

Improved Outcome of Infants Born at less than 24 Weeks of Gestation in Japan

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Abstract

Japan neonatologist association had surveyed of survival rates of infants less than 24 weeks of gestation born during 1995 to 2001 and during 2002 to 2004. There was no survival on 20th and 21st weeks of gestations, while survival rates of 22 and 23 weeks had increased from 18% to 31% and 43% to 56% respectively between two studies time periods. Their follow up data at 5 years old revealed as follows; rates of cerebral palsy (CP) with/without mental retardation (MR), MR only, blindness and infants of any aforementioned neurological sequels were 17%, 26%, 8% and 44%, respectively. Main causes of death of these infants are mostly due to extreme prematurity including fragile skin and immature immunity. To improve the outcome of infants at 22 to 23 weeks of gestation, meticulous and gentle care is essential while knowing the viability limit based on their up-to-date statistics.

Keywords: ELBW infants; Marginally viable infants; Medical ethics

Introduction

Because of the advancement of obstetrical, perinatal and neonatal managements, outcome of extremely low birth weight (ELBW) infants have been markedly improved and currently survival rate of ELBW infants born at 24 weeks or more gestations became 80% or more in Japan [1-8]. Therefore, if ELBW infant's gestational age is 24 weeks or more, active intervention for those infants is widely accepted in Japan, unless the infant has lethal problems at birth. Since the viability limit of fetus is defined to be 22 completed weeks of gestation in Japan at 1991 based on national statistics of infants less than 24 weeks of gestation, we present Japanese experience on infants at 22 and 23 weeks of gestations, to whom active medical intervention are still on debate [2].

Method and Results

Two nationwide surveys and one institutional data on ELBW infants focused on infants less than 24 weeks of gestation are presented.

Chronological changes of survival rates of ELBW infants in neonatal committee of Japan

Pediatric Association has been conducting nationwide follow up study on ELBW infants every 5 years since 1980 [6-8]. There was no survival less than 500 grams at birth before 1980 but close to half (44%) of such ELBW infants and 85% of ELBW infants above 500 grams at birth have survived on the survey of 2000 (Table 1). When the survival rates of ELBW infants (surveyed in 2005) are categorized by gestational age, there are quite different survival rates between each gestational age group (Table 2). There was no survival on 21 weeks of gestations but survival rate of infants after 22 weeks were increased along with the advancement of gestation as follows: 34% at 22 weeks, 54% at 23 weeks, 77% at 24 weeks, 85% at 25 weeks, 90% at 26 weeks, 92% at 27 weeks and 92% at 28 weeks of gestation. Based on these data, it is apparent that ELBW infants at 21 weeks or less are not viable and infants above 24 weeks of gestation have chance to survive close to 80% or more, which elucidates the importance of infants at 22-23 weeks of gestation. These infants are regarded to be marginal viable, which will require medical and ethical consideration before initiating active interventions.

Survival rates of ELBW infants less than 24 weeks of gestation according to Japan neonatologist association

It has conducted surveys at two separate time periods on survival

rates of ELBW infants less than 24 weeks of gestation born during 1995 to 2001 and during 2002 to 2004 respectively [1-8]. Reply rates were 106/198 (55%) and 114/205 (56%) and numbers of enrolled infants were 842 and 580 respectively. There was no survival on 20 and 21 weeks of gestation on both surveys. At 22 and 23 weeks of gestation, survival rates had increased from 18% to 31% and 43% to 56%, respectively (Table 3), which was a statistically significant ($P < 0.01$) improvement in survival rates in two time periods on both 22 weeks and 23 weeks of gestation categories (Figure 1). These data encourage us to pursue further improvement of medical care on these marginally viable infants. Follow up data of neurological sequels of 386 survivors out of 842 ELBW infants less than 24 weeks of gestation born in 1995-2001 were analyzed by subdividing in birth weight category (Table 4). Incidences of neurological sequels at 5 years old are as follows: CP (with/without MR), MR only, blindness and infants with any aforementioned sequels were 17%, 26 & 8% and 44% respectively. Though nearly half of such survivors are categorized to be neurologically abnormal, MR defined by IQ less than 70 could be over-diagnosed at 5 years old, since extremely preterm infants are still on the process of maturing even at 5 years

B W(g) Year	<500	500-1000
1980	0/0	493/1102 (45%)
1985	5/52 (10%)	1085/1846 (59%)
1990	9/50 (18%)	1462/2000 (73%)
1995	39/132 (30%)	1789/2287 (78%)
2000	57/153 (37%)	2238/2638 (85%)
005	94/211 (44%)	2369/2854 (83%)

[no. of survival/no. of admission (survival rate, %)]

Table 1: Chronological Changes of Survival Rate of ELBW infants (Neonatal Committee, Japan Pediatric Association).

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Gestational weeks	n (%)	n (%)	
		Born alive	Died during NICU stay
22	97	57 (58.8)	64 (66.0)
23	282	112 (39.7)	129 (45.8)
24	423	77 (18.2)	99 (23.4)
25	501	56 (11.2)	73 (23.4)
26	542	35 (6.5)	56 (10.3)
27	408	22 (5.4)	32 (7.8)
=>28	809	37 (3.9)	67 (8.3)
Unknown	3	2 (66.7)	2 (66.7)
Total	3065	398 (13.0)	522 (17.0)

Hayashi K, Horiuchi T, Kusuda S. et al, Mortality rates for extremely low birth weight infants born in Japan in 2005. Pediatrics 2009 123(2): 442-450

Table 2: Numbers of Births and Mortality Rates According to Gestational Age born in 2005.

Gestational Age	No. of Survival No. of Admission	Survival Rate
20weeks	0/4 [0/0]	0% [0/0]
21weeks	0/8 [0/0]	0% [0/0]
22weeks	44/241 [51/164]	18% [31%]
23weeks	242/568 [234/416]	43% [56%]

Table 3: Survival rates of infants less than 24 weeks of gestation (born between 1995-2001 at 112 hospitals of Japan neonatologists network) [repeated study born between 2002-2004].

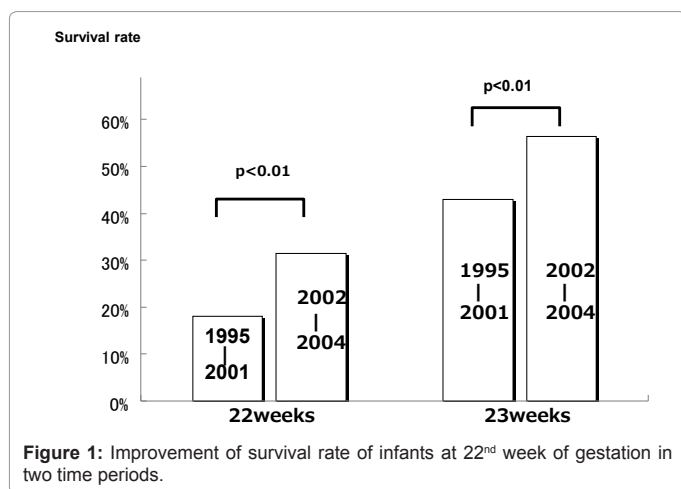


Figure 1: Improvement of survival rate of infants at 22nd week of gestation in two time periods.

after birth and are expected to improve along with the advancement of their postnatal ages. Moreover, it is rather encouraging that majority of survivors are escaped from CP and from blindness in spite of such extreme prematurity.

Survival rates of ELBW infants at Tokyo Women's Medical University (TWMU)

TWMU has been reporting relatively high survival rate of ELBW infants in the past and the data was regarded to be the benchmark on caring ELBW infants in Japan [1,3,4,7-9]. The data of TWMU on ELBW infants was also quoted in the textbook of Avery's Neonatology (6th edition) as the leading result on infants at 22-23 weeks of gestation [10]. Survival rates of ELBW infants cared at TWMU in 1984 to 2004 are shown in table 5 by gestational age categories. There was no survival at 21 weeks of gestation but were 56% and 42% survival at 22nd and 23rd weeks of gestation, respectively. When gestation age goes up to 24 and 25 weeks of gestation, survival rates of such infants were markedly

Birth Weight (grams)	Number of Admission	Number of Survive (%)	Neurological Squeal (%)			
			CP/MR	MR only	Blind	Total
>300	10	1 (10%)	1	0	0	1 (100%)
300-399	87	15 (17%)	2	5	1	7 (47%)
400-499	278	131 (47%)	19	32	6	51 (39%)
500-599	256	132 (47%)	26	33	14	59 (45%)
600-699	189	89 (47%)	13	27	9	41 (46%)
700<	22	18 (82%)	6	4	0	10 (56%)
TOTAL	842	386 (46%)	67 (17%)	101 (26%)	30 (8%)	169 (44%)

Table 4: Survival and neurological squeal rates of infants less than 24 weeks of gestation (born in 1995-2001, followed up to 5 years old).

Gestational Age (Weeks)	No. of survival/No. of admission (survival rate, %)
21	0/1 (0.0)
22	5/9 (56)
23	11/26 (42)
24	27/35 (77)
25	45/49 (92)
26	44/54 (82)
27	48/52 (92)
28	35/39 (90)
29	21/23 (91)
30	19/23 (83)
>30	14/19 (74)
TOTAL	269/330 (82)

Table 5: Survival Rate of ELBW infants Tokyo Women's Medical University (1984-2004).

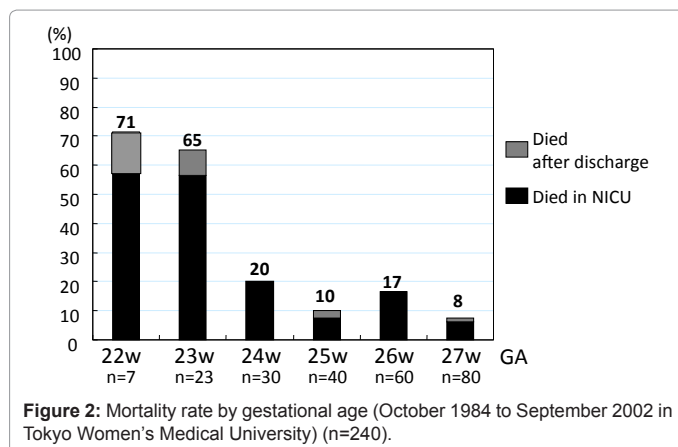


Figure 2: Mortality rate by gestational age (October 1984 to September 2002 in Tokyo Women's Medical University) (n=240).

improved to 77% and 92% respectively. It is clear that there is the apparent difference between 23rd and 24th weeks of gestation in regards to the survival rate, which is the important data on the discussion of the viability limit [1] (Figure 2).

Discussion

Since the survival of infants less than 22 weeks of gestation is negligible, it will be appropriate to recommend no active intervention on such infants unless there is strong parental wish because of the only and the last chance for the mother to have an offspring. On the other hand, if gestational age goes up to 24 weeks, survival rate increases close to 80%. Therefore, it is also appropriate to recommend active intervention unless there are apparent medical conditions to relate with lethal outcome or with severe neurological sequel. How we deal with so-called marginal viable infants of 22 and 23 weeks of gestations are

Stages	Reasons for Death Occurrence
Intrapertum	Birth asphyxia No active resuscitation due to parent's will
Early Neonatal	Respiratory instability due to immaturity Cardiovascular failure due to acute adrenal insufficiency and myocardial immaturity Intraventricular hemorrhage
Late Neonatal	Sepsis (especially Candida & nosocomial, opportunistic infection) Necrotizing enterocolitis
Post-Neonatal	Chronic lung disease, Sudden infant death syndrome, Abused child

Table 6: Causes of death of infants at 22-23 weeks of gestation.

Stages	Site of Infection
Prenatal	Antenatal steroid, tocolitic agents (intensive discussion with obstetrician and neonatologist)
At delivery	Non-traumatic, minimal handling (CS is exceptional) Deliver with intact fetal membrane and umbilical cord
After birth	<ul style="list-style-type: none"> Promote placental-fetal transfusion (cord milking) Prevention infection (prophylactic anti-fungus drugs) Steroid to stabilize blood pressure UV catheter for 5-7days to avoid excess handling Bio-protection by Colostrums, Priming intestine Meticulous follow up and support
Ethical consideration	Viability limit, Do-not-resuscitate order Escape from eugenic thought

Table 7: Specific management of infants at 22-23 weeks of gestation.

currently on debate. Though their current survival rates are close to 50%, morbidity is still high and two third of survivors have some degree of neurological handicap. Therefore, medial decision on treating such infants at 22nd and 23rd weeks of gestation should be based on the data of each institute. Our policy of TWMU is to initiate treatments on infants at 22nd and 23rd weeks unless apparent objection is expressed form parents. Therefore, it is essential to discuss with parents before initiating active intervention, desirably before birth of the infant. Frequent causes of death of infants at 22-23 weeks are shown in table 6. One of the most frequent causes of their death occurs at the time of birth due to asphyxia and due to no-resuscitation following parents' will. For better medical management of these issues, antenatal and perinatal consultations to parents are mandatory. Main medical reasons of neonatal death after birth are related with their extreme prematurity, not only of cardio-respiratory systems but also of skin fragility and immature immunity. Meticulous care to protect fragile skin and to prevent infection is as important as cardio-respiratory assist on managing these extreme premature infants [9]. Specific managements to improve outcome of infants at 22-23 weeks of gestation are suggested as shown in table 7, though some items quoted on the table are still in debate. Before birth, exchange information and discussion with obstetricians and neonatologists are essential, including use of antenatal steroids, timing of delivery and parents' will for active intervention. Though caesarian section at such early gestations are exceptional, it is desirable to deliver an infant and placenta with connecting umbilical cord as a set covered by intact fetal membrane for the better cardiovascular stabilization during and after delivery process [11]. Before cutting umbilical cord, promoting placental-fetal transfusion by cautious cord milking is helpful to maintain adequate blood volume of the infant [12]. Often postnatal steroid administration is essential to stabilize blood pressure to encounter adrenal cortical insufficiency due to extreme prematurity and stress [13]. Use of umbilical venous catheter as an infusion route for the first 5 to 7 days is inevitable to avoid excess handling to keep peripheral lines [9]. Early enteral instillation of breast milk, especially Colostrums is useful as bio-protection and gut stimulation [9]. Preventing infection by meticulous care and gentle handling to avoid excess stress are also very important. Serial C-reactive protein (CRP)

measurements is useful to early detection of infection and moreover, to reduce unnecessary use of antibiotics [14]. Lastly the optimistic attitude toward successful survival by avoiding eugenic though is the most important of all for the success of managing these marginal viable infants [9].

Conclusion

Current Japanese data on ELBW infants, especially infants less than 24 weeks of gestations are reviewed. Since survival of infants at 21st week of gestation is exceptional and of infants at 24th week of gestation are close to 80%, it is apparent that infants at 22nd and 23rd weeks of gestation are marginal viable and are on the debate of medical and ethical discussion for the feasibility of active intervention at NICU in Japan. Though there are still limited medical knowledge and technology in the care of infants at 22nd and 23rd weeks of gestation, survival rates of such infants born in 2002-2004 have shown significant improvement from those born in 1990-2001. Therefore, we should continue our efforts for the intact survival of these extreme premature infants, while knowing the viability limit based on up-to-date statistics of infants at 22nd and 23rd weeks of gestation.

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