HHS Public Access

Author manuscript

J Perinatol. Author manuscript; available in PMC 2013 March 01.

Published in final edited form as:

J Perinatol. 2012 September ; 32(9): 677–684. doi:10.1038/jp.2012.64.

Does Aggressive Phototherapy Increase Mortality while Decreasing Profound Impairment among the Smallest and Sickest Newborns?

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Abstract

Objective—Aggressive phototherapy (**AgPT**) is widely used and assumed to be safe and effective for even the most immature infants. We assessed whether the benefits and hazards for the smallest and sickest infants differed from those for other extremely low birth weight (**ELBW**; (≤1000 g) infants in our Neonatal Research Network trial, the only large trial of AgPT.

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The authors declare no other potential conflicts of interest.

Dr. Tyson drafted the manuscript and no form of payment was given him to produce the manuscript.

Study Design—ELBW infants (n=1974) were randomized to AgPT or conservative phototherapy at age 12–36 hours. The effect of AgPT on outcomes (death; impairment; profound impairment; death or impairment [primary outcome], and death or profound impairment) at 18–22 months corrected age was related to BW stratum (501–750 g; 751–1000 g) and baseline severity of illness using multilevel regression equations. The probability of benefit and of harm was directly assessed with Bayesian analyses.

Results—Baseline illness severity was well characterized using mechanical ventilation and FiO_2 at 24 hours age. Among mechanically ventilated infants ≤750 g BW (n =684), a reduction in impairment and in profound impairment was offset by higher mortality (p for interaction <0.05) with no significant effect on composite outcomes. Conservative Bayesian analyses of this subgroup identified a 99% (posterior) probability that AgPT increased mortality, a 97% probability that AgPT reduced impairment, and a 99% probability that AgPT reduced profound impairment.

Conclusions—Findings from the only large trial of AgPT suggest that AgPT may increase mortality while reducing impairment and profound impairment among the smallest and sickest infants. New approaches to reduce their serum bilirubin need development and rigorous testing.

Keywords

Phototherapy; bilirubin; severity of illness; ELBW infant; impairment; randomized clinical trial; statistical interaction; Bayesian analysis

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With the increasingly aggressive care of the most immature newborns, it is important to ensure that the therapies that they receive are both safe and effective. Yet, as Lucy has emphasized, [1] "these fetal infants are receiving many therapies… that have never been tested on this unique population."

In this manuscript we address whether aggressive phototherapy (**AgPT**), a therapy that is widely used in treating extremely low birth weight (**ELBW**; ≤1000 g), may increase the mortality of the smallest and sickest infants while reducing their serum bilirubin and risk of bilirubin neurotoxicity and neurodevelopmental impairment. Aggressive use of phototherapy has been encouraged by the neurodevelopmental delay associated with even low serum bilirubin levels among small premature infants in multiple large cohort studies.[2] However, phototherapy has been assessed in only two large randomized trials, the most recent by the 16-center Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network.[3] In this trial we randomized ELBW infants at 12–36 hours of age to AgPT (provided at a total serum bilirubin value of 5 mg/dL or higher in the first week and 7 mg/dL or higher in the second week) or to conservative phototherapy (**ConPT**) (provided at a bilirubin value of 8mg/dL or higher for 501–750g infants and 10mg/dL or higher for 751–1000g infants). We failed to demonstrate that AgPT reduced the primary outcome (death or impairment) (adjusted relative risk [**RR**] = 0.94 [95% confidence interval = 0.87–1.02]). However, AgPT did reduce neurodevelopmental impairment at 18–22 months corrected age (after term) (RR = 0.86; [0.74–0.99]), a reduction due almost entirely to a reduction in profound impairment (RR = 0.68; [0.52–0.89]).

Of concern, mortality with aggressive phototherapy was increased, albeit not significantly, in the smaller birth weight stratum (501–750 g) (RR =1.13 [0.96 to 1.34]). A potentially important though nonsignificant increase in mortality also occurred in the only other major phototherapy trial (the Collaborative Phototherapy trial conducted in the 1970s).[4,5] In this trial the RR was 1.49 (0.93 to 2.40) among ELBW infants randomized to phototherapy or no phototherapy.[6]

Although considered quite safe,[7] phototherapy may reduce the antioxidant benefits associated with moderate bilirubin levels[8,9] or cause oxidative injury or other adverse effects.[10,11,12] Such problems might increase mortality among the smallest and sickest infants with the thinnest, most translucent skin and greatest vulnerability to phototoxicity. Conversely, the benefits of phototherapy may be greatest in these infants by preventing bilirubin neurotoxicity associated with hypoalbuminemia, hemolysis, infection, hypoxia, hypercapnia, or other problems that increase bilirubin production, reduce albumin binding, or compromise the blood-brain barrier.[13,14,15]

The protocol for our Network trial included plans to relate the risks and benefits of aggressive phototherapy to baseline risk factors including measures of severity of illness. This manuscript reports our analyses assessing whether the benefits and hazards of AgPT for the smallest and sickest infants differed from those for other ELBW infants. Partly because conventional frequentist analyses do not allow the probability of benefit or harm from treatment to be calculated,[16,17] we performed Bayesian as well as frequentist analyses, as recently recommended for all clinical trials.[18]

METHODS

The trial is described in detail elsewhere[3] and summarized below.

Population

Infants with a BW of 501 to 1000 g were enrolled 12 to 36 hours after birth. Exclusion criteria included terminal illness (pH <6.8 or persistent bradycardia and hypoxemia for >2 hours), major congenital anomaly, severe hemolytic disease, and congenital nonbacterial infection. After parental informed consent was obtained, infants were stratified by center and BW (501–750g; 751–1,000g) and randomized using a centralized computer system.

Treatment

The protocol stipulated phototherapy administration during the first 14 postnatal days. Total serum bilirubin was measured in the first week at least once daily and in the second week when phototherapy had been given in the previous 24 hours or the last bilirubin exceeded 7mg/dL. Phototherapy was provided at the bilirubin values noted above and administered for at least 24 hours whenever started or restarted. The target irradiance level was 15–40μW/cm^2/nm. Irradiance was increased within this range at bilirubin thresholds of 13 mg/dL for infants 501–750g and 15 mg/dL for infants 751–1,000g. An exchange transfusion was indicated whenever the bilirubin exceeded the threshold after 8 hours of intensified phototherapy. As appropriate for an effectiveness trial, the caregivers selected the fluid

regimens, feedings, brand of phototherapy lamps, indications for mechanical ventilation and other interventions.

Outcome assessments

The outcomes included death, impairment, profound impairment, death or impairment (primary trial outcome), and death or profound impairment at 18–22 months corrected age. Outcomes at 18 to 22 months of corrected age were assessed by blinded neurological examiners and neurodevelopmental assessors trained to reliability during a 2-day workshop.[19] Impairment was defined as blindness (no functional vision in either eye), severe hearing loss (hearing loss for which bilateral hearing aids were prescribed), moderate or severe cerebral palsy, or a score below 70 on the Mental or Psychomotor Development Index of the Bayley Scales of Infant DevelopmentII.[20] Profound impairment was defined as a score of ≤50 for either index or a level of 5 for gross motor function by the modified Palisano criteria.[21] (Profound impairment was not initially defined as an outcome for the trial but was added partly because profound impairment is less likely than less severe impairment to improve with age.[22] This definition was based on prior Network studies[23] and selected before any comparison of the outcomes of treatment groups. Infants were classified as having moderate or severe cerebral palsy if they were unable to walk or required assistive devices. Hearing outcomes were determined by the neurologic examiner and from parental report.

Statistical Analyses

Baseline severity of Illness—Multiple variables that may influence risk of bilirubin neurotoxicity or need for phototherapy (resuscitation drugs, chest compressions, early-onset sepsis, administration of pressors, acidosis (pH <7.10), hemolytic disease) were assessed singly and in combination. They added little beyond mechanical ventilation and FiO_2 at 24 hours in predicting outcomes at 18–22 months. Accordingly, the latter two variables were used as our illness severity measures.

Relation of treatment, BW, and illness severity to outcome—Intention-to-treat analyses were performed; the denominator for each outcome was the number of infants randomized whose outcome was known (three infants had a missing value for mechanical ventilation.) There was no adjustment for multiple comparisons.[24] In the frequentist analyses, the adjusted RR for each outcome was estimated using robust multilevel Poisson regression analyses (with center as a random effect to account for center variability). Predictor variables included treatment (AgPT or ConPT), BW, stratum (501–750 g; 751–1000 g), mechanical ventilation, FiO_2 at 24 hours age, and interaction terms. In assessing the effects of AgPT on the smallest and sickest infants, three-way interactions and constituent terms were assessed with backward elimination of terms with a $p > 0.10$. (Because of limited power to identify interactions, a $p>0.10$ was used to reduce the risk of false negative findings.) Each final model included all main effects. The same approach was used in conducting secondary analyses for each outcome that included additional predictor variables (gestational age, sex, ethnicity, and inborn/outborn status). Bayesian statistics were used to estimate the probability of a RR <1.0 and of a RR < 0.9 with AgPT. Hierarchical analyses were performed using an extended approach of Dixon and Simon.[25] Hierarchical models

have the statistical advantage of pooling specific subgroup estimates rather than estimating an effect for each subgroup.

Bayesian models included the same predictors as in the final frequentist, multilevel Poisson regression models. For all main effects in the models, we used a neutral prior distribution centered at a RR = 1.0 with 95% credible intervals of 0.5 to 2.0 (a range that includes the values observed in the great majority of large neonatal trials[26] (~N[log RR =0, 0.125]). All interaction terms assumed independent informative Normal prior distributions centered at log RR of zero and separate variance components for the two-way and three-way interaction terms (a prior that is skeptical, a priori, about interaction terms but which allows treatment estimates to vary across subgroups). For subgroups with a small sample size or number of adverse outcomes, Bayesian models shrink the subgroup-specific estimate toward the overall estimate of treatment effect thereby reducing the likelihood of overestimating subgroup differences.[27] To perform a sensitivity analysis and assess the robustness of the disturbing results for death, we repeated the analysis assuming an optimistic prior probability with the RR centered at 0.90 (i.e., a 10% reduction in death with AgPT) and the probability of a RR>1.1 at 2%. In reporting the Bayesian analyses, we follow the guidelines developed by Sung et al.[28]

RESULTS

In all analyses, the Bayesian and frequentist models produced similar values for the RR. The tables include these values and to provide information not obtainable from frequentist statistics the (posterior) probability of a RR <1.0 and <0.9.

Death (Table 1)

Overall and for all subgroups except one, the analyses provided minimal or no evidence that AgPT increased mortality (RR≤1.01). However, 501–750 g ventilated infants (n = 696) had an *increased* RR (1.19; 95% confidence interval: 1.01–1.39) with only a 1% estimated probability of decreased mortality and thus, a 99% estimated probability of *increased* mortality with AgPT. These findings were associated with a p<0.05 for an interaction of treatment with birth weight and mechanical ventilation. The sensitivity analysis gave similar results (96% probability of increased mortality with AgPT for the 501–750 g ventilated infants) despite using an optimistic prior (0.90 relative risk for death).

Impairment or profound impairment (Table 2)

Because there was no evidence that treatment effects for these outcomes differed among the patient subgroups (no interaction terms that were significant; p values > 0.31), all subgroups were combined in the analyses. The results consistently favored AgPT (RR = 0.69–0.89) among all infants enrolled and among all survivors assessed with 96% to >99% estimated probability of a reduction in impairment or profound impairment and a 95%–97% probability of a RR <0.90 in profound impairment.

Death or impairment (Table 3)

Overall AgPT was associated with a marginally significant and potentially important overall reduction in death or impairment (RR = 0.91–0.93; upper 95% confidence or credible limits for both of 1.01) and a 95% estimated probability that the composite outcome of death or impairment was reduced (a RR <1.0). However, the findings differed by subgroup (an interaction of treatment with BW and mechanical ventilation; $p<0.05$) with less than a 50% estimated probability of a reduction in this composite outcome among ventilator treated infants ≤750 g and among nonventilated 751–1000 g infants.

Death or profound impairment (Table 4)

Overall, there was a significant reduction in death or profound impairment (RR = 0.88–0.89) with a 99% estimated probability that AgPT reduced this composite outcome. The effect of treatment differed by BW stratum irrespective of mechanical ventilation ($p=0.06$). Infants greater than 750 g BW had a RR of 0.81 with a 99% estimated probability of a reduction in death or profound impairment. AgPT did not reduce this outcome among infants in the smaller BW stratum (RR= 0.98). Results similar to those above were found using secondary models that also included gestational age, sex, ethnicity, and whether the infants were born within or outside their Network center.

Discussion

Despite concerns about extrapolating treatment effects from larger and healthier infants to the most immature infants,[1] phototherapy has been considered both effective and safe in all newborns.[7] Yet, preterm infants have been randomly assigned to treatment with phototherapy or no phototherapy in only one large trial, and it was performed decades ago.[11,12] The findings were compatible with a substantial increase in mortality with phototherapy among not only ELBW infants as noted above but also among all low BW (<2500 g) infants (n=1,063; RR =1.32 [0.96–1.82]).[13] These findings have been largely ignored because they were not significant at a $p<0.05$, an error often made in failing to recognize and seriously consider important potential treatment hazards when statistical power is limited.[29]

In our Network trial, 80% of the ConPT group received phototherapy, a factor likely to make it difficult to identify phototherapy hazards except perhaps in the most vulnerable infants. We previously reported that the absolute number of deaths among 501–750 g infants was 5% greater with aggressive than ConPT, a difference equal to the 5% absolute reduction in the number of infants with impairment and only slightly more than the 4% reduction in infants with profound impairment in this BW group.[9] Although the P value for a two-way interaction between treatment group and BW was not significant (P=0.15), power was limited, and this finding, like those in the Collaborative Phototherapy Trial, suggests the possibility of an increased mortality in the smallest infants in the trial.

This Network trial is the only large trial to date of AgPT. The preselected primary outcome was the composite outcome of death or impairment. Composite outcomes have the disadvantage that treatment may have opposite effects for the outcome components.

However, the use of composite outcomes may be unavoidable for such questions as the effect of AgPT on survival without impairment when the components (death or impairment) are competing outcomes. When, as in our analysis of ventilated 501–750 g infants, the effect of treatment appears to differ for the different components of outcome, the results for each component should be separately analyzed.

The analyses reported herein were conducted to provide the best assessment possible with the available data to evaluate whether the benefits and hazards of AgPT among the smallest and sickest infants differ from those in other ELBW infants. Because the effects of any therapy may differ considerably in different subgroups, subgroup differences should be considered in any trial.[30] Such differences are particularly important in identifying treatment hazards to which the highest risk patients may be especially vulnerable. Our trial, like almost all clinical trials, had high power only to identify overall treatment effects using conventional frequentist statistics. Even so, we identified a significant three-way interaction suggesting that AgPT increased mortality among ventilated infants ≤750 g BW. This finding was supported by the sensitivity analysis using an optimistic prior probability.

Subgroup analyses must be viewed with skepticism. However, subgroup analyses are most likely to be valid when, as in our study, they are supported by preexisting evidence, their assessment was preplanned, and they are biologically plausible.[31] Bilirubin is reported to be a powerful antioxidant. The reduction in bilirubin with phototherapy might increase the susceptibility of ELBW infants to oxidative injury.[8,9] Moreover, phototoxicity might directly result in oxidative injury to cell membranes or other adverse effects.[10,11,12] While larger and healthier infants might escape injury discernible in our trial, phototoxicity would be most likely to be identifiable in the most immature infants whose skin readily transmits light and who would be most vulnerable to oxidative injury The use of AgPT for the smallest and sickest newborns might be analogous to use of surgery (rather than radiation or chemotherapy alone) for some cancer patients to improve their long term outcome despite a greater initial risk of death.

The possibility that AgPT increases mortality of ventilated infants ≤750 g BW treated is supported by our Bayesian analyses performed to complement the frequentist analyses. Frequentist analyses assess the probability that the observed or a larger difference between groups would occur *assuming the null hypothesis is correct*. Such analyses do not assess the likelihood that the alternative hypothesis is correct. In contrast, Bayesian analyses directly assess the question: how likely is the treatment to have benefit/harm?[16,17,18, 32,33] These analyses may be most helpful in estimating treatment benefits and hazards when power is limited as subgroup analyses.[17] Bayesian analyses allow prior estimates of treatment effect to be updated using new data in estimating the (posterior) probability of benefit. Concerns about Bayesian analyses have largely been concerns that the prior probability would be derived from methodologically weak studies and be overly optimistic. These concerns do not apply to our analyses. The posterior probability that AgPT increased mortality was estimated using a neutral prior probability despite the evidence of an increased mortality in the one large prior trial of phototherapy,[4,5,6] and the values for RR were similar in the Bayesian and frequentist analyses and identified a high probability that AgPT increases

mortality while reducing profound impairment, an outcome that some people consider worse than death.[34,35]

In recent observational analyses of the Network trial,[36] higher plasma bilirubin levels on day 5 were associated with a higher risk of death or impairment among unstable infants (infants who at five days had any of various risk factors [primarily mechanical ventilation but also blood pH < 7.1, pressor therapy, a positive blood culture, or apnea and bradycardia requiring bag and mask ventilation or intubation during the prior 24 hours]). This relationship was not observed among stable infants. These analyses did not involve any assessment of the effect of AgPT, have the limitations inherent in observational analyses for making treatment inferences, and thus do not contradict our analyses. Clinical instability at age 5 days may be the result--not the cause---of bilirubin toxicity that resulted in hypoventilation, recurrent apnea, or clinical instability prompting the use of respiratory or pressor support. The presence or absence of these problems may simply be a marker for infants who experienced bilirubin toxicity or phototoxicity.

Ordinarily, evidence of treatment heterogeneity like we identified in our analyses would generate a hypothesis to be tested in future trials.[29] In this instance, there may never be another large trial comparing phototherapy to no phototherapy or AgPT to ConPT in ELBW infants. We considered whether to extend the Network trial to randomize additional infants less than 750 g BW to more precisely assess the risks and benefits of AgPT and ConPT in this subgroup. We decided against doing this partly because the findings with 684 such infants randomized suggested that any increase in survival with ConPT would be almost entirely offset by an increase in survivors with profound impairment.

The mortality findings in the Network trial prompted Watchko and Maisels to conclude that “In infants <750 g, it seems prudent to initiate phototherapy at lower irradiance levels. Irradiance levels can be increased, if necessary, or more surface …exposed to phototherapy if the bilirubin rises.”[37] It remains to be determined whether the approach would avoid an increase in mortality while maintain the reduction in profound impairment with AgPT in the Network trial. The appropriate irradiance levels and how they would be best achieved is unclear, partly because the manufacturing changes in phototherapy lamps since the prior Collaborative Phototherapy have substantially increased the irradiance levels that they deliver (mean of 22–23 μW per square centimeter per nanometer each day as measured at the infant’s skin during the Network trial[3]).

In summary, the findings from the Network trial--the only large trial of AgPT yet performed--suggest that AgPT may increase mortality while reducing impairment and profound impairment among the smallest and sickest infants. As for other neonatal therapies, phototherapy should not be assumed to have the same risks and benefits in the smallest and sickest infants as in more mature infants. Our results indicate an urgent need to develop other treatment approaches using lower irradiance levels or other treatment methods[38] that may reduce severe bilirubin neurotoxicity without risking an increase in the mortality of these infants. These treatment approaches could then be rigorously tested by comparing them to AgPT in a large randomized trial.

Acknowledgments

This study was supported by grants from the National Institutes of Health and from the Eunice Kennedy Shriver National Institute of Child Health and Human Development, Natus Medical loaned light-emitting diode phototherapy lights to each center. These lights were used at the discretion of the attending neonatologist in treating infants in either treatment group. The lights were returned to Natus Medical or purchased at a prorated price after the study. Natus Medical played no role in the study design, data collection, data analysis, or manuscript preparation or revision.

Funding/Support. The National Institutes of Health and the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) provided grant support for the Neonatal Research Network's Phototherapy Trial (ClinicalTrials.gov NCT00114543). All data analyses and interpretation were done independently of the funding agency.

Data collected at participating sites of the NICHD Neonatal Research Network (NRN) were transmitted to RTI International, the data coordinating center (DCC) for the network, which stored, managed and analyzed the data for this study. On behalf of the NRN, Dr. Abhik Das (DCC Principal Investigator) and Mr. John Langer (DCC Statistician) had full access to all the data in the study and take responsibility for the integrity of the data and accuracy of the data analysis.

We are indebted to our medical and nursing colleagues and the infants and their parents who agreed to take part in this study.

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Additional Contributions

RTI International, the data coordinating center (DCC) for the network, which stored, managed and analyzed the data for this study. On behalf of the Network, Dr. Abhik Das (DCC Principal Investigator) and Ms. Nellie Hansen (DCC Statistician) at RTU International had full access to all the data in the Phototherapy Trial and take responsibility for the integrity of the data. The following investigators, in addition to those listed as authors, participated in this study:

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Cincinnati Children's Hospital Medical Center, University Hospital, and Good Samaritan Hospital (U10 HD27853, M01 RR8084) – Kurt Schibler, MD; Edward F. Donovan, MD; Jean J. Steichen, MD; Kate Bridges, MD; Barbara Alexander, RN; Marcia Worley Mersmann, RN CCRC; Holly L. Mincey, RN BSN; Jody Hessling, RN; Teresa L. Gratton, PA; Kimberly Yolton, PhD.

Duke University School of Medicine, University Hospital, Alamance Regional Medical Center, and Durham Regional Hospital (U10 HD40492, M01 RR30) – Ronald N. Goldberg, MD; C. Michael Cotten, MD MHS; Ricki F. Goldstein, MD; Kathy J. Auten, MSHS; Kimberley A. Fisher, PhD FNP-BC IBCLC; Melody B. Lohmeyer, RN MSN; Kathryn E. Gustafson, PhD; Katherine A. Foy, RN.

Emory University, Children's Healthcare of Atlanta, Grady Memorial Hospital, and Emory University Hospital Midtown (U10 HD27851, M01 RR39) – Barbara J. Stoll, MD; Ira Adams-Chapman, MD; Ellen C. Hale, RN BS CCRC.

Eunice Kennedy Shriver National Institute of Child Health and Human Development – Linda L. Wright, MD; Elizabeth M. McClure, MEd.

Indiana University, University Hospital, Methodist Hospital, Riley Hospital for Children, and Wishard Health Services (U10 HD27856, M01 RR750) – Brenda B. Poindexter, MD MS; James A. Lemons, MD; Anna M. Dusick, MD; Dianne E. Herron, RN; Lucy C. Miller, RN BSN CCRC.

RTI International (U10 HD36790) – Abhik Das, PhD; W. Kenneth Poole, PhD; Qing Yao, PhD; Betty Hastings; Elizabeth N. McClure, MEd; Jamie E. Newman, PhD MPH; Rebecca L. Perritt, MS; Carolyn M. Petrie Huitema, MS; Kristin M. Zaterka-Baxter, RN BSN.

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University of Texas Southwestern Medical Center at Dallas, Parkland Health & Hospital System, and Children's Medical Center Dallas (U10 HD40689, M01 RR633) – Walid A. Salhab, MD; Pablo J. Sánchez, MD; Charles R. Rosenfeld, MD; Abbot R. Laptook, MD; Roy J. Heyne, MD; Sally S. Adams, MS RN CPNP; Alicia Guzman; Gaynelle Hensley, RN; Elizabeth T. Heyne, PsyD PA-C; Jackie F. Hickman, RN; Linda A. Madden, RN CPNP; Susie Madison, RN; Nancy A. Miller, RN; Janet S. Morgan, RN; Catherine Twell Boatman, MS CIMI.

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Wayne State University, Hutzel Women's Hospital, Children's Hospital of Michigan, and Sinai-Grace Hospital (U10 HD21385) – Seetha Shankaran, MD; Yvette R. Johnson, MD

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Yale University, Yale-New Haven Children's Hospital and Bridgeport Hospital (U10 HD27871, UL1 RR24139, MO1 RR125, M01 RR6022) – Richard A. Ehrenkranz, MD; Patricia Gettner, RN; Harris C. Jacobs, MD; Christine G. Butler, MD; Patricia Cervone, RN; Monica Konstantino, RN BSN; Elaine Romano, MSN; JoAnn Poulsen, RN; Joanne Williams, RN; Sheila Greisman, RN.

Note: All persons named in the Acknowledgement above have provided written permission to be named.

Abbreviations

BW	birth weight
ELBW	extremely low birth weight
AgPT	aggressive phototherapy
ConPT	conservative phototherapy

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Table 1

Death.

	Observed Data		Frequentist Analyses		Bayesian Analyses			
Subset	**Aggressive phototherapy N/ Total N (%)**	**Conservative phototherapy N/ Total N (%)**	**RR**	**95% Confidence Interval**	**Posterior RR**	**95% Credible Interval**	**Posterior Probability of RR <1.0**	**Posterior Probability of RR < 0.9**
All Infants	230/946 (24)	218/944 (23)	0.92	(0.72, 1.17)	0.97	(0.80, 1.19)	60%	22%
BW 501–750g, ventilated at 24 h age	153/353 (43)	124/343 (36)	1.19	(1.01, 1.39)	1.19	(1.02, 1.39)	1% (99% probability of increased mortality)	~0%
BW 501–750g, not ventilated at 24 h age	8/62 (13)	17/68 (25)	0.55	(0.29, 1.05)	0.65	(0.37, 1.14)	93%	87%
BW 751–1000g, ventilated at 24 h age	50/310 (16)	64/329 (19)	0.82	(0.63, 1.05)	0.79	(0.62, 1.01)	97%	85%
BW 751–1000g, Not ventilated at 24 h age	17/219 (8)	12/203 (6)	1.33	(0.63, 2.83)	1.01*	(0.56, 1.81)	49%	36%

Table 2

Impairment and Profound Impairment.*

	Observed Data		Frequentist Analyses		Bayesian Analyses			
Outcome	**Aggressive phototherapy N/ Total N (%)**	**Conservative phototherapy N/ Total N (%)**	**RR**	**95% Confidence Interval**	**Posterior RR**	**95% Credible Interval**	**Posterior Probability of RR <1.0**	**Posterior Probability of RR <0.9**
Impairment (All Infants)	235/902 (26)	275/902 (30)	0.86	(0.74, 1.00)	0.86	(0.75, 1.00)	97%	71%
Impairment (Survivors only)	235/672 (35)	275/684 (40)	0.88	(0.77, 1.01)	0.89	(0.77, 1.01)	96%	59%
Profound Impairment (All Infants)	80/895 (9)	119/896 (13)	0.69	(0.52, 0.91)	0.72	(0.56, 0.94)	99%	95%
Profound Impairment (Survivors only)	80/665 (12)	119/678 (18)	0.70	(0.55, 0.89)	0.73	(0.58, 0.91)	>99%	97%

*No significant interaction was identified; therefore same values are shown for all infants in both birth weight strata whether ventilated or not ventilated at 24 h age.

J Perinatol. Author manuscript; available in PMC 2013 March 01.

Table 3

Death or Impairment

	Observed Data		Frequentist Analyses		Bayesian Analyses			
Subset	**Aggressive phototherapy N/ Total N* (%)**	**Conservative phototherapy N/ Total N* (%)**	**RR**	**95% Confidence Interval**	**Posterior RR**	**95% Credible Interval**	**Posterior Probability of RR < 1.00**	**Posterior Probability of RR< 0.90**
All infants	465/902 (52)	493/902 (55)	0.91	(0.82, 1.01)	0.93	(0.85, 1.01)	95%	25%
BW 501–750g, ventilated at 24 h age	248/347 (71)	235/337 (70)	1.02	(0.92, 1.13)	1.01	(0.92, 1.12)	39%	1%
BW 501–750g, not ventilated at 24 h age	22/56 (39)	34/65 (52)	0.78	(0.55, 1.08)	0.80	(0.58, 1.09)	92%	78%
BW 751–1000g, ventilated at 24 h age	133/294 (45)	171/313 (55)	0.83	(0.70, 0.97)	0.82	(0.70, 0.97)	99%	86%
BW 751–1000g, Not ventilated at 24 h age	60/203 (30)	52/186 (28)	1.06	(0.79, 1.41)	1.02	(0.78, 1.34)	43%	17%

* The total N for the four subgroups does not add to the total overall N because three infants had a missing value for mechanical ventilation.

Table 4

Death or Profound Impairment.

	Observed Data		Frequentist Analyses		Bayesian Analyses			
Subset	**Aggressive phototherapy N/ Total N (%)**	**Conservative phototherapy N/ Total N (%)**	**RR**	**95% Confidence Interval**	**Posterior RR**	**95% Credible Interval**	**Posterior Probability of RR <1.0**	**Posterior Probability of RR < 0.9**
All Infants	310/895 (35)	337/896 (38)	0.89	(0.80, 0.99)	0.88	(0.79, 0.98)	99%	63%
BW 501–750g*	202/403 (50)	200/400 (50)	0.98	(0.87, 1.10)	0.98	(0.87, 1.10)	63%	7%
BW 751–1000g*	108/492 (22)	137/496 (28)	0.81	(0.68, 0.96)	0.81	(0.69, 0.96)	99%	89%

* same values for those ventilated and not ventilated at 24 h age