

# Continuous infusion method for life threatening hemorrhage of hemophilia patient

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Self-Infusion and Home Treatment  
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**Introduction and Objectives:** Continuous infusion (CI) compare to bolus infusion has a merit of factor concentrate saving as much as 30% with same hemostatic effect. According to the instruction of inside package the factor concentrate is recommend to inject within 3 hours of reconstitution at room temperature. Universally 24 hours' volume of CI were reconstituted at one time in almost all hospital. We applied this CI for life-threatening hemorrhage with a different method since 1996.

**Materials and Methods:** Thirty five of life threatening hemorrhage (Fig. 1) or major surgery from 28 patients (Table 1 and Fig. 2) were enrolled in this study for 15 years. All patients received FVIII concentrates with initial loading dose of FVIII 50U/kg and then the continuous infusion, 3 U/kg/hr for 3 days, and then gradually decreased the amount for 2 weeks. We empirically prepared the material of CI with every 2-4 hours reconstitution to keep a desired in vivo factor level. To verify of this we checked in vitro factor activity of 3 drugs as time goes on recently.

**Results:** Thirty five events were intracranial hemorrhage in 17, general surgery in 9 and orthopedic surgery in 9. Age distribution was 0-32 yr (mean; 24.8 yr). Severity was severe (16), moderate (7) and mild (5). We confirmed in vivo factor activity within permissible level in all patients. All recovered from hemorrhage or surgery and are healthy, but one had limping gate and one had mild neurologic sequelae for more than 10 years. The mean in vitro factor activity at 2, 4, 6, 8 and 24hours of reconstitution were gradually decreased to 97.7%, 95.3%, 92.9%, 90.6 and 73.0% respectively in all 3 drugs (Fig. 3 and Table 2).

**Conclusion:** All biologic products decrease their activity as time goes on even in vitro. Empirically, we reconstitute the concentrate every 2-4 hours for CI since 1996. And we confirmed the in vitro activity will decrease as time goes on. In continuous infusion we have to reconstitute the concentrate every 2-4 hours to make a desired in vivo factor level.

## References / Bibliography:

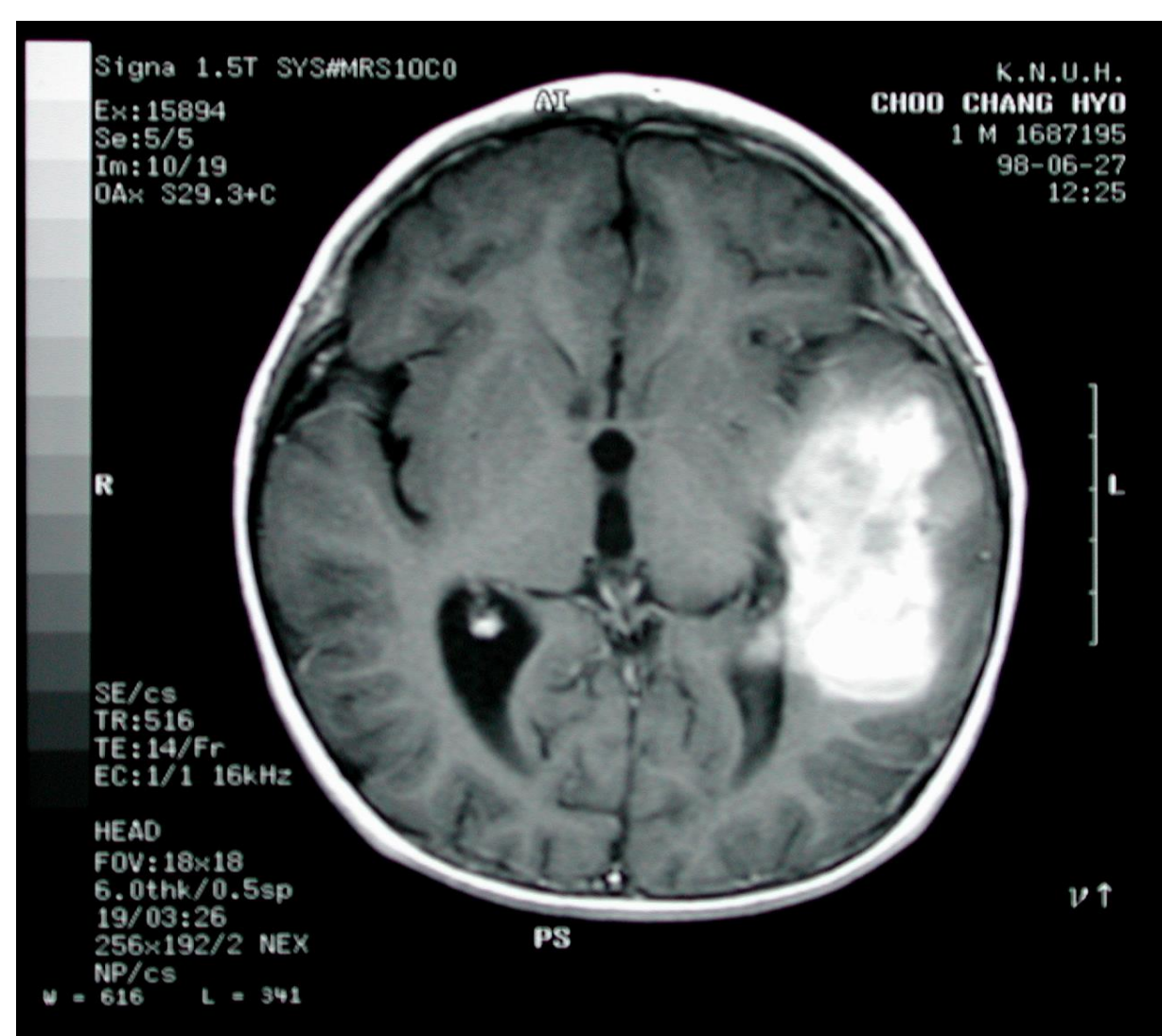


Figure 1. Intracranial hemorrhage

Table 1. Intracranial hemorrhage patient between 1966-2002

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8	Case 9
Age/Sex	18yr / M	17yr / M	26yr / M	4yr / M	1yr / M	2yr / M	3yr / M	8yr / M	2mo / M
Chief complaints	Seizure	Headache, vomiting, seizure	Headache, vomiting	Trauma & vomiting	Irritability & vomiting	Vomiting	Headache	Headache & vomiting	Seizure
Time interval*	15min	10 days	30 min	12 hours	12 hours	7 hours	4 days	3.5 hours	5.5 hours
Laboratory findings †									
aPTT	72" / 72"	48" / 48"	36" / 50"	31" / 80"	36" / 55"	64" / 70"	42" / 73"	149" / 79"	69" / 90"
Factor VIII	<12.5% / 1%	28.8% / 0.6%	not checked / 2%	88.7% / 1.1%	not checked / 15.8%	<12.5% / 0.6%	<12.5% / 0.9%	<6% / <1%	<6% / <6%
Inhibitor	(-) / (+) → (-)	(-) / (-)	(-) / (-)	(-) / (-)	(-) / (-)	(-) / (+) → (-)	(-) / (-)	(+) / (+)	(-) / (-)
Past history of ICH	GI bleeding	None	None	None	2 episodes	3 episodes	None	1 episode	1 episode
Family history of hemophilia	Positive	Positive	Positive	Positive	Positive	Positive	Positive	Negative	Negative
Hemorrhage site	Right temporo-parietal area	Left fronto-parietal area	Cerebellar vermis & 3rd ventricle	Right cerebellum & occipital area	Left parieto-temporal & IVH ( 3,4th ventricle )	Left fronto-parieto-temporal area	Right fronto-parieto-temporal & right occiput	Right fronto-temporal area	Left parietal area
Operation	Not done	Not done	Not done	Done	Done	Not done	Done	Done	Not done
Treatment with Continuous Infusion	Initial loading dose of FVIII, 50U/kg and then continuous infusion, 3U/kg/hour	Initial loading dose of FVIII, 50U/kg and then continuous infusion, 3U/kg/hour	Initial loading dose of FVIII, 50U/kg and then continuous infusion, 3U/kg/hour	Initial loading dose of FVIII, 50U/kg and then continuous infusion, 3U/kg/hour	Initial loading dose of FVIII, 50U/kg and then continuous infusion, 3U/kg/hour	Initial loading dose of FVIII, 50U/kg and then continuous infusion, 3U/kg/hour	Initial loading dose of FVIII, 50U/kg and then continuous infusion, 3U/kg/hour	FIX, 100U/kg with activated prothrombin complex concentrate (FEIBA), 75U/kg at every 12 hours	Initial loading dose of FVIII, 50U/kg and then continuous infusion, 3U/kg/hour
Prognosis	Alive for 57mo without any neurological sequelae	Alive for 51mo without any neurological sequelae	Rapid deterioration of mental status & expire	Alive for 45mo without any neurological sequelae	Alive for 47mo with mild limping gait	Alive for 37mo without any neurological sequelae	Alive for 12mo without any neurological sequelae	Alive for 2mo without any neurological sequelae	Alive for 3mo without any neurological sequelae
Prophylactic treatment	*	*	*	*	FVIII, 30U/kg 3 times a week	FVIII, 30U/kg 3 times a week	FVIII, 30U/kg 3 times a week	FIX, 30U/kg 3 times a week	FVIII, 30U/kg 3 times a week

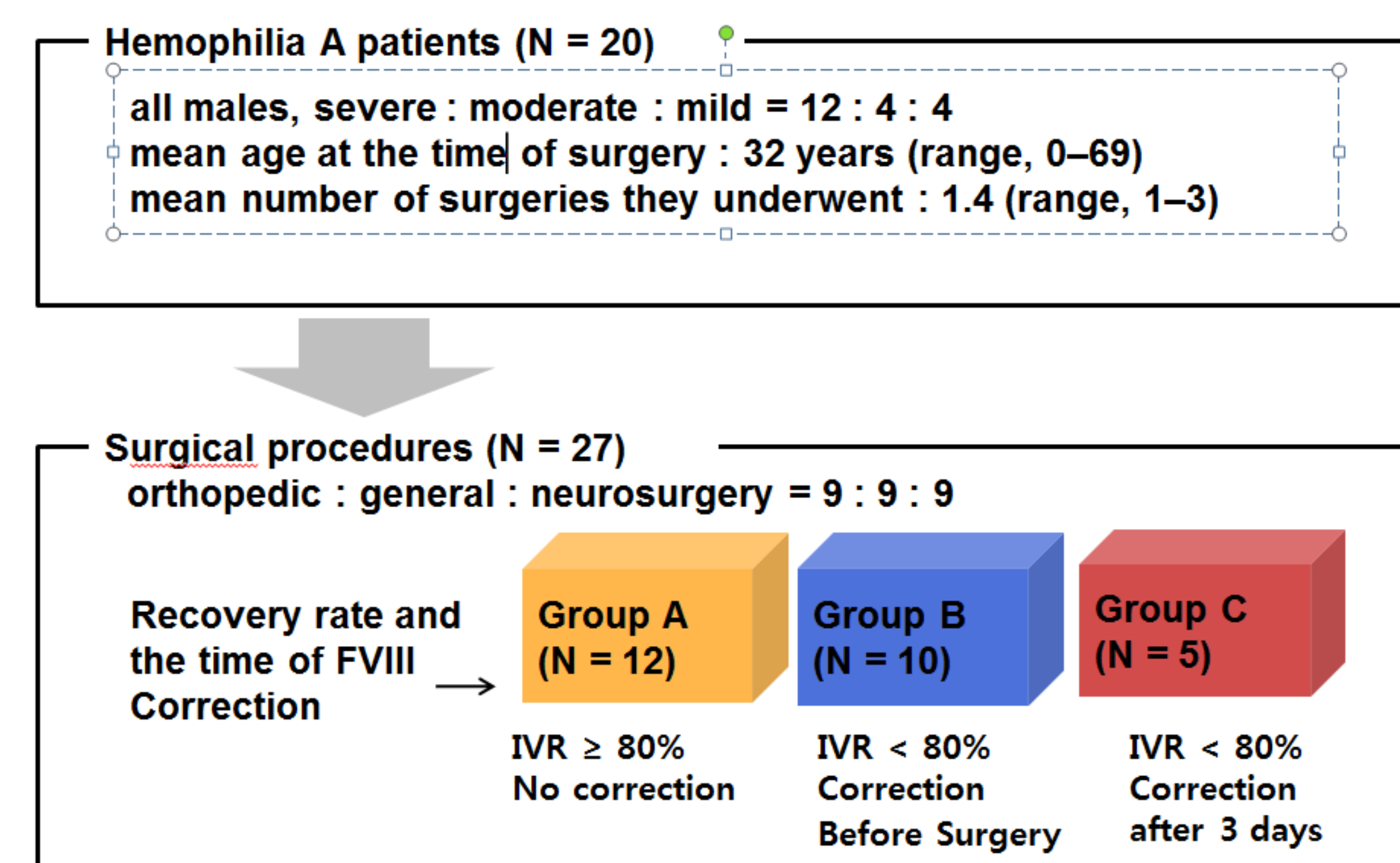


Figure 2. Major surgery between 2003-2012

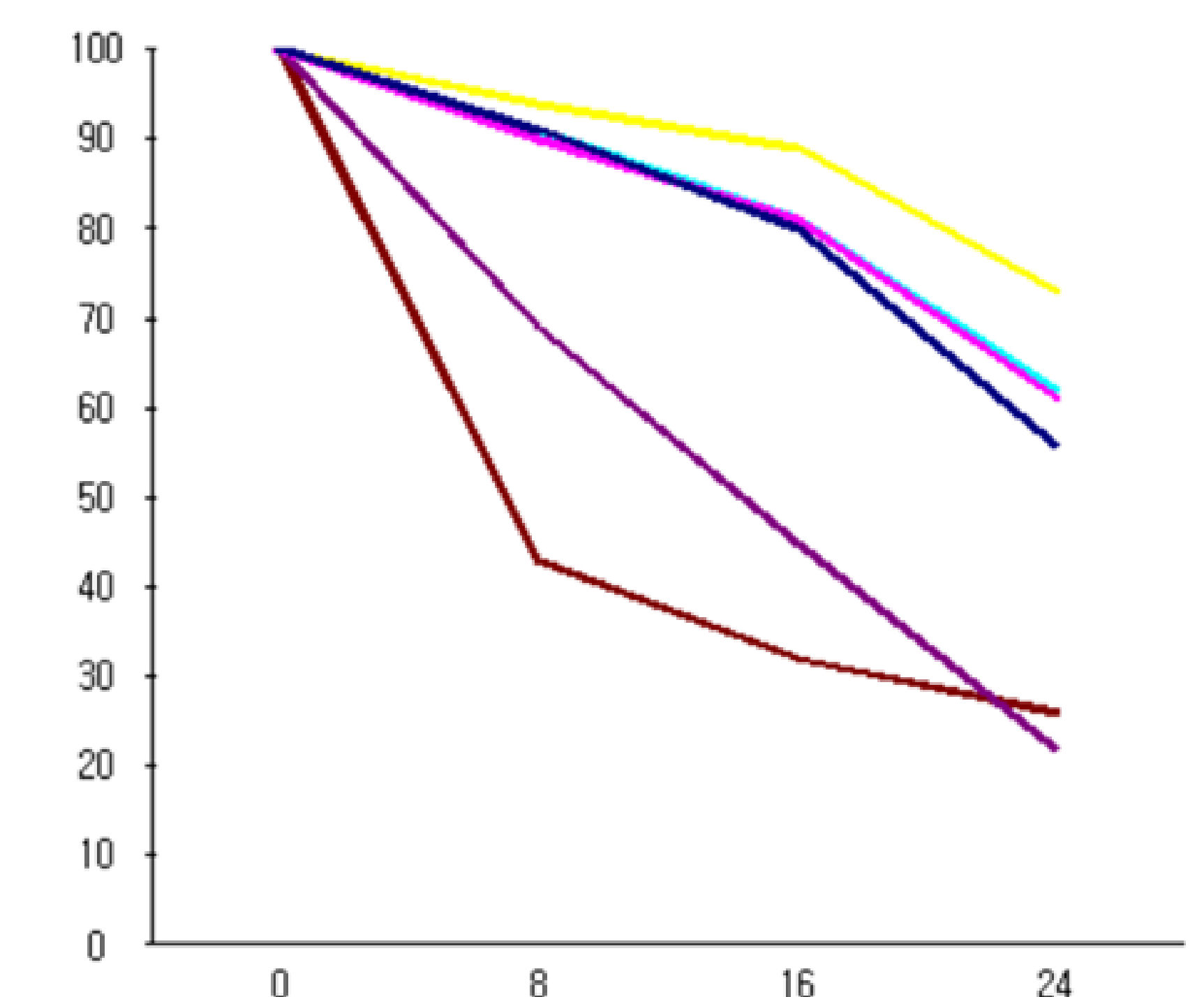


Figure 3. In-vitro factor VIII activity 0, 8, 16, and 24 hours

Table 2. In vitro factor VIII coagulant activity (FVIII:C) according to the time

		Time after reconstitution (hours)					P-value*
		0	2	4	6	8	
<b>Exposure to light</b>							
Drug A (N=5)	100	96.4 ± 2.07	93.2 ± 1.10	90.8 ± 1.10	88.0 ± 1.58	< 0.001	
Drug B (N=5)	100	97.0 ± 1.58	95.4 ± 0.89	92.4 ± 1.14	90.6 ± 1.52	< 0.001	
Drug C (N=5)	100	99.6 ± 0.89	97.2 ± 0.84	95.6 ± 0.55	93.2 ± 0.84	< 0.001	
Total (N=15)	100	97.7 ± 2.06	95.3 ± 1.91	92.9 ± 2.25	90.6 ± 2.53	< 0.001	
<b>Light shield</b>							
Drug A (N=5)	100	97.2 ± 1.30	95.0 ± 1.58	92.8 ± 1.92	91.2 ± 2.17	< 0.001	
Drug B (N=5)	100	98.4 ± 1.95	95.6 ± 1.14	94.0 ± 1.41	91.0 ± 1.41	< 0.001	
Drug C (N=5)	100	97.0 ± 1.58	95.6 ± 0.55	92.4 ± 1.52	90.6 ± 1.67	< 0.001	
Total (N=15)	100	97.5 ± 1.64	95.4 ± 1.12	93.1 ± 1.67	90.9 ± 1.67	< 0.001	

\*P-value by ANOVA between in vitro FVIII:C at 0, 2, 4, 6, and 8 hours in respective experimental conditions