Appropriate use of phototherapy on extremely premature infants and revision of jaundice treatment standards at Kobe University

— What are the High/Low modes of phototherapy devices? —

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Why is the number of cases of chronic bilirubin encephalopathy increasing among extremely premature infants?

Why is the number of cases of chronic bilirubin encephalopathy increasing among extremely premature infants? Kernicterus or chronic bilirubin encephalopathy (CBE) is a pathological condition in which neurological lesions induced by the after effect of hyperbilirubinemia toxicity persist permanently during the neonatal period. The term kernicterus refers to a pathological diagnosis, and as its Japanese name indicates, a necropsy examination of the patient shows yellowing of the basal nuclei. We are recommending differentiation of CBE, when it is referred to, from an encephalopathy induced by clinically diagnosed bilirubin[1]. The number of reports of extremely premature infants who developed CBE has been increasing since 2000[2]. I believe this is due to (1) clinical diagnoses of CBE have become available instead of diagnoses via necropsy examinations[3], and (2) while medical care of extremely premature infants has advanced and their mortality rate has fallen, control of jaundice is still carried out using only dated practices.

Jaundice treatment on extremely premature infants during the 20th century

From the 1990s to the beginning of the 2000s, a trend among Japanese medical practitioners involved applying phototherapy to extremely premature infants even when the total bilirubin (TB) was low (active phototherapy). This was because extremely premature infants would develop bilirubin encephalopathy even with relatively low TB, and phototherapy was considered to have no significant side effects. More specifically, doctors who had a tendency to presume that TB would exceed the treatment standard and therefore administer a smaller number of blood tests, and proceeded with phototherapy without actually checking the TB when infants were less than two weeks old. In addition, the treatment for jaundice was considered unnecessary after the development of a blood-brain barrier completed, which happens at two weeks of age regardless of whether infants were premature or full-term newborn. However, our recent study of the clinical course of CBE patients reported that the peak value of TB was recorded after two weeks of age for approximately 90% of infants[4].

Appropriate use of phototherapy is necessary for extremely premature infants

In the 21st century, whether active phototherapy is truly effective in preventing neurotoxicity of hyperbilirubinemia, or harmful, became a subject of discussion. In the United States, a cohort study on 1,974 extremely low weight infants born between 2002 and 2005 was conducted. As a result, the rate of death and neurological after effects did not fall. In particular, the report concluded a slight increase in the mortality rate of infants who weighed 501 to 750g at birth[5]. This showed the limit in prognosis improvement incorporating active phototherapy. Rather, it clinically suggested the harmful effect phototherapy has on extremely premature infants, leading to a shift in ideas about phototherapy to what we call "appropriate use", which requires a more thorough examination of jaundice before phototherapy is applied. Also, a recent study carried out in the United States shows that cases of pediatric cancer among those who received phototherapy increased to 9.4 cases per 100,000 children compared to those who did not[6]. Although this study did not target extremely premature infants, it became one of the most significant grounds for the necessity of appropriate use of phototherapy. It has been a while since appropriate use of various drugs were widely promoted, such as for antimicrobial agents. Phototherapy must also be treated in the same manner.

What are the High/Low modes of phototherapy devices?

Back when phototherapy devices containing fluorescent tubes were used, so-called “bi-directional irradiation” was being performed in order to avoid the use of exchange transfusion (reinforced phototherapy) if the level of bilirubin in the blood was high. The purpose of this was to increase the overall light energy. Uni-directional irradiation was about 10 to 15 μW/cm^2/nm, and bi-directional irradiation was about 30 μW/cm^2/nm (measured using the Atom Phototherapy Analyzer II). After phototherapy devices incorporating light-emitting diodes (LED) as the light source were developed and became available[7], irradiation utilizing light with energy stronger than that of fluorescent tubes became possible.

The Low mode of a LED phototherapy device is equivalent to uni-directional irradiation, and the High mode is equivalent to bi-directional irradiation. Photos of phototherapy devices commonly used in Japan, BILI-THERAPY® Spot Type (Atom Medical Corporation, Tokyo, Fig. 1) and neoBLUE® (Natus Medical Inc, Pleasanton, USA, Fig. 2) are provided below. The arrows in the pictures indicate the switches used to alter modes.

Figure 1 BILI-THERAPY® Spot Type

The switch the arrow is pointing at changes between the High and Low modes.

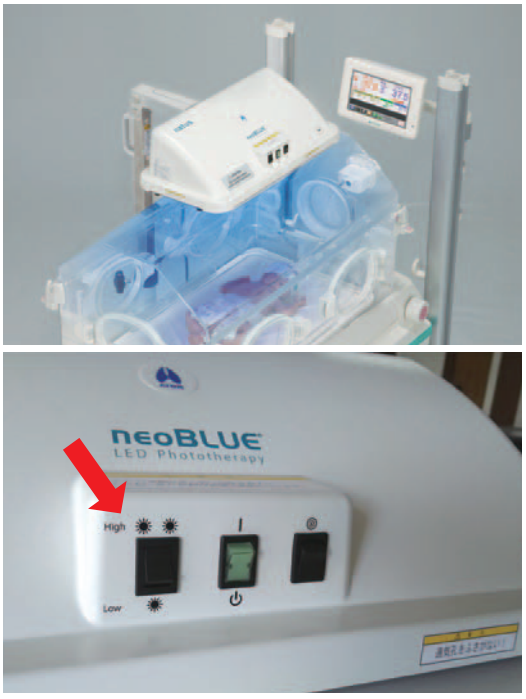

Figure 2 neoBLUE®

The switch the arrow is pointing at changes between the High and Low modes.

Jaundice treatment standard taking the appropriate use of phototherapy into account

As described above, switching the strength of light energy (High/Low modes) became easier thanks to LED phototherapy devices and their use in daily medical care becoming more common. Consequently, medical practitioners became aware of the need of a jaundice treatment standard that takes the appropriate use of phototherapy into account. Standards set by Kobe University (Nakamura, revised in 1991) are standards for introducing phototherapy and exchange transfusion treatment[8].

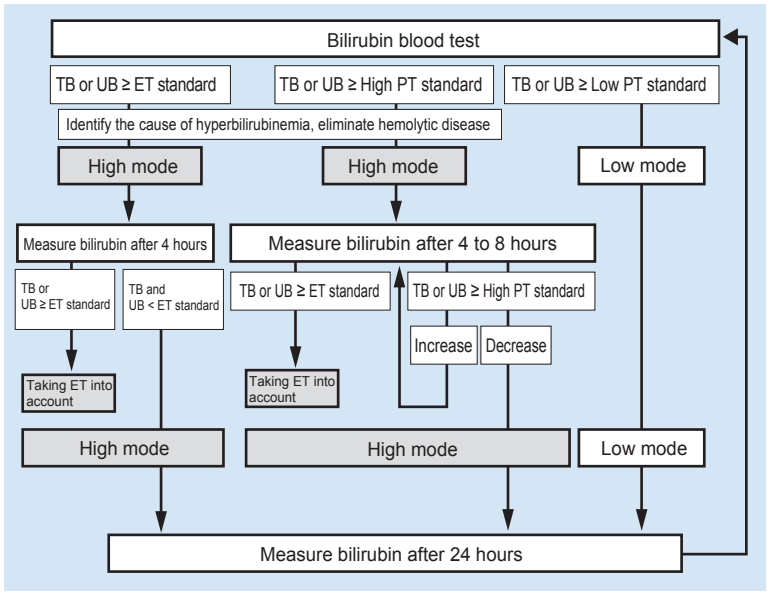

Fig. 3 Flowchart until phototherapy/exchange transfusion was introduced (Kobe University 2016)

ET: exchange transfusion, ET standard: exchange transfusion standard value, Low PT standard: Low mode phototherapy standard value, High PT standard: High mode phototherapy standard value, PT: phototherapy, TB: total bilirubin, UB: unbound bilirubin, Low mode: perform phototherapy in the Low mode, High mode: perform phototherapy in the High mode

(Ichiro Morioka, et al.: from Journal of Japan Society of Perinatal and Neonatal Medicine 2017, Nishoshi 2017)

Table 1 New standard for phototherapy/exchange transfusion treatment (Kobe University 2016)

GA or CGA	TB value standard mg/dL <24hr	<48hr	<72hr	<96hr	<120hr	120hr-	UB value standard μg/dL
22-25w	5/6/8	5/8/10	5/8/12	6/9/13	7/10/13	8/10/13	0.4/0.6/0.8
26-27w	5/6/8	5/9/10	6/10/12	8/11/14	9/12/15	10/12/15	0.4/0.6/0.8
28-29w	6/7/9	7/10/12	8/12/14	10/13/16	11/14/18	12/14/18	0.5/0.7/0.9
30-31w	7/8/10	8/12/14	10/14/16	12/15/18	13/16/20	14/16/20	0.6/0.8/1.0
32-34w	8/9/10	10/14/16	12/16/18	14/18/20	15/19/22	16/19/22	0.7/0.9/1.2
35w-	10/11/12	12/16/18	14/18/20	16/20/22	17/22/25	18/22/25	0.8/1.0/1.5

Treatment standard value varies according to weeks designated for correction

The values are the applicable standard values of Low mode phototherapy/High mode phototherapy/exchange transfusion

GA: gestational age weeks, hr: hours, CGA: corrected gestational age weeks, TB: total bilirubin, UB: unbound bilirubin, w: weeks

(Ichiro Morioka, et al.: from Journal of Japan Society of Perinatal and Neonatal Medicine 2017) 3).

These standards played a significant role in controlling CBE in full-term newborn infants[3]. However, it was created during the 1980s when the survival rate of extremely premature infants was low, so no standards were set for infants older than one week. Also, due to these standards, the number of phototherapy or exchange transfusions performed on extremely premature infants increased, which created the necessity to verify these standards for the purpose of optimizing this treatment. Furthermore, while there used to only be two treatment options for CBE for extremely premature infants, which are phototherapy, and if this was proven to not be effective, exchange transfusion was performed. However, current options to avoid a transfusion include reinforced phototherapy and albumin treatment[9].

In addition, prenatal diagnosis technology in obstetrics progressed and more accurate examinations of pregnancy (gestational age) weeks became possible. All these factors contributed to the establishment of the new three-step treatment standard by Kobe University in 2016 (Fig. 3, Table 1)[1]. Step1: phototherapy based on gestational age week and corrected gestational age week, Step 2: reinforced phototherapy, and Step 3: albumin treatment/exchange transfusion. Currently, multiple institutions are collaborating to verify the effectiveness of the standard in preventing CBE among extremely premature infants.

Operation method of Kobe University Treatment Standards 2016 [1]

(TB: total bilirubin, UB: unbound bilirubin)

1) Judge the standard values of serum TB and UB based on gestational age weeks at birth and corrected weeks using Table 1.
2) The values in Table 1 are the applicable standard values of Low mode phototherapy (Low PT)/High mode phototherapy (High PT)/exchange transfusion (ET).
3) The cases of hemolytic disease are not applied to the flowchart, and are treated according to the severity of the disease, including globulin administration, etc.
4) Start Low mode phototherapy when the Low PT standard value has been exceeded, and continue it for 24 hours. If either the serum TB value or UB value exceeds the standard after 24 hours, continue treatment. If they do not, stop the treatment. Measurement of the serum TB value and UB value must be performed 24 hours after the treatment is completed in order to check whether they increase again.
5) Start High mode phototherapy and investigate the cause of hyperbilirubinemia when the serum TB value or UB value has exceeded the High PT standard value (Measuring of albumin and direct bilirubin must be performed). Check the serum TB value and UB value again within 4 to 8 hours after the start of High mode phototherapy.
6) When the TB value is over 5 mg/dL and the direct bilirubin value is more than 10% of it, direct bilirubin may be the reason for the apparent high value of UB, therefore, the evaluation must be carried out carefully (when using UB Analyzer, Arrows, Osaka).
7) If either the serum TB value or UB value exceeds the ET standard:
a) Start the High mode phototherapy and investigate the cause of hyperbilirubinemia (Measurement of albumin and direct bilirubin must be performed).
b) If the serum UB value exceeds the ET standard, administer albumin. 1 g/kg/2 hours.
c) Check the serum TB value and UB value after 4 hours.
- Perform exchange transfusion if either the serum TB value or UB value exceeds the ET standard. However, calculate the decreasing rate of the value from the start of High mode phototherapy, and if it is estimated to fall below the ET standard within 12 hours, exchange transfusion may be withheld. Repeat checking appropriately until the value falls below the standard value.
- Continue High mode phototherapy if both the serum TB value and UB value are below the ET standard value.
- If both the serum TB value and UB value are below the ET standard value but are trending upward, repeat blood testing after 4 to 8 hours and reevaluate the status.
- If both the serum TB value and UB value are below the ET standard value and trending downward, repeat testing after 24 hours.
8) The light irradiation area shall be a distance of 30 cm from the body surface, and make sure the Low mode is 10 to 15 μW/cm^2/nm, and the High mode is 30 μW/cm^2/nm when using the Atom Phototherapy Analyzer II (Atom Medical Corporation, Tokyo).
9) When symptoms of acute bilirubin encephalopathy are observed during phototherapy, consider exchange transfusion.

[References]

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