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Incidence of Hyperbilirubinemia in Neonates of Parturients Undergoing Augmentation of Labor With Oxytocin: A Prospective Cohort Study

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Abstract

Introduction: Hyperbilirubinemia is one of the commonest problems that can occur in newborns. The vasopressin-like action of oxytocin causes osmotic swelling of erythrocytes leading to decreased deformability and hence more rapid destruction with resultant neonatal hyperbilirubinemia (NNH).

Objectives: To determine dosage and duration of oxytocin for mother during augmentation of labor.

To determine the incidence of neonatal hyperbilirubinemia in mothers given oxytocin and those in spontaneous labor.

To find association between maternal oxytocin augmentation and neonatal hyperbilirubinemia.

Materials & method: 306 full-term parturients with normal vaginal delivery from January 2017 to June 2018 were selected after ruling out exclusion criteria. Group A: 153 term babies of oxytocin augmented labor & Group B: 153 term babies of spontaneous labor. Oxytocin dosage was 5 units in 500 ml normal saline, @ 5 mIU/min and increased by 5 mIU/min half hourly until effective uterine contractions were attained. The total duration and volume of oxytocin infused were recorded in each subject. In neonatal period serum bilirubin was measured by trans cutaneous bilirubinometer on day 1 and day 3.

Results: Incidence of NNH requiring phototherapy in Group A was 38% and in Group B was 18% and the difference between 2 groups were statistically significant (p-value = 0.0001). The cut-off duration and volume of oxytocin infusion for a statistically significant increase of NNH was 292.5 minutes (p-value 0.0001) and 5101 mIU (p-value 0.0001) respectively.

Conclusion: Oxytocin is an important therapeutic agent in labor and probably its use cannot be stopped and thus its effect on erythrocytes also cannot be prevented. Oxytocin can produce neonatal hyperbilirubinemia as evidenced by this study and therefore it would be logical to prevent the hyperbilirubinemia by reducing the dose of oxytocin and by its selective use.

Keywords: Hyperbilirubinemia; Oxytocin.

Introduction

Hyperbilirubinemia is one of the most common causes of neonatal readmission to hospitals. According to statistics, hyperbilirubinemia occurs in 60% of term and 80% of preterm newborns in the first week of birth. Many a time it is physiological in the newborn because liver is not mature enough to handle the bilirubin. Early prediction will help in early discharge and prevent hospitalization of babies and mothers. Serum bilirubin levels at birth is normally 1.8–2.8 mg/dl.

The association between oxytocin use in labor and neonatal hyperbilirubinaemia is well documented. The causes include immature hepatic glucuronyl transferase,[1] anoxic liver damage,[2] enhanced placental fetal transfusion,[3] increased fragility of

erythrocyte[4] and mechanical trauma to RBC.[5]

Erythrocyte deformability is an important determinant of its lifespan,[6] and in many conditions reduced deformability results in increased hemolysis.[7]

In newborns, the metabolism of bilirubin is in transition stage from fetus to the adult. Uridine diphosphoglucuronyl transferase (UDPGT), an important hepatic enzyme for conjugation and bilirubin excretion, is detectable at 18–20 weeks of gestation. UDPGT levels in term newborns are usually less than 0.1% of adult values and it reaches adult value usually by 6–14 weeks of postnatal life.[8]

Oxytocin is often administered intravenously to induce or accelerate labor in our obstetric unit. Almost 70–75% of neonatal admissions in our neonatal ICU were due to neonatal hyperbilirubinemia requiring phototherapy. Out of this about 8–10% is having hyperbilirubinemia not accounting to identifiable cause other than maternal oxytocin use. So we have felt the need to make a critical appraisal of this possible relation between the administration of oxytocin to mother and level of bilirubin in the neonate.

This is a prospective study of groups of primigravidae and multigravidae in whom oxytocin were used to augment labor. They were compared with a group of primigravidae and multigravidae who had not received oxytocic agents. Other etiological factors of neonatal jaundice were also considered.

The rationale for the study was that the fetal erythrocyte deformability after oxytocin administration was due to osmotic swelling produced by the action of oxytocin on the erythrocyte membrane resulting in increased water intake. The other mechanisms that have been proposed to explain the higher incidence of neonatal hyperbilirubinemia and oxytocin administration are trauma to the fetal erythrocytes as a result of uterine activation, vasoconstrictive effect of oxytocin on uterine blood vessels, and hyponatremia caused by the administration of large quantities of electrolyte free diluents for oxytocin infusion. So it is logical to prevent hyperbilirubinemia by reducing the dose of oxytocin if the association is significantly high.

Jaundice is one of the most common conditions requiring medical attention in newborns. Approximately 60% of term and 80% of preterm babies develop jaundice in the first week of life and about 10% of breastfed babies are still jaundiced at 4 weeks of age. In majority with jaundice there is no underlying issue and this early jaundice is termed physiological jaundice and is generally harmless. However there are pathological causes of jaundice in the newborn, which although rare need to be diagnosed and may sometimes coexist with physiological jaundice.

Jaundice is defined as yellow discoloration of the skin and sclera caused by accumulation of bilirubin. Neonatal hyperbilirubinemia although transient, makes 75% of hospital re-admissions in the early newborn period. A hemolytic cause for the jaundice was identified in 50% of neonates. Neonatal hyperbilirubinemia is diagnosed mainly by clinical examination and serum bilirubin values. Clinically, the newborn jaundice have cephalocaudal progression.[9]

Newborn babies red blood cells have a shorter lifespan than those of adults. The concentration of RBCs in the circulation is also higher in newborns than in adults, so bilirubin levels are higher than they are later in life. The metabolism, circulation and excretion of bilirubin is also slower than in adults. Thus a degree of hyperbilirubinemia occurring as a result of this normal physiological mechanism is common in newborn babies.

Causes of physiological jaundice is attributable to physiological immaturity of neonates to handle increased bilirubin production. Clinically visible jaundice usually appears between 24 and 72 hours of birth. Total serum bilirubin in term babies usually reaches 6 to 8 mg/dl by 3 days of life and then falls. A rise up to 12 mg/dl is still considered to be in the physiological range. Levels under 2 mg/dl may not be seen until one month of age in both full-term and preterm babies. Safe bilirubin level in preterms vary according to gestational age.

Causes of pathological jaundice include group incompatibility, other causes of hemolysis, sepsis, bruising, metabolic disorders can cause pathological jaundice. Gilbert's syndrome and Crigler–Najjar syndrome are rare causes of neonatal jaundice and are caused by liver enzyme problems. Deficiency of a particular enzyme G6PD (glucose-6-phosphate dehydrogenase) can cause severe neonatal jaundice. Congenital obstruction and malformation of the biliary system like biliary atresia, causes an obstructive jaundice with conjugated hyperbilirubinemia.

Normal serum bilirubin levels at birth are 1.8–2.8 mg/dl. These levels have an increasing trend in next few days but with individual variations and it usually reaches 5–10 mg/dl by third to fourth day of life in mature infants.[10] The main concern is that it can cause kernicterus in severe cases. In

young babies, unconjugated bilirubin can penetrate the membrane that lies between the brain and the blood (blood brain barrier). Unconjugated bilirubin is potentially toxic to neural tissue (brain and spinal cord). Entry of unconjugated bilirubin into the brain can cause both short-term and long-term complications. Acute features includes lethargy, irritability, abnormal muscle tone and posture, temporary cessation of breathing and convulsions. This condition is called acute bilirubin encephalopathy (ABE).

Bilirubin is deposited particularly in a part of the brain called globus pallidus, part of the deep gray matter of the brain. On pathological examination of the brain, this produces yellow staining. This staining is referred to as kernicterus. The term kernicterus is also used to denote the clinical features of acute or chronic bilirubin encephalopathy. Features of the latter include athetoid cerebral palsy, hearing loss, visual and dental problems. The exact level of bilirubin that is likely to cause neurotoxicity in any individual newborn varies, and depends on the interplay of multiple factors which include gestational age, postnatal age, acidosis, rate of rise of serum bilirubin, serum albumin concentration and concurrent illness.

ABE has got an acute mortality of 7–10%.[12] The threshold for neurologic toxicity varies in neonates. But total serum bilirubin levels more than 25 mg/dl are considered extreme, and more than 30 mg/dl are hazardous.[12] This toxic levels of bilirubin is occurring in about 0.15% and 0.01% of term and near-term infants respectively.[11]

A lot of factors can lead to neonatal hyperbilirubinemia like gestational age, blood group incompatibility, pre-eclampsia, abnormal deliveries, certain maternal drug usage and oxytocin administration. Oxytocin is an accepted safe and effective drug for initiating uterine contractions. But a few authors have found an association of oxytocin with hyperbilirubinemia.[13–15]

Oxytocin is a hormone produced by the hypothalamus and secreted by the pituitary gland. This important hormone plays a crucial role in the childbirth process and also helps with male reproduction. Oxytocin production is controlled by a positive feedback mechanism. This mechanism allows the release of the oxytocin hormone when a trigger occurs. The hormone then causes an action in the body, such as the letdown of milk or the start of labor contractions, which signals more production of oxytocin. The feedback cycle continues until the action, such as childbirth or feeding the baby, is complete.

It is a synthetic nonapeptide discovered by Henry Dale in 1906, used as a potent uterotonic agent in obstetrics to stimulate uterine smooth muscle contraction. It is administered to mimic the endogeneous oxytocin response, which is produced by the hypothalamus and secreted from the posterior pituitary gland. During labor and birth, the primary role of oxytocin is to bind to the oxytocin receptors on the uterus and to stimulate uterine contractions, which helps to deliver the fetus from the womb. Once labor begins, the oxytocin release is regulated by a positive feedback mechanism were pressure by fetal head on the cervix and vagina creates a reflex called the Fergusson reflex. This travels primarily via the pelvic and vagal nerves, to spinal cord and brainstem nuclei to stimulate the release of oxytocin from the posterior pituitary. This oxytocin release and the resulting uterine contractions occur in pulses approximately 4–8 minutes apart, becomes more closer as labor progresses until a peak in oxytocin at the time of delivery which helps expel the baby from the uterus and birth canal.

Oxytocin is mainly used for labor induction, augmenting ineffective labor and to induce contractions after birth to reduce postpartum hemorrhage. The most common reversible complication of oxytocin administration is uterine tachysystole. Tachysystole is defined as more than five uterine contractions within a 10 minute period.

The association between labor augmentation with oxytocin and neonatal hyperbilirubinemia is well documented.[16–18] Some causes include immaturity of hepatic glucuronyl transferase enzyme,[2] anoxic liver damage,[3] enhanced placentofetal transfusion,[4] increased erythrocyte fragility[5] and mechanical trauma to erythrocytes.[1]

Augmentation of labor is defined as the artificial increase of uterine contractions prior to their spontaneous onset, which will lead to progressive effacement and dilatation of the cervix and to delivery. The most widely used method is synchronous oxytocin titration and fore water amniotomy. There is controversy regarding proper initial dose of oxytocin and mode of increment. An arithmetic increase in oxytocin dosage means small dose increments; and because it is associated with a lower incidence of uterine hyperstimulation, it has been the preferred option.[20]

Prediction of Hyperbilirubinemia:

1. Universal newborn bilirubin screening
2. End-tidal carbon monoxide estimation
3. Transcutaneous bilirubin estimation

4. Cord blood bilirubin levels

Early prediction of NNH will help in early discharge and prevent hospitalization of babies and mothers. Traditionally measurement of Total Serum Bilirubin (TSB) level was done serially. Today non-invasive techniques for Transcutaneous Measurement of Bilirubin (TCB) are used. TCB is recommended to screen infants. Determination of serum bilirubin level is indicated only in patients with elevated age specific transcutaneous bilirubin measurement, progressing jaundice, or risk for either hemolysis or sepsis.[22,23] Sampling of blood for measurement of total serum bilirubin is a painful procedure. It may increase the risk of infection, may lead to anemia in the cases of frequent sampling especially in premature newborns and also causes discomfort to infants and anxiety in parents.[22,23] On the other hand, TCB is a safe and rapid method to assess the level of bilirubin.

Transcutaneous bilirubinometer (TCB) devices are widely used for the estimation of serum bilirubin levels in term and near-term infants non invasively. The blood sampling is often done by heel prick. High correlation between cutaneous bilirubin and TSB form the basis of transcutaneous bilirubinometry. These meters work by directing light into the skin of the neonate and measuring the intensity of specific wavelength that is returned.[23] The number of wavelengths, used is variable in different transcutaneous bilirubinometers. The meter analyzes the spectrum of optical signal reflected from the neonate's subcutaneous tissues. These optical signals are converted to electrical signal by a photocell. These are analyzed by a microprocessor to generate a serum bilirubin value. The major skin components, which impart the spectral reflectance in neonate, are: (i) melanin, (ii) dermal maturity, (iii) hemoglobin, and (iv) bilirubin.

The available meters can be divided into 2 categories:

(i) Multi wavelength Spectral Reflectance meters (Bili-check) TM: It is a new product which performs a spectral analysis at more than 100 different wavelengths. By subtracting the spectral contribution of the known components, the bilirubin absorbance is quantified.

(ii) Two-wavelength (460 nm, 540 nm) Spectral Reflectance meters (Minolta, Bili-test)

The number of wavelengths varies depending on the TCB device. These devices have been shown to correlate well with serum bilirubin levels in term and near-term infants.[24–28] The American Academy of Pediatrics recommends the use of TCB devices for the evaluation of jaundice in infants 35 weeks or more gestation.[2] The optic head of the meter is gently pressed against the neonates skin (usually forehead or upper part of sternum). For correct measurement, the optic head should make full contact with the skin and there should be no gaps between the head and the skin. This should be achieved by gentle pressure. Although each transcutaneous bilirubinometer has a different detailed operating procedure, the basic principle remains the same.

Transcutaneous bilirubinometry has a very high negative predictive value, which makes it a reliable screening tool to assess jaundice in infants, with the potential to be used as a stand-alone test until values are close to phototherapy threshold, with resultant reduction in invasive testing and cost, and safe to follow the less conservative paths laid out in the AAP phototherapy guidelines.[30] So TCB measurement is a viable option in screening neonates to determine if they are at risk for clinically significant hyperbilirubinemia. Total serum bilirubin should be measured by a clinical lab if a newborn is shown to be at higher risk for clinically significant hyperbilirubinemia.

Wood et al.[53] in their studies failed to reveal a statistical significant association between incidence of NNH and oxytocin administration. On the contrary Friedman et al.[17] and Wilson and Smith et al. have found in their studies small effect of oxytocin in producing neonatal hyperbilirubinemia.

Singhi and Singh et al.[5] found 20% cases of jaundice attributed to oxytocin use in labor. Wasserstrum et al. showed that oxytocin if administered with dextrose is known to cause jaundice in newborn.

Setareh A et al. (2016)[38] conducted a prospective cohort study for a period of 6 months. In that study a total of 168 newborn infants of mothers who were managed with oxytocin during labor (either for labor induction or augmentation) and were compared with 180 newborn infants of mothers without oxytocin therapy for incidence of hyperbilirubinemia. Mothers of two groups were matched for age, parity, gestational age and birth weight.

Result of that study showed that the incidence of neonatal hyperbilirubinemia was 8.9 percent (39 cases). Demographic data of subjects were taken into account. The study finally concluded that neonatal hyperbilirubinemia was higher in oxytocin group

but this association was not statistically significant.

In a retrospective cohort study conducted in a community teaching hospital in the USA by Keren R et al. (2005),[50] a clinical risk factor score was developed and its predictive accuracy was compared with pre discharge serum bilirubin measurements plotted on the bilirubin nomogram. The study population included babies ≥ 2 kg birth weight (if ≥ 36 weeks of gestation) and birth weight ≥ 2.5 kg (if POG ≥ 35 weeks) who participated in the hospital's early discharge program and who had both pre- and post discharge serum bilirubin measured.

Hyperbilirubinemia was taken as post discharge serum bilirubin level > 95th centile on the nomogram. Hospital records were reviewed retrospectively to collect information on various risk factors. And their association with hyperbilirubinemia was explored by univariate analysis.

The newborn risk factors for jaundice includes gestational age ≤ 38 weeks or >40 weeks, large for gestational age, high pre discharge serum bilirubin and higher birth weight. The maternal factors include maternal diabetes, vacuum extraction, prolonged rupture of membrane and oxytocin use, breastfeeding and combined breast and bottle feeding. All the factors were analyzed by stepwise logistic regression, except for pre discharge serum bilirubin/risk zone, which was analyzed separately.

Results from the regression analysis showed that oxytocin use during labor (adjusted odds risk 2.0, 95% confidence interval 1.2 to 3.4) was statistically significant.

Oxytocin augmented labor can cause less fetal erythrocytes deformablility. This reduced erythrocyte deformability results in more rapid erythrocyte destruction. This is mainly due to the vasopressin-like action of oxytocin. The antidiuretic effect of oxytocin causes hyponatremia and hyposmolarity in the mother and subsequently in the fetus with water retention. Hyposmolarity causes swelling of the red blood cells by activation of electrolyte and water transport across the erythrocyte membrane and makes them fragile and susceptible to hemolysis.[1]

Maisels MJ et al. (2004)[29] studied the contribution of hemolysis to early jaundice in normal newborns. In the study they measured the end-tidal carbon monoxide concentration corrected for ambient carbon monoxide concentration in 108 jaundiced newborns and 164 control newborns for the first 4 days after birth. They found that the mean end-tidal carbon monoxide levels decreased in the control infants in the first 4 days but increased in hyperbilirubinemic group and the difference was statistically significant.

Because the ability of the newborn to conjugate bilirubin is significantly impaired, even a small increase in rate of production can contribute to hyperbilirubinemia. So in their study they concluded that increased heme catabolism is an important mechanism responsible for hyperbilirubinemia in the first 4 days after birth.

H. Guler Sahin et al.[45] conducted a study comparing effects of oxytocin infusion vs prostaglandins on NNH. A total of 100 neonates were included in the study. The first group consisted of 50 healthy babies of women who had received oxytocin infusion and the second group consisted of 50 healthy babies of women who had received 25 mcg misoprostol every 4 hourly placed in the posterior fornix for labor induction. Bilirubin and hematocrit levels were measured in all on days 1 and 4 of the neonatal period.

The levels of bilirubin in the oxytocin group were significantly higher than those in the misoprostol group on day 1 they were higher also on day 4 but was not significantly raised. To determine the pathogenesis of neonatal hyperbilirubinemia after induction of labor with oxytocin the author has compared the cord blood of healthy newborn infants. They have found no significant differences in any hematological or biochemical variables between those delivered by elective cesarean section and spontaneous labor. But the mean hematocrit levels on day 1 were in groups 1 and 2, had a significant difference between them (higher in group 2).

The levels on day 4 was again statistically significant with a *p*-value <0.05, which means that infants born after oxytocin induction showed increased hemolysis associated with significantly decreased deformability.

The author has suggested that the vasopressin like action of oxytocin caused osmotic swelling of erythrocytes leading to decreased deformability and more rapid destruction with resultant increased bilirubin production.

Another study conducted by Surabhi HS et al. (2018)[32] on neonatal hyperbilirubinemia and maternal oxytocin administration which included 456 babies after exclusion criteria and they were divided in two groups. In Group A babies were exposed to maternal oxytocin for induction of labor and in Group B babies were born of spontaneous labor. Babies were observed on day 3 for clinical

jaundice. They found that incidence of neonatal jaundice in Group A was 61.3% and in Group B was 43.4%. The study showed that maternal oxytocin used for induction of labor increase the incidence of neonatal jaundice.

Another study by Abbas SS et al.[33] a prospective cohort study was conducted in the neonatal unit of a tertiary care center over a period of 6 months. After exclusion, 308 babies were divided in two groups. Group A babies exposed to maternal oxytocin for induction of labor and Group B babies born of spontaneous labor with oxytocin use for augmentation of labor. Babies were observed daily for clinical jaundice till discharge. Results showed 52% incidence of neonatal jaundice in Group A and 12% in Group B, with a relative risk 4.3 (95% confidence interval: 2.69–6.73). This study also concluded the effect of oxytocin on jaundice.

In the neonate, whose hepatic enzymes are unable to cope with the increased bilirubin production as a result of this rapid erythrocyte destruction, hyperbilirubinemia ensues clinically.

The other mechanisms that have been proposed to explain the higher incidence of neonatal hyperbilirubinemia and oxytocin administration are trauma to the fetal erythrocytes as a result of uterine activation, vasoconstrictive effect of oxytocin on uterine blood vessels, hyponatremia caused by the administration of large quantities of electrolyte free diluents for oxytocin infusion. In-vitro studies showed a time related and dose related reduction in erythrocyte deformability in response to oxytocin administration.[19]

A wide variation in labor duration has been observed in different women (Albers, 1999;[54] Vahratian et al., 2006;[55] Neal et al., 2010[55]). Slow progress of labor is more common in nulliparous women. This delayed progress is often associated with birth complications, concerns for fetal well-being, and negative birth experiences, and is considered to be one of the indications for an emergency cesarean section in labor.

A few evidences showed that oxytocin administration is associated with an increase in spontaneous vaginal birth (Wei et al., 2012[46]) while some other studies conclude that oxytocin does not affect mode of delivery (Bugg et al., 2013). Healthy pregnancy outcomes and positive experiences are main issues for women in labor. Some positive outcomes are expected by augmentation of labor from oxytocin like shorter duration of labor and spontaneous vaginal delivery.

Dencker A et al. (2009)[52] conducted a study on early versus delayed oxytocin augmentation in nulliparous women with prolonged labor (a randomized control trial). In this study healthy nulliparous women with normal pregnancies, spontaneous onset of active labor, a cervical dilatation of 4 to 9 cm and no progress in cervical dilatation for 2 hours and for an additional one hour if amniotomy was performed due to slow progress. 630 women were randomly allocated either augmentation of labor by oxytocin infusion i.e. early oxytocin group; or to postpond oxytocin augmentation for another 3 hours i.e. expectant group.

The result was that with cesarean section rate, it was 9% with early oxytocin group and 11% with expectant group. The instrumental vaginal delivery was 17% and 12% respectively. Early initiation of oxytocin resulted in a mean decrease of 85 minutes in the delivery interval. So this study showed that early administration has got equal benefits. Here in our study we also started oxytocin infusion once the women get in active labor.

Many studies have examined the effects and safety of high dose oxytocin regimen compared to low dose oxytocin regimen for labor augmentation on perinatal outcomes. Almost all the studies proved that high dose oxytocin regimen (starting dose at 5 mIU/min and increment of 5 mIU/min) is associated with a shorter duration of 1st stage of labor in both nulliparas and multiparas. It has not increassd the cesarean rate or adversely affected the perinatal outcomes. It may, in turn, shown to have reduced the risk of chorioamnionitis meconium staining, and neonatal fever.[21] While some researchers suggests the use of dosing regimens and protocols with the lowest total dose of oxytocin with a resulting decrease in side effects and other adverse outcomes.

Lutfun Naher Begum et al. (2013)[35] conducted a prospective randomized control trial to evaluate the effect of continuation and discontinuation of oxytocin infusion on maternal and neonatal outcome once the active phase of labor is established. In this study a trial was conducted on 100 pregnant women in whom labor was induced on obstetric ground. Patients were randomly divided in two groups. In the first group oxytocin infusion continued throughout labor (Infusion of oxytocin was started in incremental doses until 5 cm cervical dilatation and to be maintained at that level, throughout the labor) and in the second group oxytocin infusion discontinued after establishment of active phase of labor (Infusion of oxytocin was started incrementally but discontinued when

cervical dilatation reached 5 cm).

The result showed consumption of total oxytocin dose, induction-delivery interval, uterine hyperstimulation, cesarean section rate were significantly less in oxytocin discontinued group. Concurrently in oxytocin-continued group rate of postpartum hemorrhage (PPH), neonatal asphyxia, hyperbilirubinemia were higher in comparison to oxytocin discontinued group. Incidence of neonatal hyperbilirubinemia in oxytocin-continued group was about 14%, whereas there was none in Group B. An increased incidence of neonatal hyperbilirubinemia has been observed when the mother is given a total oxytocin dose more than 4500 mu.[5]

Study concluded that continuous oxytocin infusion during active phase of labor increases chance of cesarean section, PPH and also of neonatal asphyxia, hyperbilirubinemia. Discontinuation of oxytocin infusion reduces labor risk and gives good neonatal outcome.

The occurrence of high neonatal bilirubin levels in induced labors is certain. A study was conducted by Manjula BG et al.[51] to compare intermediate dose oxytocin regimen (3 mIU/min) with high dose regimen (6 mIU/min). In the study a total of 200 women planned for induction of labor were randomized to receive high and intermediate dose oxytocin. The study observed a cesarean rate 18% vs 6% with *p*-value = 0.009; contraction abnormalities 35% vs 14% with *p*-value = 0.0005; and neonatal bilirubin levels 7.99 ± 2.70 vs 6.80 ± 2.65 with a *p*-value = 0.002 were higher with high dose regimen than intermediate dose regimen. Hence this study propose that the intermediate dose oxytocin regimen should be preferred over high dose regimen.

Another large prospective cohort study of children delivered at and above 35 weeks of gestation were compared those with TSB levels greater than 13.5 mg/dl with those who have levels less than 13.5 mg/dl.[37] At two years follow up, no significant difference is noted in rates of cerebral palsy, developmental delay, visual abnormalities or deafness. But the cohort with TSB more than 19 mg/dl were noted with an increased risk of attention deficit disorder with a relative risk of 1.9. At the same time another four studies with follow up of around 6.5 to 17 years showed no relationship between low IQ scores and hyperbilirubinemia.[29]

The anxiety engendered in the mother of a jaundiced infant, and the need sometimes to prolong hospital stay and mother infant separation until jaundice has cleared was also a concern. A study was conducted on perceptions of mother towards neonatal hyperbilirubinemia and its management. The result showed that some mothers believed that they had caused the jaundice by using the phrases like 'not being a good mother'. Most mothers indicated that the blood testing process was difficult to watch and they used phrases like 'suffered' to describe the reactions of their newborns. Study concluded that as bilirubin levels increased and higher levels of interventions were needed, mother's concerns increased (Patricia R et al., 2003).[42]

Postnatal readmission of mother or neonate is an outcome studied in relation to care pathways rather than individual intrapartum interventions, so this variable is not present in cohort studies on oxytocin use. No direct association has been shown between oxytocin use and postnatal depression, but postnatal depression is linked with postnatal readmission of the mother (Sword et al., 2011).[41]

A prospective observational study was conducted by Sujatha S.G, Sreenivasan V.K, et al., (2017)[4] in a tertiary care hospital in South India in 2016 (over a period of 5 months) using Drager JM103 TCB meter on 200 term babies up to 7th postnatal day with equal gender distribution. The study excluded preterm babies, post-dated babies, babies who received phototherapy, those who underwent exchange transfusion and sick term babies. They used Fitzpatrick scale to categorize the babies based on skin color ranging from I to VI, from light skin color to the darkest skin color. The study measured TCB and serum bilirubin simultaneously in clinically jaundiced babies. Sternal TCB values were measured.

Blood for serum bilirubin was collected simultaneously through venepuncture after strict aseptic precautions and the values were recorded and compared with TCB values. Analysis of data was done using SPSS23 software. Pearson correlation coefficient was calculated to find positive correlation between TCB and Total Serum bilirubin.

The result of the study was out of the total 200 babies, 6 babies were in Group 2 (3%), 100 babies in Group 3 (50%), 83 babies in Group 4 (41.5%) and 11 babies in Group 5 (5.5%). Though the Pearson correlation was linear in all the groups, it was lesser in the dark skinned babies. So the study therefore concluded that assessment of jaundice by TCB meter is not accurate in dark skinned babies. Hence serum bilirubin must be done in those babies before

intervention. Still it can be used as a valid screening tool.

Amandine Rubio et al.[33] studied the diagnostic accuracy of transcutaneous bilirubinometry in very preterm newborns. In the prospective study total serum bilirubin (TSB) and TCB measurements were recorded in a multicenter sample of newborns <30 weeks of gestational age (GA). TCB specificity, sensitivity, positive and negative predictive values and likelihood ratios for the detection of neonates requiring phototherapy were calculated over the first 15 days of life, with or without phototherapy. Aim of the study was of achieving a detection rate of hyperbilirubinemia of over 95%.

Almost 481 measurements were analyzed in 167 preterm patients. Mean GA of the study group were 27.6 ± 1.6 weeks. The rates of newborns requiring phototherapy were 52% in the first 3 days, 16% from the 4th to the 7th day, and 2% during the second week. Similar diagnostic performance were observed among babies with or without phototherapy.

TCB sensitivity decreased over time from 100% (93.9–100.0) to 50% (1.3–98.7). Specificity showed an inverse evolution from 14.8% (7.0–26.2) to 80.7% (72.2–89.2). The negative predictive values which varied from 95.5 to 100.0 had the best outcome. False negatives were rare in the study (0.8% of measurements). The study therefore concluded that among very preterm babies, TCB measurements might be useful for screening for neonatal jaundice in the first 2 weeks of life. In case of a TCB value below the phototherapy threshold, invasive TSB quantification could be unnecessary.

Saad Abdullah Alsaedi et al. (2018)[39] conducted a study to determine whether transcutaneous bilirubin measurements (TCB) before and during phototherapy taken from covered skin during phototherapy correlate with total serum bilirubin (TSB) levels. The study was a prospective observational study included healthy term newborns who required TSB measurements. TCB measurements of the same were taken from the forehead before starting and during phototherapy using the bilichek device. Blood for TSB measurement was collected within 5 minutes of TCB measurements. Correlations and mean differences between TCB and TSB before and during phototherapy were calculated.

Paired TSB and TCB measurements before and during phototherapy in 151 newborns were performed. The mean gestational age, TSB and TCB measurements before phototherapy were recorded (183.8 ± 41.6 and 190.5 ± 43 μmol/L, respectively). TSB and TCB measurements were recorded during phototherapy (191.8 ± 39.4 and 187.8 ± 45.3 μmol/L, respectively). Linear regression analysis showed a significant correlation between TCB and TSB before starting phototherapy and during phototherapy (r: 0.85; $p < 0.001$ and r: 80.0; $p < 0.001$), respectively.

They concluded that TCB measurements from covered skin in jaundiced term infants during phototherapy correlate with TSB and can be used to monitor bilirubin levels during phototherapy.

American Academy of Pediatrics (AAP)[30] recommends that neonate discharged should have a follow-up visit after 48 to 72 hours for any significant jaundice and other problems.[14] This recommendation is not appropriate for our country due to poor access to health care facility. NH which may be overlooked or delay in recognition by parents, because lack of knowledge. By predicting the neonates at risk for significant NH early at birth, we can design and implement the follow-up program in these risk groups, cost effectively.

Materials and Methods

Full-term parturients attending at our institute from January 2017 to June 2018 were selected. The subjects were divided into two equal groups. The first group with term babies of women with oxytocin augmented labor and second group consisting of term babies of women with normal vaginal delivery following spontaneous onset of labor, forming the control group.

All healthy term (≥ 37 weeks) normal birth weight babies born to mothers between the age of 18 and 35 during the study period were eligible for inclusion in the study.

Rh incompatibility, ABO incompatibility, Cephalohematoma, low birth weight (lbw, i.e. birth weight <2500 g) babies, those who required extensive resuscitation, neonatal sepsis, instrumental deliveries (forceps and vacuum), cesarean sections, birth asphyxia, respiratory distress, meconium stained amniotic fluid and newborns with Apgar score of less than 7/10 at 5 minutes and those parturients suffering from diabetes mellitus, thyroid dysfunction, coagulation disorders, pregnancy induced hypertension, cardiac disease or any other medical comorbidities were excluded.

A group of mothers with normal antenatal check up, and ≥ 37 weeks of gestation, were randomly

selected and studied prospectively. POG was calculated from the first day of the last menstrual period. Rhesus negative mothers were excluded. Mothers whose labor was augmented by oxytocin infusion were matched with mothers of similar maternal age, gestational age (≥ 37 weeks), in whom labor started spontaneously. Control group patients did not receive oxytocin. Amniotomy was done once patients were in active labor in both groups. There were equal number of primi- and multigravidas in both the study and control group.

In oxytocin augmented labors, the rate of oxytocin infusion was: 5 units of oxytocin in 500 ml normal saline. The oxytocin infusion was initiated at a rate of 5 mIU/min and increasing by an additional 5 mIU/min in every 30 minutes until effective uterine contractions were accomplished. The details of maternal age, gestational age, labor duration, mode of delivery, birth weight of the babies, total volume of fluid administered until delivery and total oxytocin dose were recorded in each case.

The clinical condition of the newborn babies was assessed by 5 minute Apgar score. All babies were given routine care and 0.4 ml vitamin K intramuscularly just after birth. They were examined by a pediatrician within 24 hours of birth and daily progress was recorded. In the neonatal period, serum bilirubin was measured by transcutaneous bilirubinometer.

All data was expressed as mean ± standard deviation (SD). The statistical test used was unpaired *t* test to compare dose of oxytocin used for induction of labor and the serum bilirubin levels obtained on day 1 and day 3. A *p*-value of <0.05 was considered as statistically significant.

Our study mainly aimed at calculating the incidence of neonatal hyperbilirubinemia among oxytocin augmented group. The study was an observational study. The bilirubin values were reliably estimated on day 1 and day 3 by trans cutaneous bilirubinometer which was free of cost. So there was no additional intervention needed for this study. Moreover our study did not affect obstetricians decision in giving oxytocin. Hence no ethical issues were involved.

Results

There was 306 eligible parturients during this period. Data collected were analyzed using appropriate statistical software. Of the 306 healthy term babies born during the study period, 153 were exposed to maternal oxytocin (Group A) and 153 babies were born of spontaneous labor (Group B).

There were 77 males and 76 females in Group A while in Group B, there were 62 males and 91 females. Out of 77 male babies 31 diagnosed with neonatal hyperbilirubinemia and underwent phototherapy and out of 76 female babies 28 were hyperbilirubinemic and underwent phototherapy in Group A.

Out of 62 males in Group B, 13 had hyperbilirubinemia and treated with phototherapy and 15 out of 91 female babies had hyperbilirubinemia and treated with phototherapy (Table 1). We didn't encounter any positive correlation between jaundice and neonate's gender and it was not statistically significant.

Table 1: Phototherapy vs Sex Cross tabulation

Phototherapy	Sex		Total
	Male	Female	
No	95 (68%)	124 (74%)	219
Yes	44 (31%)	43 (25%)	87
Total	**139**	**167**	**306**

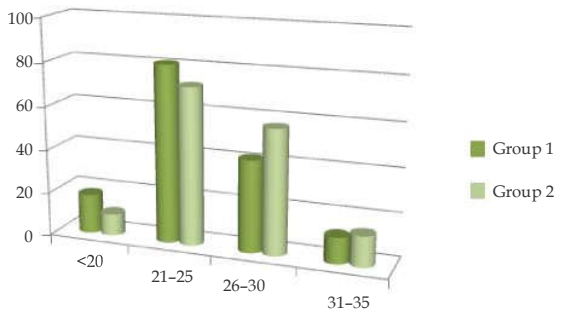

Fig. 1: Age distribution in both groups.

The mean birth weight in Group A was 3134 ± 359 g and in Group B was 3005 ± 294 g. There was no statistical difference between the birth weights of the two groups. Mean maternal age in Group A was 24.69 ± 3.559 and in Group B was 25.38 ± 3.414. Age distribution in each group is showed in (Fig. 1). The difference in the proportion of group for maternal age as a factor for neonatal hyperbilirubinemia was not statistically significant (*p*-value = 0.083)

Parity is considered to be a confounding factor as studies have demonstrated a risk association with NNH. In this study, we had selected equal primis and equal multigravidas in both groups. There were 86 primigavidas each and 67 multigravidas each in both Group A & Group B. Out of total 306 mothers, 73 were A Positive, 99 were B Positive, 45 were

AB Positive and 89 were O Positive (Table 2). The difference in the proportion of groups for maternal blood group was statistically not significant (*p*-value = 0.081)

Table 2: Analysis of blood group in Group A & Group B

Maternal blood group	Group		Total	*p*-value (chi-square test)
	Group B	Group A		
A POS	34	39	73	0.081
B POS	51	48	99	
AB POS	16	29	45	
O POS	52	37	89	

In Group A, 59 babies and 28 babies in Group B developed hyperbilirubinemia (Table 3). Our findings showed that the incidence of NNH requiring phototherapy in Group A was 38% and in Group B was 18% and the difference between 2 groups were statistically significant (*p*-value = 0.0001).

Table 3: Table showing incidence of neonatal hyperbilirubinemia in Group A & Group B

Group	Phototherapy		Total	*p*-value (Chi-square test
	No	Yes		
1	94	59	153	
2	125	28	153	0.0001
Total	**219**	**87**	**306**	

Mean peak bilirubin level on postnatal day 1 in Group A with NNH was 9.3119 ± 1.6268 mg% and without NNH was 6.0606 ± 2.0942 mg% and in Group B with NNH was 8.8964 ± 1.7464 mg% and without NNH was 4.4362 ± 2.0521 mg% respectively (Table 4). Mean peak bilirubin level on postnatal day 3 in Group A with NNH was 15.5719 ± 1.2195 mg% and without NNH was 10.0671 ± 2.5196 mg% and in Group B with NNH was 15.4168 ± 1.9530 mg% and without NNH was 8.1672 ± 2.460 mg% respectively.

Table 4: Mean bilirubin values in Group 1 on day 1 and day 3 with NNH vs without NNH

Bilirubin	Phototherapy		*p*-value (Independent *t* test)
	Yes	No	
Day 1 Bili	9.3119 ± 1.62683	6.0606 ± 2.09424	0.0001
Day 3 Bili	15.5719 ± 1.21955	10.0671 ± 2.51965	0.0001

Within each group the hyperbilirubinemia on day 1 and day 3 was statistically significant for those babies who were treated with phototherapy. Mean serum bilirubin level on postnatal day 1 in Group A was 7.3144 mg% and in Group B was 5.2524 mg% (Table 5). The mean serum bilirubin levels on postnatal day 3 in Group A was 12.1899 mg% and in Group B was 9.4939 mg% respectively (Table 5). The difference in the proportion of groups for mean serum bilirubin on day 1 and day 3 were found to be statistically significant (*p*-value 0.0001).

Table 5: Comparison of mean bilirubin values in Group A & Group B on day 1 and day 3

Group		*N*	Mean	Std. Deviation	*p*-value (Students *t* test)
Day 1 Bili	1	153	7.3144	2.49282	0.0001
	2	153	5.2524	2.64033	
Day 3 Bili	1	153	12.1899	3.41734	0.0001
	2	153	9.4939	3.59039	

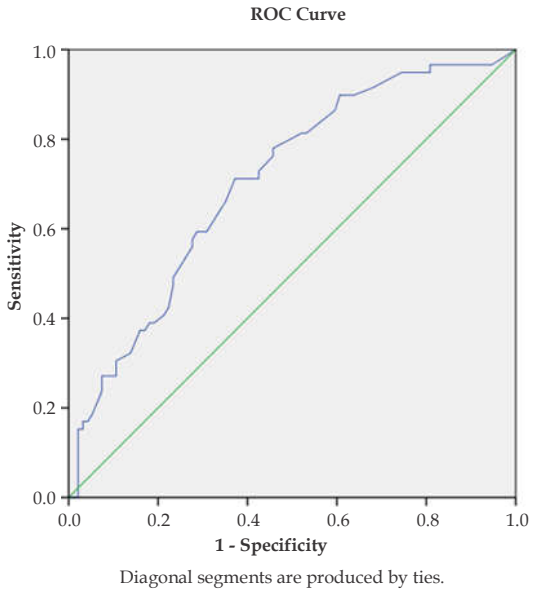

Fig. 2: ROC curve showing volume distribution.

Mean maternal oxytocin volume infused was 3564.64 ± 2620.58 mIU in those with neonatal hyperbilirubinemia treated with phototherapy and was 2030.90 ± 1745.506 mIU in those without subsequent neonatal hyperbilirubinemia. Mean oxytocin rate and duration in those with NNH treated with phototherapy and those who were within the normal range of bilirubin for the gestational age were 29.69 ± 12.164, 242.27 ± 108.424, 23.62 ± 11.703 and 170.00 ± 92.216 respectively. The *p*-value calculated for oxytocin rate, duration and volume in study subjects were 0.002, 0.0001, 0.0001 respectively by Mann–Whitney *U* test which indicates a statistically significant association for duration dosage and total volume of oxytocin administered causing neonatal hyperbilirubinemia. Cut-off volume of oxytocin according to ROC curve was 5101 mIU

with AUC 0.706 and it is statistically significant (*p*-value 0.0001) (Table 6, Fig. 2).

Table 6: Area under the curve. Test result variable(s): Total volume (mIU)

Area	Std. Error[a]	*p*-value	Asymptotic 95% Confidence Interval	
			Lower Bound	Upper Bound
.706	.043	.0001	.622	.789

The volume distribution in Group A was closely analyzed showing a total of 90 received <2500 mIU/min throughout active phase of labor, 46 received volume range between 2500 and 5000 mIU/min and 17 received volume ≥ = 5000 mIU/min.

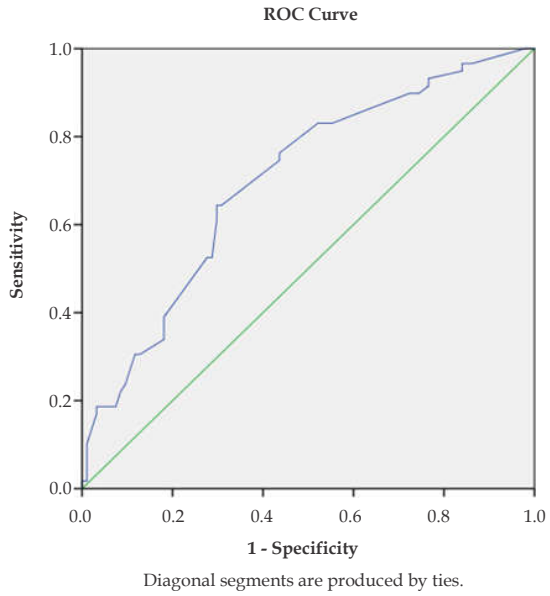

Fig. 3: ROC curve plotting oxytocin duration.

Volume distribution showed that out of 90 subjects in Group A who received <2500 mIU/min volume throughout active phase of labor 24 (26%) experienced NICU admission for neonatal hyperbilirubinemia in the postnatal period. Out of 46 subjects in Group A who received in range of 2500–5000 mIU/min volume throughout active phase of labor 20 (43.5%) experienced NICU admission for neonatal hyperbilirubinemia in the postnatal period. Out of 17 subjects in group A who received ≥ = 5000 mIU/min volume throughout active phase of labor 14 (82.35%) experienced NICU admission for neonatal hyperbilirubinemia in the postnatal period. This confirms the findings of association of NNH with increase in oxytocin volume. Also total duration of infusion of oxytocin was calculated and found to be 242.27 ± 108.424 minutes in phototherapy group compared to 170.00 ± 92.216 minutes in those without subsequent neonatal sequel.

Cut-off duration of oxytocin observed is 292.5 minutes by ROC curve with AUC 0.7. It is found to be statistically significant with a *p*-value = 0.0001. This implies above 292.5 minutes oxytocin administration has got a chance for neonatal hyperbilirubinemia (Fig. 3, Table 7). None of the babies required exchange transfusion during the study period. The incidence of neonatal jaundice in Group A and in Group B was 0.38 and 0.18 respectively. The result of the study showed that there was an increase in incidence of neonatal hyperbilirubinemia in oxytocin augmented group compared to the spontaneous labor group which is statistically significant (*p*-value = 0.0001).

Table 7: Area under the curve. Test result variable(s): oxytocin duration

Area	Std. Error[a]	Asymptotic Sig.[b]	Asymptotic 95% Confidence Interval	
			Lower Bound	Upper Bound
.700	.043	.0001	.615	.784

The Pearson correlation for oxytocin rate and day 1 and day 3 bilirubin were 0.382 and 0.414 with a *p*-value of 0.001 and 0.001 respectively. The Pearson correlation for oxytocin duration and day 1 and day 3 bilirubin were 0.452 and 0.454 with a *p*-value of 0.001 and 0.004 respectively. The Pearson correlation can be interpreted as: The oxytocin duration and rate of infusion is having a fair strength of linear relationship with bilirubin values on day 1 and day 3 of newborn life and it is statistically significant.

Discussion

Bilirubin toxicity remains a significant problem despite recent advances in the care of neonates with jaundice. Kernicterus, though infrequent, is the cause of 10% of the mortalities and at least 70% of the long-term morbidities in these neonates.[4] Oxytocin crossing the placenta resulting in erythrocyte deformability was shown in the in-vitro studies which help us to explain the clinical observations that the NNH after induction of labor is related to the dose and the duration of oxytocin administered.

Many studies on neonatal bilirubin levels and the use of oxytocin for the management of labor have produced conflicting results but it has been widely accepted that oxytocin infusion during labor increased the risk of neonatal

hyperbilirubinaemia.[1,2,5,16,32] Our study result is having similarity with the studies of Awasthi et al. (1998),[18] Abbas et al. (2015),[33] and Rostami et al. (2005),[19] regarding oxytocin effect on neonatal hyperbilirubinemia which showed significant correlation between the neonatal hyperbilirubinemia with the oxytocin induction of labor (p = .002).

When we compared our study (study 2) with a study conducted by Shagun Gupta et al.[10] on neonatal hyperbilirubinemia after induction of labor with oxytocin with an average dose of oxytocin for induction as 4500 mU (range 2500 to 7500 mU) (study 1). In study 1, 56% had NNH while in study 2, 38% had NNH. In our study group majority of Group 1 (those delivered with oxytocin augmentation) were infused with a volume of <2500 mIU of oxytocin and we found that only 26% newborns had NNH. As the volume increased in the rest the incidence of NNH also spiked approaching 43.5% and 82.35% in groups with 2500–5000 mIU and ≥ 5000 mIU of oxytocin respectively, which is in consistent with study Group 1 indicating a positive correlation of increase in dosage and volume of oxytocin with resultant jaundice requiring phototherapy.

Lutfun Naher Begum et al. (2013)[35] conducted a prospective randomized control trial which showed an increased incidence of neonatal hyperbilirubinemia when the mother is given a total oxytocin dose more than 4500 mu, a similar result with Singhi S and Buchan C et al. studies.[5,43] In our study we found that a cut-off duration of oxytocin to be 292.5 minutes and a cut-off total volume infusion of oxytocin to be 5101 mIU, above which noted a statistically significant increase in newborn jaundice requiring phototherapy.

In this study we used high dose oxytocin regimen, i.e. 5 mIU/min and titrated it half hourly till adequate contractions obtained. A study conducted by Manjula BG et al.[51] compared high dose and intermediate-dose regimen of oxytocin (6 mIU/min vs 3 mIU/min) with a statistically significant (p-value 0.002) correlation of jaundice with high-dose regimen (neonatal bilirubin levels 7.99 ± 2.70 vs 6.80 ± 2.65 mg/dl in high-dose vs low dose). Our study is also consistent with the above finding (neonatal bilirubin level 8.8964 ± 1.75 mg/dl) suggesting that it would be better to stick on intermediate-dose regimen especially in low-risk gravidae whose NNH rate was significantly influenced by the mere use of oxytocin.

A comparison of day 1 bilirubin from our study with cord bilirubin values by D'Souza SW et al.[1] in relation to dosage of oxytocin showed similar results with values approximately 8, 9, 9.8 mg/dl and 5.2, 5.64, 6.7 mg/dl for oxytocin volume <2500, 2500–5000, ≥ 5000 mIU respectively. In our study (Study 1) the Pearson correlation between oxytocin rate and duration with day 1 bilirubin was 0.382 and 0.452 respectively. D'Souza SW et al. study showed the correlation between the cord plasma bilirubin and the total dose of oxytocin to be, r = 0.47 (p < 0.000001) (study 2). On comparison both the studies showed fair strength of linear relationship with bilirubin values which are statistically significant.[1]

There is, at present, no evidence to suggest that such high bilirubin levels are directly harmful to the child in the long-term. A prospective cohort study by Omigbodun AO et al.[37] states that with TSB more than 19 mg/dl there is an increased risk of attention deficit disorder with a relative risk of 1.9. Even though our study showed a significant increase in bilirubin values in relation to oxytocin use, none of our babies had bilirubin values more than 19 mg/dl. This shows that mere oxytocin use may not result in a very high bilirubin value probably in the range of intense phototherapy or exchange transfusion and there is no long-term harm to the baby.

However, the immediate concern is the anxiety engendered in the mother of a jaundiced infant, and the need to prolong hospital stay and mother infant separation until jaundice has cleared.

In this study gestational age and birth-weight did not differ in the groups, and cannot therefore account for the differences seen. Maturation of liver enzymes in the fetus may occur at or around the time of the spontaneous onset of labor. They may not have developed to the same extent when labor is induced or augmented by artificial rupture of membrane and use of various agents like oxytocin (which we used in our study) and prostaglandins (PG E1, PG E2). This supports the idea put forward by Davies et al.[2] that the surge of fetal cortisol production which seems to accompany spontaneous labor, may contribute to the induction of hepatic enzyme systems, some of which are known to be corticosteroid inducible.

In our study the diluent used was 0.9% normal saline. Omigbodun et al. reported that isotonic saline appeared to be associated with low neonatal bilirubin levels. The study said 5% dextrose, a salt free fluid as a diluent increased the risk of transplacental hyponatremia in mother and neonatal hyperbilirubinemia as a consequence.[36] In our study since we used 0.9% normal saline, the

diluent effect is not encountered as a confounding factor for jaundice.

The present findings in our study were consistent with the results reported by Ghaemi et al.[48] Patil et al.[47] Keren et al.[50] and Chang et al. (2011)[49] that oxytocin with hypoosmotic effects due to its vasopressin-like action, causes water retention in red blood cells of infants and diminishes the ability of cells to change, i.e. reduced deformability and thereby increases red blood cell lysis while passing through blood vessel. In neonates, whose hepatic enzymes are unable to cope with the increased bilirubin production due to hemolysis, clinical hyperbilirubinemia ensues.

Oxytocin is an important therapeutic agent in obstetrics and probably its use cannot be stopped and thus its effect on erythrocytes also cannot be prevented. But it is reasonable to reduce the total dose of oxytocin to be infused to a minimum, especially when additional risk factors for hyperbilirubinemia co exist and the neonates whose mothers received oxytocin during labor should be closely monitored and followed up after discharge for the development of hyperbilirubinemia.

Conclusion

Our study concludes that maternal oxytocin used for augmentation of labor can cause higher bilirubin values in the early neonatal life in term babies without discernible cause on routine investigations. As oxytocin is an important therapeutic agent in labor and probably its use cannot be stopped, it is logical to prevent hyperbilirubinemia by reducing the total dose of oxytocin infusion to less than 5000 mIU and by its selective use. The limitations of our study was that the sample size was less and further study with larger sample is required. Anticipated balance between maternal benefits and neonatal harm were not explored in this study which might provide an equilibrium to define the adequate dosage and timing of oxytocin to be administered.

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