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A Randomized Controlled Trial Comparing the Duration of Phototherapy Following NICE and AAP Guidelines in Neonatal Hyperbilirubinemia.

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ABSTRACT

Background: Aims and Objectives: To compare duration of phototherapy between AAP and NICE guidelines in neonatal hyperbilirubinemia. **Methods:** In an open labelled study 130 babies with non-haemolytic hyperbilirubinemia were randomised to receive phototherapy following one guidelines between AAP and NICE. In this study we compared AAP 2004 and NICE 2010 guidelines to see whether following any of these two guidelines leads to phototherapy for longer duration. The primary outcome variable was duration of phototherapy and the secondary outcome variable was failure of phototherapy, defined as inability to reduce the TSB level of 2-3 mg/dl from baseline within 6 hours of phototherapy or inability to reduce TSB below exchange level. **Results:** Median age at onset of phototherapy was 77.55(19.43)hours in AAP group and 73.57(12.93) hours in NICE group, median gestational age was 37weeks in AAP group and 38weeks in NICE group, mean birth weight 2377.92gm in AAP group and 2457.10 gm. in NICE group, mean serum bilirubin at the onset of phototherapy was 18.77(1.570) mg/dl in AAP group and 18.24(1.89)g/dl in the NICE group. Average spectral irradiance was 55.8(µw/cm2/nm) in the study. Median duration of phototherapy in NICE as well as AAP group was 18 hours. There was no treatment failure in either group. Neurological examination was done at 40 weeks and 3 moths of corrected age. No abnormal neurological examination or BERA finding was reported in any of the babies. **Conclusion:** There is no difference in duration of phototherapy in any of the guidelines.

Keywords: Phototherapy, AAP, NICE, TSB.

INTRODUCTION

Over 60% of all newborns develop neonatal jaundice, & in 2% of these babies TSB level may reach upto 20mg/dl.[1,2] In India those babies born in hospital,3% develop serum total bilirubin (TSB)levels more than 15 mg/dl.[3] Health care providers recognize worldwidethat severe neonatal jaundice is a 'silent' cause of significant neonatal morbidity and mortality.[4-8] Phototherapy is the most effective therapy in lowering serum bilirubin when wavelength of the light output is in blue to green spectrum (420 to 490nm).As the potential recipients always outnumber in resource constrained setting, the proper and effective use of instruments becomes more important.[9,10] In our study we compared AAP 2004 and NICE 2010 guidelines to see whether following any of these two guidelines leads to phototherapy for longer duration. In a resource constrained setting, a guideline which treats babies for a shorter duration with equal efficacy will be more acceptable as regards the economic point of view. The guideline which allows us to treat babies for a shorter duration while being safe and efficient will also allow us to treat more number of babies.

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Aim and Objective:

To compare duration of phototherapy between AAP and NICE guidelines in neonatal hyperbilirubinemia

MATERIALS AND METHODS

1. Type of study: Open labelled, Prospective, Randomized, Controlled, and Interventional Study.
2. Place of the study: The study was conducted at the Department of neonatology, SSKM hospital and IPGMER, Kolkata, a 100 bedded tertiary care NICU.
3. Sample size and its calculation: Sample size for the study was calculated on the basis of duration of treatment (Phototherapy) as the primary outcome measure. Each group consisted of 64 no of babies. This sample size is able to detect a difference of 6

hours of phototherapy between the two groups as significant with 80% power and 5% probability of type 1 error. The effect size was based on a previous study by Barak et al.[11] The calculation assumes a standard deviation of 12 hours for the parameter and a two tailed testing. Sample size calculation was done with the help of nMaster 2.0 version of software (Department of Biostatistics, CMC Vellore, India).

Sample Recruitment Procedure:

Definition of population: All the consecutively born healthy new born babies between 35-42 weeks of gestational age. For the purpose of study the term healthy will mean a new born that is on oral feeds and with stable vital parameters.

Inclusion criteria:

- All babies requiring phototherapy for neonatal hyperbilirubinemia between 35-42 weeks of gestation was included in the study.
- Parental consent was compulsory before any baby is included in the study.

Exclusion criteria:

- Any baby having major congenital malformation was excluded.
- Babies with haemolytic jaundice were excluded.

Study period:

- 1st March 2015 to 30th June 2016 for data collection.
- 1st July 2016 to 30th September 2016 for data analysis.

Outcomes: primary and secondary

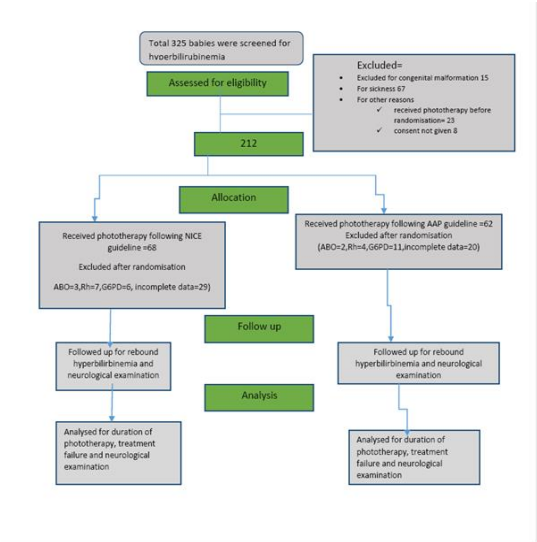
- Primary Outcome: The primary outcome variable is duration of phototherapy.
- Secondary outcome: The secondary outcome variables are treatment failure and rebound hyperbilirubinemia.

Treatment failure is defined as inability to reduce the TSB level of 2-3 mg/dl from baseline within 6 hours of phototherapy or inability to reduce TSB below exchange level.

Safety issues: Babies were examined for hearing at the time of discharge by BEAR test and neurological was done at completion of 40 weeks of gestation & 3 months of corrected age.This trial was approved by ethical committee of IPGME&R and SSKM Hospital,Kolkata.

Study technique: This is an open labelled, single centre, prospective, randomized controlled Trial. Total 130 no. of babies with neonatal jaundice requiring phototherapy, admitted in NICU of SSKM and IPGMER hospital, Kolkata during the study period were included in the study after their parents have given informed consent in writing. Babies with major congenital malformation and jaundice due to hemolysis were excluded from the study.

Randomization and allotment: By computer generated random numbers.Concealment of allotment was done bysequentially numbered opaque sealed envelope.



Methodology: Babies were screened for jaundice when appeared to be icteric. All the babies who were healthy and between 35-42 weeks of gestational age were allocated randomly to a group if they were found to have jaundice at a level that required to be treated with phototherapy. Babies with hyperbilirubinemia requiring treatment with phototherapy were treated either of this two groups (NICE vs AAP) after randomisation. Gestational age was calculated using New Ballard Score or first trimester USG report/dating scan. After randomization and allocation, one group (NICE group) received phototherapy as per the NICE 2010 phototherapy guidelines, while the other group (AAP group) was treated with phototherapy according to the AAP 2004 phototherapy guidelines. Photo therapy was started when the bilirubin level crossed the threshold in gestational age appropriate treatment chart in the NICE group and hour specific nomogram in the AAP group.All the babies were tested for total serum Bilirubin by standard Lab. Methods.Direct Coombs test, Reticulocyte count, G-6-PD level and other relevant investigations were done on clinical discretion and unit policy.Photo therapy was given by lullaby LED phototherapy device of GE health care, United States from a distance of 35cms in each group as per maker's suggestion. As per the makers statement this distance is likely to give an irradiance of > 45 µWcm-2nm-1in the high irradiance mode and > 22 µWcm-2nm-1 in Low irradiance mode. In this study phototherapy was always given in high irradiance mode.

Irradiation of this instrument was checked according to unit protocol. Irradiance was found to be 55.9 µWcm-2nm-1 at end of this study, with a mean

irradiance of 57.1 µWcm-2nm-1. Eyes were shielded by eye patch and scrotum in male babies was covered, otherwise the maximum surface area was exposed to light. Babies were kept in supine position if not otherwise indicated for any medical reason using LED phototherapy unit. The serum bilirubin level was assessed at start, after 2 hours of starting phototherapy (to exclude increasing trend that may reach exchange level)and then every 6 hours and charted on the appropriate charts.Nursing care was imparted according to unit protocol. No additional IV fluid was administered during photo therapy if not indicated for other reasons. Brief interruptions in phototherapy for breast feeding were accepted. Photo therapy of NICE group babies were stopped once the serum bilirubin level dropped below 50 µmol/litre (3mg/dl) from the threshold level for phototherapy as per NICE 2010 neonatal hyperbilirubinemia guidelines.Similar approach were followed for AAP group babies though when to stop the phototherapy is not clearly mentioned in AAP guidelines. Babies were assessed for rebound hyperbilirubinemia 12 hours after stopping phototherapy.

Evaluations of hearing were done for all babies at the time of discharge. Neurological examination was done at 40 weeks of gestation and three months of age. Duration of phototherapy was recorded for each baby along with relevant details using predesigned proforma.

Study analysis:

Data was summarised by descriptive statistics namely mean and standard deviation for numerical variables and counts and percentage for categorical variables. Numerical variables was compared between groups by 'student's' independent samples t test if normally distributed or by Mann-whitney u test if otherwise. Chi square test or Fisher's exact test was employed for intergroup comparison of categorical variables. All comparison was two tailed. $P<0.05$ was considered statistically significant.

RESULTS

Total 325 babies with neonatal jaundice of gestational age between 35- 42 weeks, out of this 195 babies were excluded. The reasons of exclusion are: Rh incompatibility (11), G-6-PD deficiency (17), ABO incompatibility (5),congenital anomaly (15),babiesreceived phototherapy before randomization (23),incomplete data/ blood sample collection (49),parents declined to give consent (8) and severe illness (68). The rest 130 babies fulfilled all the criteria needed for the study were ultimately taken for analysis. Out of these 130 babies 52 babies were treated as per NICE (UK) phototherapy charts and the remaining 78 babies had undergone as per AAP guideline. The primary outcome variable of this study was duration of phototherapy for both groups. The babies were then followed for decline of serum bilirubin by measuring serum bilirubin level at 2 hours of phototherapy, then at 6,12,18,24, 30and 36 hours. The data thus obtained has been statistically analysed and salient findings have been represented in form of charts and tables Data was analysed by descriptive statistics namely mean and standard deviation for numerical variables and counts and percentage for categorical variables. Numerical variables were compared between groups by 'Student's independent sample t test if normally distributed and Mann-Whitney U test if otherwise. Chi square or Fischer's exact test was used for inter group comparison of categorical variables.

Median age at onset of phototherapy was 77.55(19.43)hours in AAP group and 73.57(12.93) hours in NICE group,median gestational age was 37weeks in AAP group and 38weeks in NICE group, mean birth weight 2377.92gm in AAP group and 2457.10 gm in NICE group,mean serum bilirubin was 18.77(1.570) mg/dl in AAP group and 18.24(1.89) mg/dl in the NICE group.Others baseline demographic variables were also similar [Table 1] in both the groups.At any point of time similar percentage of babies was receiving phototherapy in both the groups.

The key findings of the study were:

- The duration of phototherapy between the guidelines was similar with a median duration of 18 hours; p = 0.145.[Table 2]
- There was no treatment failure or bilirubin induced encephalopathy in any of the groups.
- Rate of decline in serum bilirubin was similar between the groups; there was no significant difference in overall as well as gestational age specific decline of serum bilirubin. [Table 3]

Table 1: Baseline demographics of all subjects participating in the study.

		AAP (n=62)	NICE (n=68)	Significance
Birth Weight	Mean	2377.92	2457.10	P=0.407
	Median	2314	2398.50	
	Inter Quartile Range	1947-2769	2050.50-2862.50	
Gestational Age	Mean	37031	37031	0.843
	Median	37.00	38.00	
	Inter Quartile Range	36-39	36-38	
Male Sex		46.88%	53.13%	0.863
Mode of Delivery	Caesarean Section	54.84%	45.16%	0.837
	Vaginal Delivery	51.02%	48.98%	
	Forceps Delivery	1		

Age of onset phototherapy (hr)	Mean (SD)	77.55 (19.43)	73.57 (12.93)	0.169
Weight at onset phototherapy	Mean (SD)	2095.45(644.93)	2197.07(633.93)	0.367
Serum Bilirubin at start of phototherapy	Mean (SD)	18.77(1.570)	18.24(1.89)	0.086
Hematocrit	Mean (SD)	50.58(3.39)	50.06(3.41)	0.383
Reticulocyte Count	Mean (SD)	3.38(0.97)	3.57(1.02)	0.277
Average Spectral Irradiance	(µw/cm2/nm)	55.8	55.8	

Table 2: Depicting duration of phototherapy in AAP and NICE Group

Number of babies receiving phototherapy	NICE(68)	AAP(62)
For maximum of 12 hours	22	11
For maximum of 18 hours	22	26
For maximum of 24 hours	16	13
For maximum of 30 hours	7	11
For maximum of 36 hours	1	1

Table 3 showing decline in mean serum bilirubin level in the two groups in different time frame

	Fall in mean TSB /hour at onset	Fall in mean TSB /hour at 2hr	Fall in mean TSB /hour at 6hr	Fall in mean TSB /hour at 12hr	Fall in mean TSB /hour at 18hr	Fall in mean TSB /hour at 24hr	Fall in mean TSB /hour at 30hr	Significance
NICE (68)	0.5±0.3	0.3±0.1	0.3±0.1	0.4±0.3	0.5±0.3	0.6±0.1	0.5±0.3	P=0.828
AAP (62)	0.5±0.3	0.4±0.1	0.3±0.1	0.3±0.2	0.5±0.3	0.5±0.2	0.5±0.3	
Total (130)	0.5±0.3	0.4±0.1	0.3±0.1	0.4±0.3	0.5±0.3	0.5±0.2	0.5±0.3	

Figure 1 showing duration of phototherapy

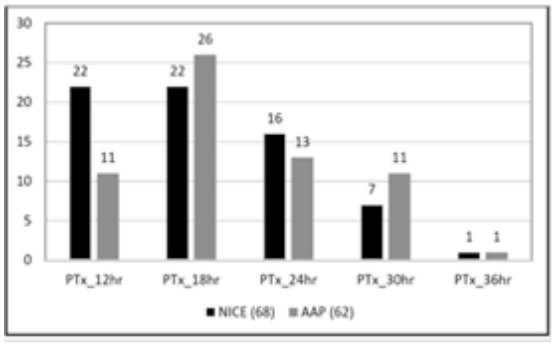
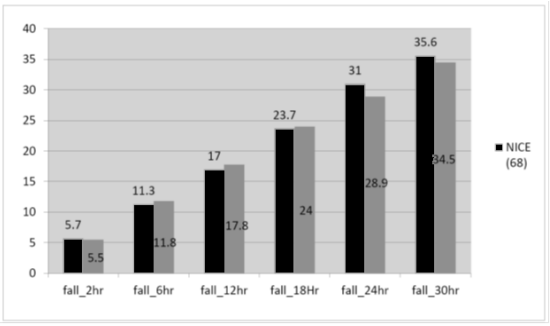


Figure 2 showing Percentage of fall in serum Bilirubin level in predefined time epochs in AAP and NICE group in the study.



DISCUSSION

There is no uniform guideline that is followed for phototherapy all over the world; different countries have their own guidelines which differ in the threshold of starting and stopping phototherapy. Different guidelines have tried to define severe hyperbilirubinemia differently. Some (USA, India)defined it as a TSB over 95th percentile of a specific, hour-based monogram while others (Australia, UK) recommended different TSB percentiles based on gestational age.[12-15]

In this single centre study total 130 babies were randomized to receive phototherapy by one of the two guidelines among AAP and NICE phototherapy guidelines. We have used similar irradiance for both the guidelines. Babies were monitored for duration of phototherapy, rate of decline of serum bilirubin level and treatment failure. Both the guidelines were found to be similar in regards duration of phototherapy, rate of decline of serum bilirubin level and treatment failure.

Baseline Demographic profile was similar in both the groups. In this study the gestational age (p=0.843) and age of onset of phototherapy (p=0.905) were statistically similar in between the groups. Risk factors that can affect bilirubin level like breast feeding (p=0.349) and oxytocin administration (p=1.0) were similarly distributed.

The endpoint of phototherapy for NICE treatment protocol is very clear, and stops when the serum bilirubin falls more than 51 micromole/litre below the hour specific threshold of phototherapy. The AAP guideline is not very clear in this respect , but in this study we have taken a conservative approach like NICE guideline and stopped phototherapy in the AAP group in the same manner like that of NICE guideline(3 mg/dl below the phototherapy cut off).

In our knowledge, there was no previous study that compared these two guidelines in any aspect, so duration of phototherapy among these two groups could not be compared with previous studies. However we tried to compare duration of phototherapy, treatment failure and rate of decline in serum bilirubin with other studies that used high intensity phototherapy

The median duration of phototherapy (18hours) in this study was similar in between the AAP and NICE groups. With phototherapy being started at a same point and ends at a same point, risk factors remaining balanced between groups with similar devices used in both the groups; that's why duration of phototherapy was found to be similar. We compared our study for duration of phototherapy with two other studies that used high intensity phototherapy. One of these studies was conducted by Kumar Pet al at 2010 and another was conducted by Decarvalho et al at 2010.[16,2] The duration phototherapy in the current study was lower than that conducted by Kumar et al. The higher duration in their study may be due to the fact that they had higher number of babies who needed instrumental delivery, oxytocin use was much higher, babies with G-6P D deficiency were included, irradiance was lesser in comparison to our study and also rate of exclusive breast feeding was higher in that study.

There was no treatment failure in either group. The babies in our study were inborn, being treated in a tertiary care hospital and was under regular observation, allowing hyperbilirubinemia to be detected early before bilirubin load approaches exchange level. We had also adopted a conservative approach and stopped phototherapy only when serum bilirubin level was lower than51 micromole/l from the hour specific threshold. The mean irradiance of our lullaby LED device was 55.8µw/cm2/nm. In this study, babies with haemolysis were excluded. So our study group had a low bilirubin level, were detected early and treated with a highly efficient device and were off phototherapy only after reaching a position which lessens the chance of treatment failure. All these adequately explain this finding of not having treatment failure. In the study of Decarvalho100 also babies were treated with high intensity phototherapy and there was no treatment failure. The mean irradiance level in that study was lesser than our study (mean irradiance=30µw/cm2/nm) but with greater surface area of exposure by addition of multiple phototherapy unit.

The rate of decline of serum bilirubin was similar between the groups. There was no statistically significant difference in the overall rate of decline and in the gestational age specific subgroups as analysed by the independent sample't' test. Baseline serum bilirubin level is a factor that determines the rate of decline in serum bilirubin and any group having higher baseline serum bilirubin level would have a higher rate of decline in serum bilirubin101. So to compare between groups it is essential for the groups to have a comparable serum bilirubin level. In our study baseline serum bilirubin level was comparable (18.24 in NICE VS 18.77 in AAP group). We compared our study with that of Decarvalho et al. for comparing rate of decline and percentage of fall in serum bilirubin/hour.[2] The rate of decline in serum bilirubin level and percentage of fall in serum bilirubin level was more in the study of Decarvalho et al, the reasons may be babies in that study had baseline serum bilirubin level higher than that of the current study, the mean post natal age was much higher (6.9±2.8 days)as compared to the present study and top feeding was the preferred type of feeding in that study. All these could have helped to reduce serum bilirubin faster.

In our study the mean decline in TSB level was also higher than that in the study by Kumar et al (0.25 mg/hr in the AAP group and 0.23mg/dl mg/hr in the NICE group vs 0.19 mg/dl).16 The baseline serum bilirubin level was higher in our study groups (18.24 and 18.77 mg/dl in NICE and AAP group respectively vs 16.8 and 16.9) in comparison to that in the study by Kumar et al. Irradiance was higher in our study, the proportion of formula feeding babies was also higher in our study while induction of labour by oxytocin administration was lower. All these explain the higher rate of decline in serum bilirubin in our study.

The babies were followed up for neurological examination at completion of 40 weeks and corrected age of three months and hearing examination was done by BERA at discharge. There was no incidence of hearing impairment or neurological abnormality in any babies treated.

Limitations of the study:

1. The study was not blinded.
2. Sample size was small.
3. The current study compared babies of gestational age of 35 weeks and above. The preterm babies of lesser gestational age who has the chance of suffering from low bilirubin encephalopathy could not be covered in the current study.

CONCLUSION

There is no difference in duration of phototherapy between AAP and NICE guidelines for treatment of neonatal jaundice.

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