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Percentile analysis of plasma total bilirubin—How different will the rate of phototherapy for jaundice of neonates be by different standards?

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ABSTRACT

Phototherapy of a jaundiced neonate is usually started when bilirubin exceeds a threshold in the standard. There are several standards used in the developed countries even though the guideline of American Academy of Pediatrics is considered to be a global standard. Although the purpose of phototherapy is the prevention of kernicterus, nowadays the prevalence of kernicterus in otherwise healthy term neonates in the developed countries is rare. Meanwhile several potential adverse effects of phototherapy have been reported. In the present study we tried to estimate how different the rate of phototherapy for the jaundice of neonates at lower risk of kernicterus would be by different standards. For this purpose, we utilized the records of plasma total bilirubin (TB) values of 1893 healthy neonates of 38 weeks and more which were measured on day 6 for the percentile analysis. However, this database did not include the TB values of the neonates who received phototherapy by day 6. Then the database was corrected with an assumption that TB on day 6 would have been normally distributed if no phototherapy had been performed. The mean and the standard deviation (SD) of corrected database were 11.29 mg/dl (193 µmol/l) and 3.63 mg/dl (62 µmol/l), respectively. Using a standard distribution with these mean and SD, the percents of TB values which exceed 18.0, 19.0, 20.0 and 21.0 mg/dl on day 6 were estimated 3.22%, 1.70%, 0.82% and 0.35%, respectively. Results of the present report would help to estimate the relative rate of phototherapy that is performed for the neonates who are term and otherwise healthy by different standards.

Keywords: Neonatal Jaundice; Bilirubin; Phototherapy; Kernicterus

1. INTRODUCTION

Neonatal jaundice is caused by plasma increase of unconjugated (indirect) bilirubin that occurs as results of excessive bilirubin production and delayed clearance of bilirubin from the blood. Although jaundice in the neonatal period is fundamentally harmless, some neonates need to be monitored because bilirubin is potentially toxic to the central nervous system. Elevated levels of plasma bilirubin, hyperbilirubinemia, can lead to bilirubin encephalopathy and subsequently kernicterus, with devastating, permanent neurodevelopmental handicaps.

There are two major treatments of hyperbilirubinemia: exchange transfusion and phototherapy. Exchange transfusion is performed for few neonates who are in a threatening condition of developing kernicterus. Meanwhile phototherapy is applied for much more neonates with less risk of kernicterus. Phototherapy of a jaundiced neonate is usually started when total bilirubin (TB) in the blood exceeds the threshold value in the standard. Various standards are used even among the developed countries [1]. Many of standards are categorized by gestational age including the guideline of American Academy of Pediatrics (AAP), because prematurity is one of a risk factors for kernicterus [2-6], and some standards are categorized by birth weight—for example the standards in Japan are all categorized by birth weight [7-9]. In the standards like Canadian guideline; low birth weight (<2500 g) is independently listed as a risk factor [5].

The rate of phototherapy is rather variable in the literatures [1,11-14]. But because neonatal jaundice is so common, many neonates at lower risk, most of whom will be unaffected, are treated to prevent kernicterus that would occur rarely [10]. Although reports of clinically

significant adverse effects from phototherapy are rare, several possible side effects have been reported [15-18].

The purpose of the present study is to estimate how different the rate of phototherapy for the jaundice of the neonates at lower risk of kernicterus will be by different standards used in developed countries. For this purpose, we tried to perform a percentile analysis of TB.

2. MATERIALS AND METHODS

The definition of the neonates at lower risk of kernicterus as the participants in this study was according to the categorization of neonates in the guideline for phototherapy of AAP [6]. In this guideline, neonates at lower risk of kernicterus are defined as those whose gestational age are 38 weeks and more and who are not associated with any additional risk factors for kernicters, like isoimmune hemolytic disease, glucose-6-phosphate dehydrogenase deficiency, asphyxia, sepsis, acidosis, etc. So the neonates whose gestational ages were 38 weeks and more and who were not with any risk factors for kernicterus were chosen as the participants in this study.

In Social Health Insurance Medical Center, newborn infants usually stay at hospital for 6 days and more. A blood sampling for the screening of inherited metabolic disorders will be performed in principle on day 6, otherwise on day 7, and a plasma TB value is measured simultaneously. In the present report we used these data of plasma TB values on day 6 recorded between 1999 and 2008.

2618 neonates were born in our hospital from 1999 to 2007, and the number of the neonates whose gestational ages were 38 weeks and more and who were not with any risk factors for kernicterus was 2279. In these 2279 neonates, 124 neonates received phototherapy by day 6. Excluding these 124 neonates, blood samplings were performed for 1893 neonates on day 6 and for 262 neonates on day 7. Therefore we used 1893 data of TB measured on day 6 for the analysis.

TB was measured by optical density method using Bilmeter A (Mochida-Siemens, Tokyo, Japan).

Phototherapy used to be performed in our hospital by a standard that was established by modifying one of standards in Japan (**Table 1**) until 2007. As described above standards in Japan are categorized by the birth weight. The threshold TB values of the standard in our hospital shown in **Table 1** were actually applied for 112 out of 124 neonates who received phototherapy and whose birth weights were more than 2500 g. For the other 12 neonates whose birth weights were 2020 - 2474 g, the lower TB values were applied as thresholds for phototherapy.

Statistical analyses were performed with a PC utilizing StatView ver. 5 (SAS Institute Japan, Tokyo, Japan). These analyses includes one-sample Kormogorov-Smirnov test to examine whether data are normally distributed.

This work was approved by institutional review board in Social Health Insurance Medical Center.

3. RESULTS

The histogram of TB data of 1893 neonates was shown in **Figure 1**. We named these data as database 1. The mean and the standard deviation (SD) of database 1 were 10.87 mg/dl (186 μmol/l) and 3.25 mg/dl (55 μmol/l), respectively. However, database 1 did not contain the TB data of the neonates who received phototherapy by day 6 to avoid the influence of phototherapy in the analysis. Then we tried to correct database 1 by adding the missing data which should have been included if no phototherapy had been performed until day 6.

To correct database 1 we assumed that TB on day 6 would have been normally distributed if no phototherapy had been performed. First of all, we estimated the number of missing data. As described above, 124 out of 2279 neonates whose gestational ages were 38 weeks and more and who were otherwise healthy neonates received

Table 1. Standards of phototherapy for the neonates at lower risk of kernicterus in Japan (whose birth weights were 2500 g and more and who are not associated with any risk factors).

Hour after birth	24 h	48 h	72 h	96 h	120 h
Day	Day 2	Day 3	Day 4	Day 5	Day 6
Institute	Threshold value (mg/dl)				
Kobe University [7]	10	12	15	18	18
Our Hospital (~2007)	10	14	16	17	18
Murata F [8]	12	15	17	18	19
The University of Tokyo [9]	10	14	17	19	20

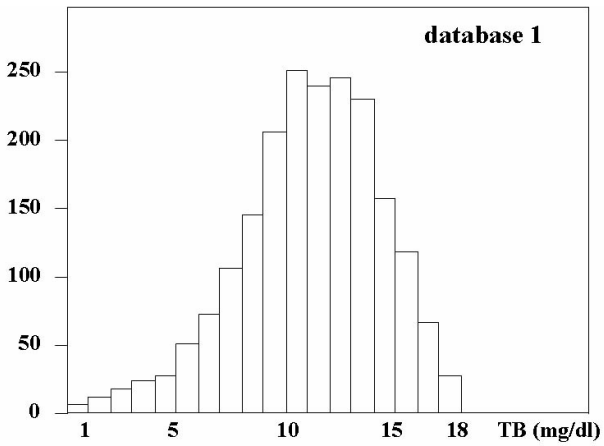


Figure 1. Histogram of TB on day 6 of the neonates whose gestational ages were 38 weeks and more and who are not associated with any risk factors for kernicterus (database 1).

phototherapy by day 6. Using these numbers we calculated that the rate of phototherapy for such neonates was 5.44%. With an assumption that database 1 did not include 5.44% of higher TB data, the database 1 (1893 data) was considered to consist of 94.56% of the data of corrected database. Therefore the data number of corrected database and the number of missing data could be calculated 2002 and 109, respectively. Second, we estimated the mean of the corrected database. Database 1 should be missing the highest 109 TB data by phototherapy, so it is possible to calculate the approximate mean value by excluding the lowest 109 TB data from database 1. We named such a database as database 2, and the mean of database 2 was calculated as 11.29 mg/dl (193 μmol/l). Third, to estimate missing highest 109 TB data, we calculated them with the following expression with an assumption that the distribution of TB values is symmetrical to the center value (the mean value).

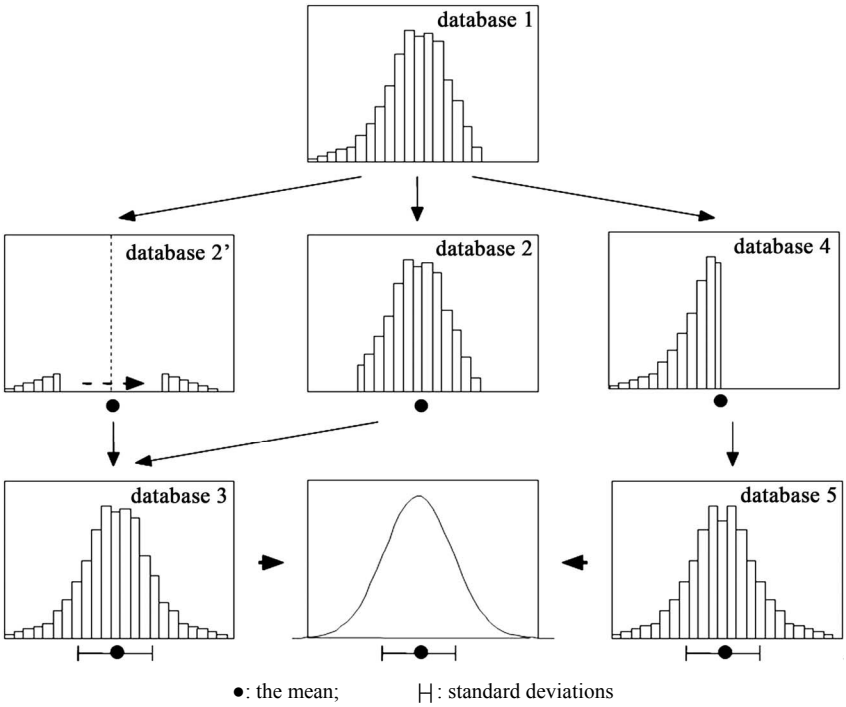
$$11.29 \times 2 - \mathrm{TB} \quad (1)$$

with the expression (1), the highest 109 TB data were calculated using the lowest 109 TB data, and 218 data that consisted of highest 109 TB data and lowest 109 TB data were named as database 2'. Finally, database 3 was established by adding database 2 and database 2'. As the matter of course the mean of database 3 was 11.29 mg/dl, and the SD became 3.63 mg/dl (62 μmol/l). To confirm that database 3 can be used for the percentile analysis, a one-sample Kormogorov-Smirnov test was performed for database 3, and there was no statistically significant difference between database 3 and the standard distribution that has same mean and SD as those of database 3 ($p = 0.331$). The calculating process was shown in **Figure 2**.

The mean and the SD of corrected database can be calculated in different way by the lower 1001 TB data of database 1 (database 4). The highest TB data of database 4 was 11.3 mg/dl. To estimate missing higher 1001 TB data, we calculated them with the following expression with an assumption that the distribution of TB values is symmetrical to the center value.

$$11.30 \times 2 - \mathrm{TB} \quad (2)$$

Then database 5 was established by adding database 4 and the higher 1001 data calculated using the expression (2). The mean and SD of database 5 became to 11.30 mg/dl and 3.63 mg/dl, respectively. Bilmeter A, with which we measured TB, can display the data of TB to the first place of a decimal point. Therefore the means of database 3 and database 5 are considered to be same, and SD of them was also same so far calculated (**Figure 2**).



Database 1: Raw histogram of 1893 TB data. Database 2: The histogram that does not contains the lowest 109 data of database 1. Database 2': The histogram that consists of the lowest 109 data of database 1 and the 109 data which are calculated by the expression (11.29 × 2 – TB) with the lowest 109 data. Database 3: The histogram that is established by adding database 2 and database 2'. Database 4: The histogram that consists of the lower 1001 data of database 1. Database 5: The histogram that consists of 1001 data of database 4 and the 1001 data which are calculated by the expression (11.30 × 2 – TB) with the 1001 data of database 4.

Figure 2. Calculating process of corrected database.

Using a standard distribution that has same mean and SD as those of database 3, the percents of TB values which exceed 18.0, 19.0, 20.0 and 21.0 mg/dl (308, 325, 342 and 359 μmol/l) on day 6 were estimated 3.22%, 1.70%, 0.82% and 0.35%, respectively.

4. DISCUSSION

The rate of phototherapy is rather variable in the reported studies [1,11-14]. It depends on how high the general level of bilirubin of the studied neonates was, how bilirubin was measured, and what kind of a standard for phototherapy was used. Although AAP guideline is considered to be a global standard, the evidence base for any standards of phototherapy is weak and various standards are used as national guidelines even among the developed countries (**Table 2**) [2-6]. In Japan no guideline has been established, and several standards are used (**Table 1**) [7-9]. We used to have our own standard in our hospital until 2007, however, the rate of phototherapy was so high that we changed our standard to Murata's standard in 2008 (**Table 1**).

Phototherapy is believed to be a convenient and safety treatment of neonatal jaundice; however, several possible side effects have been reported. One hazard which had concerned investigators was the possibility of retinal damage to infants exposed to phototherapy [15]. This hazard is now avoided by attaching neonates with an eye-musk. Reported cutaneous side effects include transient rashes and the uncommon bronze baby syndrome, and a more hazardous side effect is ultraviolet burn [16]. Recent study suggested that intensive phototherapy might increase the number of atypical melanocytic nevi identified at school age [17]. The potential of phototherapy to damage DNA based on animal or cell-culture studies have been described, and one study suggests that phototherapy increases DNA damage also in human newborns [18].

The purpose of the present study was to estimate how different the rate of phototherapy for the jaundice of the neonates at lower risk of kernicterus would be by different standards. For this purpose we utilized recorded data of plasma TB values on day 6. It is usual to let the neonates stay in the hospital for 6 days and to perform blood sampling for the screening of inherited metabolic disorders on day 6 in Japan. And we have measured plasma TB simultaneously on day 6 since 1999. These are the reason why we arbitrary chose the plasma TB measured on day 6 in the present report. Although there are several assumptions in the present study, the results suggest that when a threshold TB value on day 6 is elevated by 1 mg/dl the percent of neonates whose TB values exceed the threshold on day 6 will become approximately half.

The actual rate of phototherapy for the neonates at lower risk of kernicterus in our hospital was 5.44%, however, the results of percentile analysis indicated that the percent of TB values which exceeded 18.0 mg/dl that is a threshold value on day 6 for a neonate at lower risk was 3.22%. One possible cause of this discrepancy is that the neonates at lower risk of kernicterus defined in the analysis contained those whose birth weights were less than 2500 g. Actually 12 neonates received phototherapy by the lower thresholds of TB. To examine the influence of these neonates, we performed another analysis for the neonates whose birth weights were 2500 g and more, who are categorized into neonates at lower risk in Japanese standards. The actual rate of phototherapy of such neonates was 5.61% and the result of analysis indicated that the percent of TB values which exceeded 18.0 mg/dl for such neonates was 3.40%. Therefore an influence of the neonates of lower birth weights (<2500 g) on the result of analysis seems little. Meanwhile the discrepancy may be related to the natural course of neonatal jaundice. The lower percent of TB which exceeds 18.0 mg/dl in the percentile analysis suggests that TB values on day 6 of some neonates who received phototherapy before day 6 might have become lower than 18.0 mg/dl if phototherapy had not been performed.

We should discuss the limitation of this study. First of all, calculated data are only TB measured on day 6. Histograms of TB on another day should be different and the results of percentile analysis should be also different. Second, there are several ways to evaluate bilirubin value, bilirubin oxydase method, non-invasive transcutaneous method, to measure free bilirubin, etc. The results of percentile analysis should be different when bilirubin is measured by different methods. Third, we could not analyze the peak TB values of neonatal jaundice, and it is unable to compare the results of present study with other reports for peak TB values. Forth, we cannot predict the rate of phototherapy in the neonatal period pass by the calculated results in the present study.

Kernicterus is devastating neurological disorders which used to be a major cause of athetoid cerebral palsy. Al-

Table 2. Guidelines of phototherapy for the neonates at lower risk of kernicterus in the Western world (whose gestational ages were 37 or 38 weeks and more and who are not associated with any risk factors).

Hour after birth		24 h	48 h	72 h	96 h	120 h
Day		Day 2	Day 3	Day 4	Day 5	Day 6
Country	Establish	Threshold value (mg/dl)				
Israel [2]	2008	10	14	16	17.5	18.5
South Africa [3]	2006	10	14	16.5	18	18.5
Canada [4]	1999	10	15	18	19	19
UK [5]	2010	11.5	14.5	17.5	20.5	20.5
USA [6]	2004	12	15	17.5	19.5	21

though the prevalence of kernicterus in term infants is rare now, it is still being reported in North America and Western Europe in addition to less developed parts of the world [19]. However, in these countries, neonates stay at hospital only for few days, and it has been proposed that to search for validated criteria for follow-up of jaundiced infants after discharge are more important than revision of existing guideline for phototherapy [20].

As suggested in the present report the rate of phototherapy would be dependent on the stringency of standards. The Norwegian Pediatric Association established their national guideline in 2006. Recently, Bratlid *et al*. reported that with this guideline fewer babies in Norway received phototherapy and that no cases of chronic kernicterus have been reported since 2006 [21]. There is a possibility that the neonatal jaundice for otherwise healthy term neonates is being over-treated in the countries where stringent standards are used. Results of the present report would help to estimate the relative rate of phototherapy that is performed for the neonates who are term and otherwise healthy by different standards.

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