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Does anaesthesia in mothers during delivery affect bilirubin levels in their neonates?

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Purpose: This study aimed to assess whether different anesthetic techniques and oxytocin use applied during delivery affect transcutaneous bilirubin levels during the first 24 hours in neonates.
Methods: A total of 1,044 neonates delivered by either caesarian section (C/S) or normal vaginal delivery (NVD) were included in the study. They were classified into 5 groups as follows: group 1: born by C/S using general anesthesia, group 2: C/S using spinal anaesthesia, group 3: C/S using general anesthesia after failed spinal block, group 4: by NVD without anesthesia, and group 5: oxytocin-induced vaginal delivery without anesthesia. Transcutaneous total bilirubin levels (TBLs) were measured during the first 24 hours and on the fifth and eighth days of life and the levels in different groups were compared.
Results: The TBLs were significantly higher in neonates delivered by C/S using general anesthesia rather than spinal anesthesia ($P<0.001$), and both groups had higher levels than those born by NVD without anesthesia ($P\leq0.001$). However, the group receiving general anesthesia after failed spinal block was found to have the highest bilirubin level. Moreover, TBLs were significantly higher with the use of oxytocin ($P\leq0.001$).
Conclusions: C/S and general anesthesia adversely affect the bilirubin levels in neonates, and the use of oxytocin during vaginal delivery also increases TBLs in neonates.

Key words: Anesthesia, Jaundice, Delivery, Neonates, Hyperbilirubinemia

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Introduction

Jaundice is one of the most common causes of health problems, observed in 60% of term and 80% of preterm infants in the first week of life[1]. Hyperbilirubinemia may lead to neurotoxicity. There is no definite safe level for bilirubin, therefore early detection and treatment of neonatal hyperbilirubinemia is crucial in the prevention of kernicterus[2,3].

In addition to the classic risk factors such as maternal diabetes, blood group incomptability, and premature deliveries, more liberal use of oxytocin to induce labor and certain drugs used by the mother were proposed to be contributers to the increase in neonatal jaundice[4-6].

Anesthesia and particular anesthesiology techniques have also been included among factors that may influence neonatal hyperbilirubinemia[6,7]. However, literature concerning the role of anesthesia and particular techniques in hyperbilirubinemia at caesarean sections is limited[6,7]. In literature, there are a few studies on vaginal delivery[8].

Therefore, in this study, we aimed to determine the effects of different anesthesiological strategies on neonatal hyperbilirubinemia in both cesarean section and vaginal deliveries. Moreover, we wanted to compare general anesthesia and spinal anesthesia in C/S, also we wanted to establish the effect of oxytocin induced labor on the neonates.

Materials and methods

A total of 1,044 infants delivered by both C/S and vaginal delivery at the Department of Obstetrics and Gynecology, Ain-Shams University Hospitals were enrolled in the study. Women with uncomplicated pregnancies who delivered full term neonates were included in this study, either by elective C/S (n=565) or uncomplicated vaginal deliveries (n=479). Exclusion criteria were: Rh incomptability, ABO and subgroup incomptabilities, positive direct Coombs test, fetal anomalies, meconium aspiration, APGAR scores of ≤8 at 1 minute and ≤10 at 5 minutes, preterm (<37 weeks) infants, or a history of maternal drug use known to influence neonatal bilirubin levels.

1. Ethical approval of studies

The study was approved by the Ethics Committee of Ain-Shams University Hospitals and verbal consent was obtained from the parents or guardians of the neonates who served as subjects in the study.

The neonates were classified according to the method of delivery and anesthetic agents as: group 1: caesarian section (C/S) using general anesthesia with thiopental Na and isoflurane; group 2, C/S using spinal anesthesia with bupivacaine hydrochloride; group 3, C/S using general anesthesia after failed spinal block; group 4, normal vaginal delivery (NVD)/without anaesthesia, can be considered as controls; group 5, oxytocin-enhanced vaginal delivery without anesthesia.

Indications for C/S were often previous uterine incisions, less frequently cephalopelvic disproportion, malpresentation and patient preference. General anaesthesia was used for the patients who did not accept or who had contraindications for regional anaesthesia.

2. Anaesthetic techniques

For general anesthesia, thiopental sodium 5–7 mg/kg and succinylcholine 1.5 mg/kg for initial induction, followed by atracurium besylate 0.25 mg/kg were administered intravenously during C/S. After muscular relaxation, endotracheal intubation was performed. For the maintenance of anesthesia, 100% O_2 and 1%–2% minimum alveolar concentration of isoflurane were used. The time from the onset of general anesthesia to clamping of the cord was 6–8 minutes.

For C/S in the spinal anesthesia group, 1,000 mL 0.9% NaCl was administered in 30 minutes (Preloading). Hydration was maintained with 0.9% NaCl at a rate of 10 mL/kg/hr. Spinal anesthesia was performed by using 26-G spinal needles into L3–4 or L4–5 intervertebral space, in the sitting position. Once free flow of cerebrospinal fluid was observed, 0.5% heavy bupivacaine hydrochloride approximately 2 mL, and fentanyl 15 μg were injected. The period from the onset of spinal anesthesia to clamping of the cord was 8 μg 10 minutes. No anesthetic agent was used in groups 4 and 5.

The surgical technique was uniform in all women and umbilical cord blood gas sampling was performed immediately after clamping the cord. All newborns were evaluated for APGAR scores at the 1st and 5th minutes, and 2 mL of blood were drawn for a blood count and direct and total bilirubin measurements at the 24th hour and 5th day of life.

The need for phototherapy was determined according to the normogram described by American Academy of Pediatrics Subcommittee on Hyperbilirubinemia for designation of risk with respect to the postnatal age in hours and total bilirubin levels.

transcutaneous bilirubin (TCB) level was measured using Konica Minolta/Air Shields (Jaundice Meter JM 103, Draeger Australia Pty. Ltd., Notting Hill, Australia), because it is a noninvasive technique.

The JM-103 determines the yellowness (bilirubin) of the subcutaneous tissue of a neonate by measuring the difference in the optical densities of reflected light at 450 and 550 nm by the newborn skin. Because there is a linear correlation with total serum bilirubin (TSB) and the difference in the absorbance, the TSB can be estimated[9]. In this study, the Minolta JM-103 probe was placed against the forehead and sternum of the infant in a supine position. Then a computerized average of 3 consecutive readings over each measurement site was displayed as the TCB level in mg/dL. The mean of the 2 measurements from forehead and sternum was used in statistical analysis.

Blood samples were drawn from a peripheral vein and TSB levels were measured in laboratories of Ain-Shams University Maternity Hospital using the method of direct spectrophotometry.

3. Statistical analysis

Data were analyzed using IBM SPSS Statistics ver. 21.0 (IBM Co., Armonk, NY, USA). The results were expressed as mean±standard deviation (SD) for quantitative parametric measures in addition to Median Percentiles for quantitative nonparametric measures and both number and percentage for categorized data. The following tests were done; *t* test for independent groups; comparison between 2 independent groups for nonparametric data using Wilcoxon rank-sum test, comparison between 2 dependent groups for nonparametric data using Wilcoxon signed-rank test; chi-square test to study the association between each 2 variables or comparison between 2 independent groups as regards the categorized data; Pearson correlation test for relationships between variables. The results were considered to be statistically significant at $P<0.05$, highly significant at $P<0.01$, nonsignificant at $P>0.05$.

Results

This study was conducted on 1,044 healthy newborns, 501 male (48%) and 543 female patients (52%), recruited randomly from delivery room of Gynecology and Obstetrics Hospital, Ain-Shams University. It included 5 groups: group 1, 251 C/S with general

anaesthesia; group 2, 259 C/S with spinal anaesthesia; group 3, 55 C/S with general anaesthesia after failed spinal block; group 4, 233 normal spontaneous vaginal delivery (NSVD) without anaesthesia and without oxytocin; group 5: 246 vaginal delivery without anaesthesia and with oxytocin.

All cases were full-term newborns with gestational age ranging from 38 to 41 weeks with no significant difference in gestational age between different groups (P=0.17), and their birth weight ranging from 2.5 kg and 4.5 kg (mean±SD, 3.12±0.48 kg) as shown in (Table 1), with no significant difference in birth weight between the groups. The mean age of mother was higher in the C/S groups with general anaesthesia (29.048±5.69 years) and the group with general anaesthesia after failed spinal block (30.82±3.6 years), than the group of NSVD (28.71±5.27 years) and the group with vaginal delivery induced by oxytocin (24.4±3.62 years) but the difference was not statistically significant. As regard parity of mothers 368 of mothers (36.8%) were primigarvidas, 302 (30.2%) were para 1, 170 (17%) were para 2, 121 (12.1%) were para 3, while 39 (3.9%) were grand multiparas.

The neonates delivered by C/S were classified according to anaesthesiological methods as: group 1 (general anaesthesia with isoflorane), group 2 (spinal anaesthesia with bupivacaine), and group 3 (general anaesthesia after failed spinal block), and the TBLs were compared.

The serum levels of bilirubin in the general anesthesia group on days 1, 5, and 8 were significantly higher 3.18±1.08, 11.91±3.63, 8.49±3.10, respectively compared to those in mothers receiving spinal anesthesia (1.86±1.01, 8.49±4.02, 6.60±3.22, respectively, P<0.001) (Table 2). Also when comparing groups 1 and 3, it was found that the serum bilirubin levels were significantly higher in group 3 on days 1, 5, and 8 than group 1 (5.32±1.01, 16.68±2.09, and 10.42±1.96, respectively, P<0.001).

When the C/S group were compared with the NSVD group and oxytocin-induced vaginal delivery group; the serum levels of bilirubin in group 3 on days 1, 5, and 8 were significantly higher compared to values in group 4 who did not receive any type of anaesthesia (0.98±0.70, 5.33±2.85, and 4.87±2.58, respectively, P<0.001). Also, the TBLs in group 1 were higher than group 4 (P<0.001).

Moreover, comparing the serum bilirubin levels on days 1, 5, and 8 in groups 4 and 5, it was found that levels of total bilirubin were significantly higher in group 5 (1.91±0.97, 9.62±2.97, and 6.46±2.66, respectively, P<0.001) (Table 3).

The study also showed that only 108 of the total studied neonates (10.3%) needed phototherapy for treatment of hyperbilirubinemia; distributed as follows: 40 (37% of neonates needing phototherapy, 15.9% within the group) in group 1, 18 (16.6% of neonates needing phototherapy, 6.9 within the group) in group 2, 25 (23% of neonates needing phototherapy, 45.4% within the group) in group 3, 6 (5.5% of neonates needing phototherapy, 2.5% within the group) in group 4, 19 (17.5% of neonates needing phototherapy, 7.7% within the group) in group 5.

Table 1. Maternal and neonatal demographic data in different groups

Group	Maternal age (yr)	Gestational age (wk)	Birth weight (kg)
1 (n=251)	29.05±5.69	38.65±0.83	3.12±0.49
2 (n=259)	27.65±5.07	38.94±0.88	3.16±0.42
3 (n=55)	30.82±3.60	39.08±1.21	3.39±0.44
4 (n=233)	28.71±5.27	39.32±0.93	3.18±0.43
5 (n=246)	24.42±3.62	39.34±0.87	3.01±0.36

Values are presented as mean±standard deviation.

Table 2. Comparison of total bilirubin levels on days 1, 5, and 8 between groups delivered by caesarian section

Day	Group 1 (n=251)	Group 2 (n=259)	Group 3 (n=55)	*P* value	
				Group 1 vs. 2	Group 2 vs. 3
1	3.18±1.08	1.86±1.01	5.32±1.01	<0.001*	<0.001*
5	11.91±3.63	8.49±4.02	16.68±2.09	<0.001*	<0.001*
8	8.49±3.10	6.60±3.22	10.42±1.96	<0.001*	<0.001*

Values are presented as mean±standard deviation.
Group 1, born by caesarian section (C/S) using general anesthesia; group 2, C/S using spinal anaesthesia; group 3, C/S using general anesthesia after failed spinal block.
*Highly significant between the groups.

Discussion

Jaundice is a common problem seen in both term and preterm infants, and different causative factors have been reported in recent years[10]. This study was done to question the effect of different anesthetic techniques and mode of delivery on neonatal jaundice. Alkan et al.[10] reported in his study that although the inclusion criteria of the study did not involve infants with risk factors of neonatal jaundice, TCB levels were higher than 5 mg/dL in 27.6% of the study group.

Table 3. Comparison of total bilirubin levels mean±SD) on D1, D5 and D8 between group delivered by C/S with general anesthesia and vaginal delivery group and between group 4 (NSVD) and group 5 (oxytocin-induced vaginal delivery)

Day	Group 4 (n=233)	Group 5 (n=246)	Group 1 (n=251)	*P* value	
				Group 4 vs. 5	Group 4 vs. 1
1	0.98±0.70	1.91±0.97	3.18±1.08	<0.001*	<0.001*
5	5.33±2.85	9.62±2.97	11.91±3.63	<0.001*	<0.001*
8	4.87±2.58	6.46±2.66	8.49±3.10	<0.001*	<0.001*

Values are presented as mean±standard deviation.
Group 1, born by C/S with General anesthesia; group 2, C/S using spinal anaesthesia; group 3, C/S using general anesthesia after failed spinal block; group 4, born by spontaneous vaginal delivery without anesthesia; group 5, born by oxytocin-induced vaginal delivery.
*Highly significant between the groups.

The present study showed significantly higher bilirubin levels in group of general anaesthesia compared to the group where mothers received spinal anesthesia (P<0.001). This is in agreement with the Turkish study by Demiraran et al.[11]; where significantly higher direct bilirubin levels at 5th day in the total intravenous anesthesia (TIVA) group compared to spinal anesthesia group.

In this study, total bilirubin levels in the first 24 hours for C/S groups were significantly higher than vaginal delivery groups receiving no anesthesia. It was significantly higher in both the general anesthesia and spinal anesthesia groups than in the groups without anesthesia (P<0.001).

De Amici et al.[6] mentioned that among all newborns delivered by C/S, some had more intense physiological jaundice and it was likely that anesthetic technique could be among factors influencing neonatal jaundice.

Gale et al.[12] reported a significant correlation between C/S and increased bilirubin levels. Their study has revealed that preterm labor, vacuum, forceps, low birth weight and maternal age increased bilirubin levels. The present study has also demonstrated that C/S increased neonatal bilirubin levels, however, we excluded in this study factors like; prematurity, instrumental deliveries, and low birth weight. This is similar to results shown by the Turkish study; Eskicioglu et al.[13] reported that total bilirubin levels in the first 24 hours for C/S groups were significantly higher than vaginal delivery groups.

Osborn et al.[14] reported significant correlations between jaundice and C/S and anaesthesia. However, Phuapradit et al.[15] have reported the absence of a correlation between C/S and neonatal hyperbilirubinemia. Moreover, Alkan et al.[10] found that the mode of delivery did not affect the TBL and emphasized that the route of delivery had no effect on neonatal TCB levels during the first 24 hours.

It is expected that anesthetic agents used during C/S cross the placenta, considering the time from induction of anesthesia to clamping of the cord, being highly lipid soluble, they freely cross the placenta. Therefore, it is likely that anesthetic technique can be included among factors with possible influence on neonatal jaundice[16].

Previously, it was shown that Porpofol (used for induction in general anesthesia) produced an in vitro concentration-dependent inhibition of uridine diphosphate-glucuronyltransferase, an enzyme in human liver that is responsible for glucoronidation of unconjugated bilirubin. Thus, it may be hypothesized that the mechanisms responsible for increased bilirubin levels with inhalation anesthetics may be shared by Propofol[16].

De Amici et al.[6] found that isoflorane anesthesia (general) caused higher neonatal bilirubin levels and more intense physiological jaundice than sevoflurane anesthesia probably due to the immaturity of neonatal liver enzymes.

Clark and Landaw[17] reported that neonatal jaundice associated with maternal anesthesia, especially bupivacaine hydrochloride (used in spinal anesthesia) may be explained by the observation that local anesthetic agents (lidocaine, mepivacaine) cross the placenta, bind to red cell membrane and reduce its filterability, resulting in shortened red cell survival. The present study revealed that neonatal bilirubin levels increased with bupivacaine hydrochloride.

In earlier studies, both bupivacaine and levobupivacaine used in regional anesthesia were shown to cross the placenta and were taken up into fetal tissues. Fetal serum concentrations and fetal tissue distribution were similar for each agent[18].

However, Alkan et al.[10] showed that bupivacaine did not affect neonatal bilirubin levels and that sevoflurane increased bilirubin levels; where TCB levels in sevoflurane group were significantly higher than bupivacaine hydrochloride group.

In our study 108 neonates of the total studied neonates (10.3%) had hyperbilirubinemia necessitating phototherapy, with the highest proportion in general anaesthesia group 40 neonates (37% of neonates needing phototherapy) and the combined general and spinal anaesthesia group 25 neonates (23%), and lowest proportion in the NSVD group receiving without anaesthesia; 6 neonates (5.5 %). This is in agreement with Demiraran et al.[11], where the TIVA group had the highest percentage of newborns requiring phototherapy. We found almost same proportion in spinal anaesthesia group 18 neonates (16.6%) and oxytocin-induced vaginal delivery group 19 neonates (17.5%).

In the present study, the general anesthesia group had the highest percentage of newborns requiring phototherapy (35%) when compared to all other groups. This was the same result as the study done by Demiraran et al.[11] in Turkey, however, the differences among groups were not significant.

It is well known that oxytocin stimulates uterine motility and increases neonatal bilirubin levels[4]. The association between oxytocin and neonatal hyperbilirubinemia was documented by means of increased erythrocyte fragility. The effect of oxytocin on erythrocyte destruction during oxytocin induced labor has been reported[4].

In this study we found that bilirubin levels were significantly higher in mothers receiving oxytocin than in the group without oxytocin (P<0.001). These are the same results observed by Oral et al.[4], who said the fact that oxytocin has a vasopressin (antidiuretic hormone, ADH) like-effect. The action of ADH to increase the permeability of the red blood cell membrane to water mediated through (cyclic adenosine monophosphate). ADH attaches to specific receptors on the membrane-bound adenocyclase. It is well known that oxytocin stimulates uterine motility and increases neonatal bilirubin levels.

One of the limitations of this study is that it has limited clinical significance because the phototherapy is the clinically important outcome. In order to reach a clinically significant difference in phototherapy need between the groups, a very high number of patients would be required. Therefore, we set total bilirubin as primary outcome to guide the forthcoming studies with higher number of patients. Secondary outcome was the phototherapy need for babies.

In conclusion, general anesthesia and maternal C/S seem to adversely affect bilirubin levels in their neonates.

Conflicts of interest

No potential conflict of interest relevant to this article was reported.

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