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BILIRUBIN LEVEL IN INFANTS BANE OR BOON

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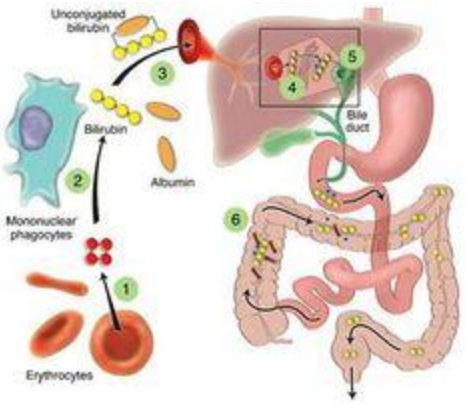
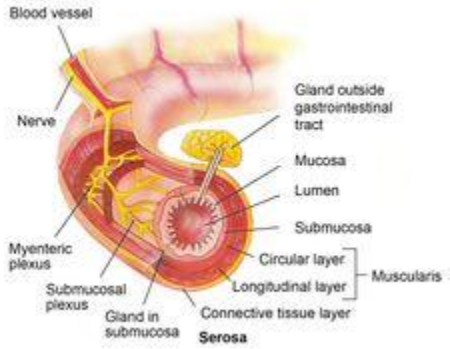
ABSTRACT
Many illnesses in preterm infants, such as chronic lung disease, necrotizing enterocolitis, retinopathy of prematurity and intracranial hemorrhage, are thought to be related to the action of reactive oxygen species. They occur because the antioxidant system of preterm infants is highly stressed and incompletely developed. Several reports have emphasized the antioxidant role of bilirubin, which in human neonatal plasma seems to have a greater antioxidant capacity than urates, α-tocopherol, or ascorbates. Bilirubin reactions involving free radicals or toxic products of oxygen reduction have been well documented.[2] In particular, unconjugated bilirubin is able to scavenge singlet oxygen with high efficiency, to react with superoxide anions and peroxyl radicals, and to serve as a reducing substrate for peroxidases in the presence of hydrogen peroxide or organic hydroperoxides.[1] However, although the antioxidant effect of bilirubin as a scavenger of reactive oxygen species is well documented in vitroand animal studies, its role in vivo has not been clarified in preterm infants. Yigit *et al* reported that serum malondialdehyde concentrations were higher in infants with hyperbilirubinemia than in controls and other authors have found a significant correlation between serum bilirubin and total antioxidant capacity of the plasma.[3]

KEYWORDS: Necrotizing enterocolitis, urates, α-tocopherol or ascorbates.

INTRODUCTION
The hypothesis of our study was that changes in plasma bilirubin levels may influence the antioxidant system and oxidative stress in newborn infants. Therefore, our aim was to investigate the possible correlation between plasma bilirubin level and oxidative stress and the antioxidant capacity of plasma in preterm infants. To this end, we planned a prospective study in which the plasma levels of total bilirubin (Btot), total hydroperoxide (TH), and protein SH groups and the total antioxidant capacity of plasma (TAC) were concurrently measured. Potentially toxic oxygen free radicals (OFRs) are generated continuously in neonates. Under physiological conditions, the human body has developed a complex network of antioxidant defenses sufficient to protect cells against oxidative damage. Oxidative stress results from a loss of this protective balance either because of overproduction of free radicals or because of inadequate antioxidant defenses.[4] In prematures, the concentrations of most antioxidant enzymes are reduced, particularly during the early neonatal period. Impaired antioxidant defenses, occurring at a time when OFR production is both frequent and severe, render the premature neonate extremely susceptible to the development of OFR-mediated diseases. During the first days of life when antioxidant defenses are reduced, serum bilirubin is increased physiologically. Because bile pigments protect easily oxidizable substances from destruction, it has been suggested that bilirubin functions as an antioxidant in term neonates. Nevertheless, neonatal hyperbilirubinemia is still widely regarded as clinically problematic and bilirubin is regarded as a toxic metabolic waste.[4] However, the physiologic early neonatal increase in serum bilirubin may provide a protective antioxidant defense mechanism to compensate for otherwise deficient antioxidant enzymes, especially in premature neonates with increased susceptibility to OFR-mediated diseases. We tested this possibility by examining the relationship between serum bilirubin concentration and antioxidant activity in the blood of premature infants.[5]

OBJECTIVE
To assess the hypothesis that changes in plasma total bilirubin levels (Btot) can influence the antioxidant system and oxidative stress in preterm infants.





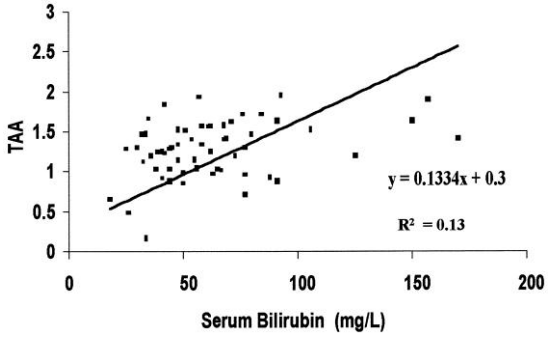
METHODS

Twenty two healthy preterm infants who presented with visible non-hemolytic hyperbilirubinemia were studied at the mean (SD) age of 3.7 (1.5) days. Btot, plasma total hydroperoxide concentration (TH), plasma protein SH group concentration and total antioxidant capacity of the plasma (TAC) were measured at study entry and after 24 hours.

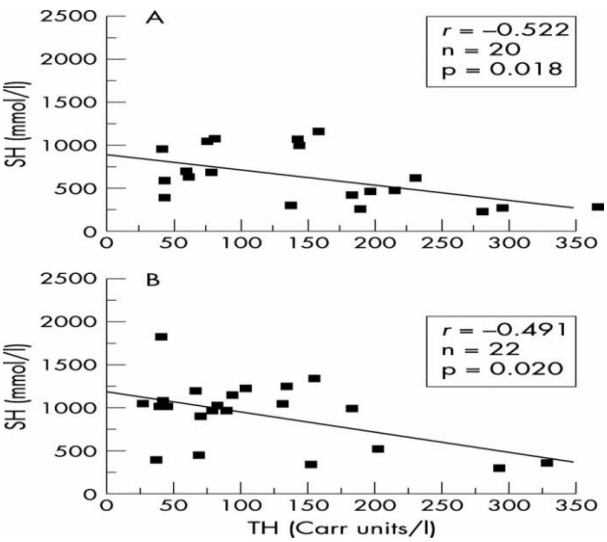
RESULTS

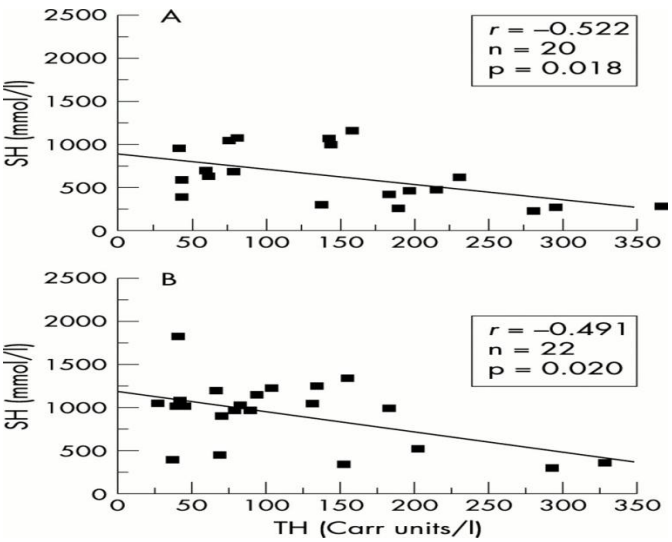
Btot did not correlate with TH, TAC, or protein SH group concentration, but a significant correlation was found between TH and TAC, TH and protein SH groups, and TAC and protein SH groups, both at study entry and after 24 hours.[6]

OBSERVATION



The mean birth weight of the infants was 1374 ± 659 g, and the mean gestational age was 30.4 ± 3.6 weeks. The mean Apgar scores were 7 ± 6 and 5 ± 6 at 1 and 5 min, respectively. A total of 85 samples were taken, with 11 of the infants having three or more serial samples taken. Serum bilirubin was significantly correlated (P = 0.005) with total antioxidant status (Fig. 1⇓). Other than through its effect on bilirubin concentrations, treatment with phototherapy had no independent effect on TAA (P = 0.24). Gestational age did not affect TAA (P = 0.81; only the initial TAA value was considered for those infants with several measurements). Birth weight (P = 0.67), the sex of an infant and the concentration of inspired oxygen (P = 0.22) were not significantly correlated with TAA7. Mean total antioxidant status values were related to postnatal day of life (DOL),[7,8] with an initial increase from day 2 to 4, followed by a decrease during the remainder of the first week of life Best subset regression of the entire data sample, with TAA as the dependent variable and an F-to-remove of 3.9, confirmed that TAA can be predicted from a linear combination of the bilirubin at time of sampling and the DOL studied and that both bilirubin and DOL have independent effects on TAA. Variables tested and found not to add to the predictability of TAA included birth weight, gestational age, sex, use of phototherapy and FiO_2. Spearman correlation revealed no correlation between the variables bilirubin and DOL.





RESULTS

Our present findings extend previous reports. Stocker et al. showed that bilirubin at physiologic concentrations can protect linoleic acid from oxidation in vitro. Farrera et al. compared the peroxyl antioxidant trapping potential of various substances and found that free bile pigments showed higher activity than did the vitamin E analog Trolox. According to Frei et al., bilirubin contributes ~10% of the total antioxidant status. Serum antioxidant potential in prematures increases over the first 4 days of life, as does serum bilirubin. However, a direct correlation between serum bilirubin and antioxidant potential has not been shown previously in prematures.

Animal studies support a protective effect of hyperbilirubinemia. Dennery et al. exposed Gunn rats to hyperoxia and demonstrated that jaundiced rats had less oxidative damage, as evidenced by the lower concentrations of lipid peroxides, conjugated dienes, and carbonyl proteins in jaundiced rats than in nonjaundiced rats.[11] In term human infants, Belanger et al detected a decrease in antioxidant capacity after exchange transfusion, implying a correlation between bilirubin removal and antioxidant capacity.[12] Gopinathan et al. observed a direct correlation between serum bilirubin and total antioxidant potential at birth in term infants, which they did not find in prematures.[13] However, as a result of aggressive phototherapy in these premature infants, their bilirubin at 5 days reached only a mean of 54 ± 21 mmol/L (3.9 ± 2.4 mg/dL). Thus, there was not a wide enough range of bilirubin values to demonstrate any correlation, even should one exist. Benaron et al. and Hegyi et al. noted lower serum bilirubin concentrations in neonates with oxygen radical-mediated diseases as compared with control, age-matched infants. These data imply that bilirubin may be consumed in response to the generation of oxygen-derived free radicals, supporting an active clinical role for bilirubin as an antioxidant. Conversely, a retrospective study of early bilirubin concentrations in relation to the subsequent development of retinopathy of prematurity in prematures did not demonstrate any such correlation.[14] However, all clinical studies of this type are hampered by the fact that clinical disease is multifactorial and that the relationship with bilirubin, if one exists, may well be more complex than a direct correlation. Oxidative stress may consume available antioxidant resources as suggested above, or conversely, it may induce antioxidant release or some combination thereof. We have, therefore, correlated serum bilirubin not with clinical disease, but rather with a biochemical index of antioxidant status, demonstrating that bilirubin does contribute to the total antioxidant potential of the premature neonate. We recognize that the fact that some of our babies were sampled more than once whereas others only were sampled once represents a possible limitation to our study.[15] As such, these data do not purport to represent the general antioxidant status of premature infants. Nevertheless, they do demonstrate a positive relationship between serum bilirubin and antioxidant status. Bilirubin management in the term neonate is currently in a state of flux. Therapeutic recommendations that have been accepted for years are being reevaluated and liberalized. Our observations, if further validated, suggest that the time may have arrived to also reevaluate clinical bilirubin management of the preterm infant. However, these relationships are complex and multifaceted.[16] Thus, any consideration of potential clinical applications of this information may be undertaken only with extreme caution and with additional supportive data.[17]

CONCLUSION

The decrease in plasma bilirubin was contemporary with an increase in plasma antioxidant capacity and decrease in oxidative stress in preterm infants. This may be the result of the pro-oxidant effect of haem oxygenase, mediated by iron release, which may outcompete the antioxidant properties of bilirubin. We measured the peroxyl radical-trapping capability of human blood as an indicator of total antioxidant activity (TAA). This method, based on the method of Miller et al.[14] Uses the peroxidase activity of metmyoglobin combined with its interaction with a phenothiazine compound to form a radical cation intermediate as a measure of antioxidant status. The method derives from the observation that when 2, 2′-azinobis-(3-ethylbenzothiazoline-6-sulfonic acid) (ABTS) is incubated with a peroxidase (such as metmyoglobin) and hydrogen peroxide, the relatively long-lived radical cation, ABTS·+ is produced.[11] In the presence of antioxidant reductants and hydrogen donors in plasma, the absorbance of this radical cation is quenched to an extent related to the antioxidant capacity of the fluid.[10] The system is calibrated with a 2.4mmol/L solution of Trolox (an α-tocopherol analog with good water solubility). Results correlate with the sum of the individual radical-trapping capabilities of the major antioxidants in plasma. Mean values ± SD were calculated for continuous variables and compared by the Student *t*-test.[9] Correlations between clinical variables were analyzed using a Pearson correlation. Combined analysis was performed using a best subset regression model, followed by a Spearman correlation to define correlations between variables.

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