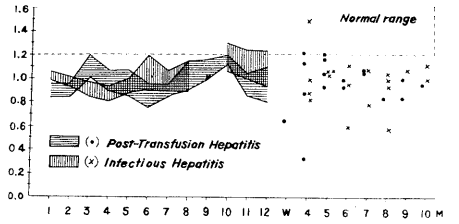

Fig. 4 A/G

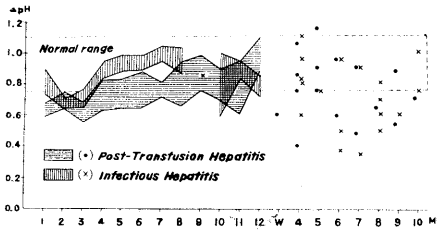

Fig. 5 Serum Cholinesterase

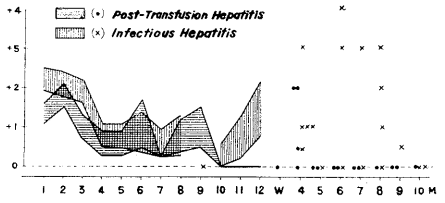

Fig. 6 CCF Test

* standard error $= \pm \sqrt{\frac{\Sigma(\bar{x}-x)^2}{n-1}} \times \frac{1}{\sqrt{n}}$

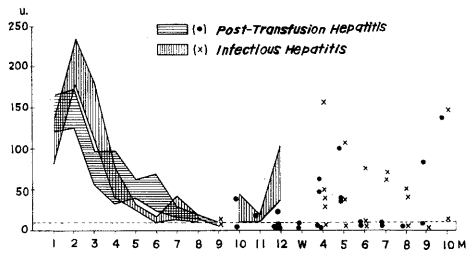

Fig. 7 Serum GPT

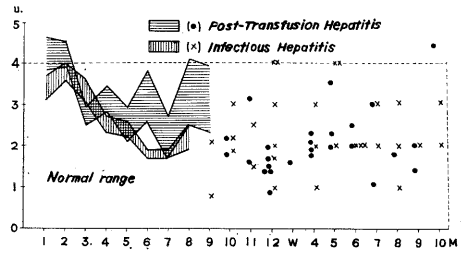

Fig. 8 Serum Alkaline Phosphatase

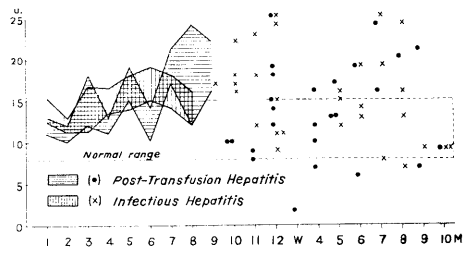

Fig. 9 Phenol T. T.

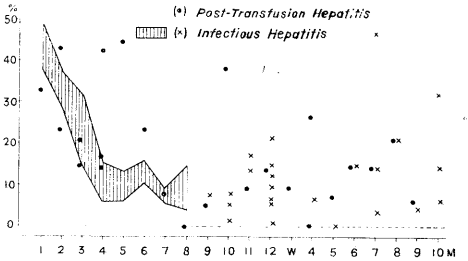

Fig. 10 BSP Test

Table 5. Number of cases Examined (n)

	Week	1	2	3	4	5	6	7	8	9	10	11	12
Fig. 1	Post-transfusion hepatitis	27	13	7	6	7	7	3	6	3	2	2	5
	Infectious hepatitis	9	23	8	9	11	10	6	4	4	3	2	4
Fig. 2—9	Post-transfusion hepatitis	28-29	13-15	8-9	6	6-7	6-7	4-6	4-6	3-4	3	3	6
	Infectious hepatitis	11-13	29-31	5-8	8-9	10-11	8-9	5-6	5	1	4	3	5
Fig. 10	Infectious hepatitis	4	17	4	10	11	7	8	8	1	3	2	7

Level of serum bilirubin in both types of hepatitis reached a peak at the second week and declined rapidly to the normal level between the 9th and 12th week. Thereafter, a relapse was noted in some cases of both groups. The bilirubinemia was slightly low in post-transfusion hepatitis during the first five weeks.

The same changes as demonstrated on bilirubinemia were revealed on the levels of serum transaminase activity in both types of hepatitis.

Level of serum albumin of post-transfusion hepatitis was slightly lower than that of infectious hepatitis. In the later slightly decreased level of serum al-

bumin which was shown during the second to fourth week returned rapidly to the normal level, but no definite change was demonstrated in the former.

No definite change of serum globulin concentration was demonstrated in either types of hepatitis. The ratio of serum albumin to globulin (A/G) was decreased in the early stage of both types of hepatitis and restored to the normal level at the 10th week. A relapes was noted thereafter.

The level of serum cholinesterase activity in both types of hepatitis was low in the first three weeks and it revealed a relapse in some cases more than four months after the onset. It seemed that the level of serum cholinesterase activity of post-transfusion hepatitis was rather low.

Positivity of cephalin-cholesterol flocculation test in both types of hepatitis was somewhat high in the first two weeks, and a relapse was noted in some cases more than two months after the onset.

Values of the phenol turbidity test in some cases were increased with the lapse of time, but there was no difference in either types of hepatitis.

Abnormal bromsulphthalein retention test of infectious hepatitis returned to normal within ten weeks from the onset of jaundice, and it revealed a relapse after the 11th week in some cases. The same tendency was suggested in post-transfusion hepatitis.

In summary the degree of hepatic dysfunction judged from serum bilirubin and transaminase level was mild in patients with post-transfusion hepatitis. However, the chinical pictures of both types of hepatitis were essentially similar. In both types of hepatitic patients a relapse was seen after the fourth month.

Summary and Conclusion

The statistics were gathered from patients excluding those who had received an operation of the liver, pancreas, spleen or metastatic cancer.

Among 745 patients who have answered the questionaire about post-transfusion hepatitis, the frequency of jaundice was 10.0 per cent.

Incidence of post-transfusion jaundice was high among the patients with upper abdominal surgical disease and low among the patients with gynecological, neurosurgical and orthopedic diseases. We are alarmed at the possibility of artificial invasion of intestinal virus into the portal system during an upper abdominal operation.

Frequency of jaundice after blood transfusion was distinctly increased in relation to blood volume, especially when it exceeded 600 m*l*.

Incidence of post-transfusion jaundice did not seem to be influenced by pre-transfusion general physical condition and liver function.

The incubation period of post-transfusion hepatitis was 10 ± 4 weeks.

It was impossible to distinguish the difference in the clinical pictures of post-

transfusion hepatitis and infectious hepatitis.

Referrences

1) Kitamoto, O. & Takayama, H. : *Naika* (in Japanese), **14** : 37, 1964.
2) Ichida, F. & Suzuki, S, : *Igaku no ayumi* (in Japanese), **34** : 245, 1960.
3) Mizuno, A. : *Japanese J. Clin. Med.*, (in Japanese), **21** : 2028, 1963.
4) Nunobiki, T., et al : *J. Japanese Soc. Int. Med.*, (in Japanese), **48** : 120, 1959.
5) Ueno, Y. et al : *Japanese J. Clin. Med.* (in Japanese), **17** : 1823, 1959.
6) Schoen, H., et al : *Dtsch. med. Wschr.*, **85** : 265, 1960.
7) Bang, N. U., et al : *J. A. M. A.*, **171** : 2303, 1959.
8) Neefe, J. R.: *Diseased of the Liver*, Edited by Schiff, L., J. B. Lippincott Co., Philadelphia, 1963.