



## Evaluation of the Effects of Different Anesthetic Techniques on Neonatal Bilirubin Levels

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### Abstract

**Objectives:** The aim of the present study was to determine whether different anesthetic techniques applied for vaginal delivery and cesarean section affect neonatal bilirubin levels in the first 24 hours of life.

**Materials and Methods:** A total of 511 neonates delivered by vaginal route or cesarean section were included in the study. The neonates were classified according to method of delivery and anesthetic agents as group A (cesarean section / general anesthesia with sevoflurane), group B (cesarean section / spinal anesthesia with bupivacaine hydrochloride), group C (vaginal delivery with episiotomy / local anesthesia with prilocaine hydrochloride) and group D (vaginal delivery/ no anesthesia). The levels of neonatal serum bilirubin in the groups were compared.

**Results:** There was no difference between group A and group B in terms of neonatal bilirubin levels ( $p = 0.98$ ). Depending on the use of prilocaine hydrochloride as local anesthetic agent in the vaginal delivery, there was no significant difference between the groups C and D, in terms of the neonatal bilirubin levels ( $p = 0.99$ ). The serum levels of bilirubin in cesarean section groups were significantly higher than those of the vaginal delivery groups ( $p < 0.001$ ).

**Conclusion:** Prilocaine hydrochloride used for episiotomy did not exert any effects on neonatal hyperbilirubinemia. However, cesarean section with sevoflurane and bupivacaine hydrochloride seemed to result in increased bilirubin levels.

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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 defined safe level of bilirubin, therefore early detection and treatment of neonatal hyperbilirubinemia is crucial in the prevention of bilirubin-induced encephalopathy (2,3). However, neonatal jaundice is sometimes harmless. Monitoring bilirubin levels over multiple hospital visits and readmitting infants to the hospital for phototherapy may cause anxiety to the parents, adversely affect the parent-infant relationship. Furthermore, readmissions and treatment increase health care costs overall (4).

It has long been known that hyperbilirubinemia is likely to develop in premature infants, due to immaturity of glucuronyl transferase enzyme system. Some other reasons of concern include blood group incompatibility, more liberal use of oxytocin for inducing labor, certain drugs used by the mother, abnormal deliveries (forceps, breech and vacuum) (5,6).

It is expected that anesthetic agents cross the placenta, considering the time from induction of anesthesia to clamping of the umbilical cord. Therefore, it is likely that anesthetic technique can be included among factors with possible influence on neonatal jaundice (7). Recently, Alkan et al. showed that bupivacaine did not effect neonatal bilirubin levels and that sevoflurane increased bilirubin levels (8). Demiraran et al. mentioned that bupivacaine was better than sevoflurane considering neonatal hyperbilirubinemia (6). The studies investigating the effects of anesthesia and particular techniques on neonatal hyperbilirubinemia are commonly confined to cesarean sections (C/S) (5, 7). In literature, there are a few studies on vaginal delivery (8). In addition, studies related to this issue compared general, epidural, spinal, and total intravenous anesthesia; however, to our knowledge, the effect of local anesthesia for episiotomy during the vaginal delivery on neonatal bilirubin levels has not been mentioned thus far. Prilocaine hydrochloride is a local anesthetic agent that

can be used for episiotomy. This agent may lead to methemoglobinemia, hence it is not recommended for babies who are younger than 3 months of age (9, 10). To our knowledge, the effect of prilocaine on jaundice of newborn infants born by vaginal route has not been reported.

Therefore, in this study, we aimed to determine the effects of local anesthesia with prilocaine hydrochloride in vaginal delivery on neonatal jaundice in the first 24 hours of life. Moreover, we wanted to compare general anesthesia with sevoflurane and spinal anesthesia with bupivacaine hydrochloride in C/S.

## Material & Methods:

The study was approved by Ethics Committee of Celal Bayar University. It is a study that included ASA I-II status, uncomplicated deliveries by elective C/S (n=189) and uncomplicated vaginal deliveries (n=322) at the Departments of Obstetrics between June-2012 and March-2013. Exclusion criteria were Rh incompatibility, positive direct Coombs test results, fetal anomalies, fetal growth retardation, APGAR scores of <8 at 1 min and <10 at 5 min, preterm (<37 weeks) infants, or a history of maternal drug use known to influence neonatal bilirubin levels. Indications for C/S were often previous uterine incisions, less frequently cephalopelvic disproportion, malpresentation and patient preference. The neonates were classified according to the method of delivery and anesthetic agents as:

Group A (C/S / general anesthesia with sevoflurane),

Group B (C/S / spinal anesthesia with bupivacaine hydrochloride),

Group C (vaginal delivery with episiotomy / local anesthesia with prilocaine hydrochloride),

Group D (vaginal delivery/ no anesthesia),

For induction, propofol 2 mg/kg and atracurium besylate 0,5 mg/kg were administered intravenously during C/S for the general anesthesia group. After muscular relaxation, endotracheal intubation was performed. For the maintenance of anesthesia, 50% O<sub>2</sub>, 50% N<sub>2</sub>O, and 1-2% minimum alveolar concentration of

sevoflurane 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, 1000 ml 0.9% NaCl was administered in 30 minutes. Hydration was maintained with 0.9% NaCl at a rate of 10ml/kg/h. Spinal anesthesia was performed by using 26 gauge spinal needles into L3-4 or L4-L5 intervertebral space, in the sitting or lateral decubitus position. Once free flow of cerebrospinal fluid was observed, 0.5% heavy bupivacaine hydrochloride 2cc, and fentanyl 15 mcg were injected. The period from the onset of spinal anesthesia to clamping of the cord was 8-10 minutes. Prilocaine hydrochloride (2%) at a volume of 5 cc was injected into the muscular perineal area for episiotomy in group C. The cord was clamped in 8-10 minutes after injection. No anesthetic agent was used in group D.

The blood samples drawn from the heel into the hematocrit pipette were centrifuged, and then, measured by B-105 digital bilirubinometer (Erma Inc., Japan) with spectrophotometric method. Considering exclusion and inclusion criteria, maternal and gestational age, birth weight and gender of the neonate, route of delivery, and anesthetic agents, bilirubin levels in the first 24 hours were recorded from patient files.

The data was analyzed by using descriptive statistical methods (frequency count, mean and standard deviation), t test for independent groups, chi-square test for categorical variables, Pearson correlation test for relationships between variables, one-way analysis of variance (ANOVA) and post hoc tukey test to compare difference between groups. P values less than 0.05 were accepted as significant.

### Results:

A total of 511 pregnant women were included in the study, and there were no significant differences between groups in terms of birth weight and gender of neonates ( $p = 0.89$  and  $p = 0.90$ , respectively). The maternal age was significantly lower in group C (vaginal delivery/local anesthesia with bupivacaine hydrochloride) than those of group A (C/S /general anesthesia with sevoflurane), group B (C/S/ spinal anesthesia with bupivacaine hydrochloride)

and group D (vaginal delivery /no anesthesia) ( $p = 0.007$ ,  $p = 0.001$  and  $p < 0.001$ , respectively). Gestational age was lower in the C/S groups (group A and B) than those of the vaginal delivery groups (group C and D), but the difference was not significant statistically ( $38.8 \pm 1.1$  and  $39.2 \pm 1.3$  weeks respectively,  $p=0.65$ ). There was no difference between group A and group B in C/S groups in terms of gestational age ( $p=0.86$ ). Likewise, a significant difference was not observed between group C and group D in vaginal delivery groups for gestational age ( $p=0.77$ ). Demographic data is given in table 1.

The serum levels of bilirubin in the C/S groups ( $6.2 \pm 1.6$  mg/dl) were significantly higher than those of the vaginal delivery groups ( $5.4 \pm 0.9$  mg/dL) ( $p < 0.001$ ).

There was no difference between (group A and group B in terms of neonatal bilirubin levels in the first 24 hours of their life ( $p=0.98$ ). The serum levels of bilirubin in each group are given in table 2. Depending on the use of local anesthesia, there was no significant difference between the groups C and D, who had vaginal delivery, in terms of the neonatal bilirubin levels ( $p=0.99$ ).

The correlation between the characteristics showing significant differences among the groups and the neonatal bilirubin levels were evaluated. The serum levels of bilirubin declined with increasing gestational age, but the negative correlation was not statistically significant ( $r = -0.06$ ,  $p = 0.12$ ). There was a positive correlation between maternal age and bilirubin levels. However, this correlation was neither statistically significant ( $r = 0.07$ ,  $p = 0.08$ ).

### Discussion:

To our knowledge, this is the first study to question the effect of local anesthesia on neonatal jaundice. No difference was observed in terms of bilirubin levels between neonates born by vaginal delivery with local anesthesia for episiotomy and those without anesthesia. Total bilirubin levels in the first 24 hours for C/S groups were significantly higher than vaginal delivery groups. However, neonatal bilirubin levels did not differ among groups

receiving anesthesia with sevoflurane and bupivacaine hydrochloride.

Phuapradit et al. have shown the absence of a correlation between C/S and neonatal hyperbilirubinemia by (11). Recently, Alkan et al have emphasized that the route of delivery had no effect on neonatal transcutaneous bilirubin levels during the first 24 hours of life (8). However, Gale et al. reported a significant correlation between C/S and increased bilirubin levels (12). Their study has revealed that preterm labor, vacuum, forceps, low birth weight, maternal age increased neonatal bilirubin levels similarly, and the present study has demonstrated that C/S increased neonatal bilirubin levels in the first 24 hours of life.

Prilocaine hydrochloride, as a local anesthetic, is one of the agent's causative of methemoglobinemia especially during the first 3 months of life (9, 10). Infants younger than 3 months of age are particularly vulnerable to hemoglobin oxidation, as cytochrome b5 reductase levels is nearly the half of adult levels (9, 10, 13). However, it has been determined in this study that prilocaine hydrochloride as a local anesthetic had no effect on neonatal bilirubin levels. The absence of effect may be due to the maternal administration of a low dose of drug. Clark and Landaw reported neonatal jaundice associated with maternal anesthesia, especially bupivacaine hydrochloride that might be possibly explained by observations that local anesthetic agents (lidocaine, mepivacaine) cross the placenta, bind to red cell membrane and reduce its filterability, resulting in shortened red cell survival (14). The present study revealed that neonatal bilirubin levels increased in association with spinal anesthesia with bupivacaine hydrochloride.

Alkan et al. mentioned that transcutaneous bilirubin levels in sevoflurane group were significantly higher than bupivacaine hydrochloride group (8). However, Ozçakır et al. founded out that different anesthesiology strategies including sevoflurane, or bupivacaine hydrochloride had no effect on neonatal jaundice (5). Demiraran et al. reported that there was no difference on total bilirubin levels between

sevoflurane and bupivacaine hydrochloride on the first day postpartum (6). Our findings support the latter two studies. Sevoflurane doses were the same in both Demiraran's and our study (1-2 minimum alveolar concentration). Alkan et al. administered a lower dose of sevoflurane (up to 0.8 minimum alveolar concentrations) (8). However, the difference may be attributed to the interval of time between the delivery of a baby and induction of anesthesia.

Gale et al. showed that a high bilirubin level was significantly associated with male sex, vacuum or forceps, short gestation, lower birth weight, and older maternal age in a large population study (12). Therefore, we aimed to standardize the groups in terms of these conditions; maternal and gestational ages were different between the groups, though not statistically significant. Most of the previous studies investigated the effects of anesthesia in C/S groups (5-7). The studies including vaginal delivery for which anesthetic agents were not applied as a control group were extremely rare (8). In this study, a significant difference for sevoflurane and bupivacaine hydrochloride - but not for prilocaine hydrochloride - compared to vaginal delivery without anesthesia was observed.

It is well known that oxytocin stimulates uterine motility and increase neonatal bilirubin levels (15). We didn't question the administration of oxytocin in the study groups. Although oxytocin administration is more commonly expected in vaginal deliveries, bilirubin levels of the vaginal delivery group were lower than the C/S group. A shortcoming of this research may be that bilirubin levels were followed up in the first 24 hours, including only the predischarge levels. In other studies, a longer term follow-up, until the fifth postnatal day was accomplished, covering a wider range of time for the presence neonatal jaundice (5).

### **Conclusion :**

It has been shown in the present study that local anesthesia with prilocaine hydrochloride did not affect bilirubin levels in neonates born by vaginal delivery during the first postnatal day. In the first 24 hours of life, significantly higher neonatal bilirubin

levels in C/S groups were observed than vaginal delivery groups, whereas a lack of a significant difference in neonatal bilirubin levels was evident, concerning sevoflurane and bupivacaine.

**Conflicts of interest:**

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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**Table 1:** Maternal and neonatal demographic data in groups (mean± SD)

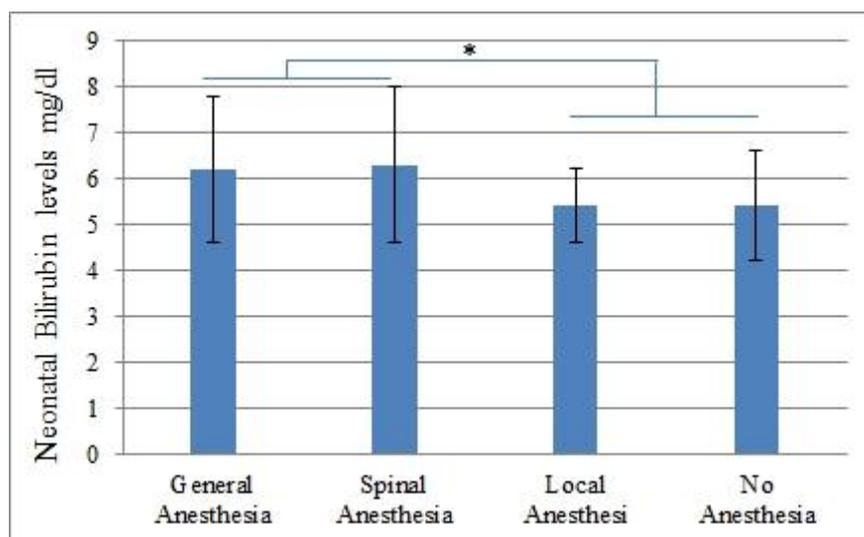
	Cesarean delivery		Vaginal Delivery	
	General Anesthesia Group A (n=140)	Spinal Anesthesia Group B (n=49)	Local Anesthesia Group C (n=238)	No Anesthesia Group D (n=84)
Maternal age (year)	28.07±4.78	29.30±5.23	26.29±5.22	29.94±5.66
Neonatal Birth weight (g)	3275±405	3251±452	3297±423	3280±418
Neonatal Sex (male/female)	71/69	26/23	129/109	47/37
Neonatal Age (week)	38.9±1.1	38.4±1.1	39.2±1.3	39.3±1.3

SD: Standard Deviation

**Table 2:** Neonatal bilirubin levels according to applied anesthetic technique in the maternal delivery groups

Bilirubin (mg/dl)	General anesthesia	Spinal anesthesia	Local anesthesia	No anesthesia	P values
Total bilirubin levels in the first 24 hours	6.2±1.6a	6.3±1.7a	5.4±0.8b	5.4±1.2b	<0.0001

Different letters indicates statistical importance between the groups. One-way Analysis of Variance (ANOVA) was applied to results. SD: Standard Deviation, P <0.0001

**Figure 1:** Neonatal bilirubin levels (mg/dl) according to applied anesthetic technique in the maternal delivery groups. One-way Analysis of Variance (ANOVA) was applied to results. Mean±SD, \* P <0.0001

## References:

1. Chowdhury AD, Hussey MH, Shortland DB. Critical overview of the management of neonatal jaundice in the UK . *Public Health* . 2007 Feb ;121 (2):137–43.
2. Amin SB, Lamola AA. Newborn jaundice technologies: unbound bilirubin and bilirubin binding capacity in neonates. *Semin Perinatol*. 2011 Jun;35(3):134-40.
3. Petrova A, Mehta R, Birchwood G, Ostfeld B, Hegyi T. Management of neonatal hyperbilirubinemia: pediatricians' practices and educational needs. *BMC Pediatr*. 2006; 6:6.
4. Kemper K, Forsyth B, McCarthy P Jaundice, terminating breast-feeding, and the vulnerable child. *Pediatrics*. 1989; 84(5): 773–8.
5. Ozcakır HT, Lacin S, Baytur Y, Luleci N, Inceboz U. Different anesthesiologic strategies have no effect on neonatal jaundice. *Arch Gynecol Obstet* 2004; 270: 179–81.
6. Demiraran Y, Albayrak M, Seker IS, Kaynak G, Iskender A, Sezen GY, Ozdemir I. Effect of anesthesiological strategies on neonatal bilirubin levels during cesarean section: a prospective and randomized trial. *Arch Gynecol Obstet* . 2011; 284:1059–65.
7. De Amici D, Delmonte P, Martinotti L, Gasparoni A, Zizi S, Ramajoli I, et al. Can anesthesiologic strategies for caesarean section influence newborn jaundice? A retrospective and prospective study. *Biol Neonate*. 2001; 79: 97–102.
8. Alkan S, Tiras U, Dallar Y, Sunay D. Effect of anaesthetic agents administered to the mothers on transcutaneous bilirubin levels in the neonates. *Acta Pædiatrica*. 2010; 99: 993–6.
9. Rehman HU. Methemoglobinemia. *West J Med*. 2001 Sep; 175(3):193-6.
10. Ozdogan H, Osma S, Aydin GB, Dinc A, Ozgun G. Methemoglobinemia presenting in a circumcised baby following application of prilocaine: a case report. *J Med Case Rep*. 2010; 4:49.
11. Phuapradit W, Chaturachinda K, Auntlamai S. Risk factors for-neonatal hyperbilirubinemia. *J Med Assoc Thai* .1993; 76: 424–8.
12. Gale R, Seidman DS, Dolberg S. Epidemiology of neonatal jaundice in the Jerusalem population. *J Pediatr Gastroenterol Nutr* .1990; 10: 82–6.
13. Clark DA, Landaw SA. Bupivacaine alters red blood cell properties: a possible explanation for neonatal jaundice associated with maternal anesthesia. *Pediatr Res*. 1985;19:341–3
14. Meisel P, Meisel M. Do drugs in pregnancy modify neonatal jaundice?. *Zentralbl Gynakol*. 1993; 115(7):301-8.