



Original Article

Do postpartum nonsteroidal antiinflammatory drugs (NSAIDs) affect neonatal hyperbilirubinaemia?

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ABSTRACT

Objective: There has been no previous study on the interaction between neonatal hyperbilirubinemia and NSAID use in breastfeeding mothers. This study aimed to investigate whether postpartum analgesics (with NSAIDs) can affect neonatal hyperbilirubinaemia.**Materials and methods:** Mothers who gave birth between January 2017 and December 2017 were included. Those who were not exclusively breastfeeding, gave premature birth, who underwent caesarean section, or whose infants had abnormalities such as an imperforated anus, diaphragmatic hernia, or ovarian tumour were excluded. Mothers were divided into 2 groups based on the analgesics received postpartum: acetaminophen and NSAID (non-steroidal anti-inflammatory drug; flurbiprofen) users. Multivariable logistic regression was adopted to estimate the risk of hyperbilirubinaemia with the use of different kinds of painkillers.**Results:** In total, 1153 mothers were reviewed. After applying the exclusion criteria, 480 mothers were finally included in the analyses. Among them, 348 (72.67%) and 132 (27.33%) mothers received acetaminophen and flurbiprofen, respectively. Seven (2.01%) and 1 (0.76%) newborn had hyperbilirubinaemia among the acetaminophen and flurbiprofen users, respectively. Hyperbilirubinaemia risk of infants whose mothers were flurbiprofen users was not significantly different from that of infants whose mothers were acetaminophen users (adjusted odd ratio = 0.50, 95% confidence interval = 0.06–4.50, p-value = 0.4552).**Conclusions:** Breastfeeding mothers receiving flurbiprofen do not have increased risk of neonatal hyperbilirubinaemia.© 2020 Taiwan Association of Obstetrics & Gynecology. Publishing services by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Introduction

Almost all newborns experience a total serum bilirubin (TSB) level higher than 1 mg/dL, which results in neonatal jaundice with accompanying clinical signs, such as yellow discolouration of the skin and sclera [1]. Neonatal jaundice is a natural phenomenon that usually resolves within the first week of life due to liver maturation. However, neonatal hyperbilirubinaemia remains the main reason for readmission during the neonatal period for most infants [2]. Neonatal hyperbilirubinaemia is defined as TSB >95th percentile

for age in hours (as [Supplementary data](#)) in term newborns, which requires follow-up and treatment. Infants with hyperbilirubinaemia had a higher risk of developing severe hyperbilirubinaemia that could progress to bilirubin-induced neurologic dysfunction (BIND) [3,4], occurring when bilirubin crosses the blood–brain barrier, thereby inducing cerebral palsy, hearing loss, and kernicterus and may be causing long-term sequelae [5]. Although neonatal hyperbilirubinaemia is a common occurrence, it is of interest because of its extreme consequences and it can also be a source of considerable potential concern. Clinicians should be aware of the several independent risk factors for hyperbilirubinaemia, and neonates with more than one risk factor need to be closely monitored [6]. Early detection of infants with high risk of developing severe hyperbilirubinaemia is a key point in reducing

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the burden of this potentially devastating condition within the first 14 days of life [7]. Several independent risk factors for severe hyperbilirubinaemia and BIND were identified in the 2004 American Academy of Pediatrics (AAP) Practice Guideline, which include pre-discharge total serum bilirubin of more than the 95th percentile for age in hours, jaundice within the first 24 h of life, exclusive breastfeeding, haemolytic disease, cephalohematoma caused by instrumental delivery, and east Asian ethnicity [8].

Most non-steroidal anti-inflammatory drugs (NSAIDs) have demonstrated their effectiveness for postpartum pain caused by episiotomy, other perineal traumas, caesarean delivery, or uterine contractions and are widely used during the postpartum period [9]. However, the American Academy of Pediatrics had also mentioned that many NSAIDs will displace bilirubin; hence, they may be contraindicated when nursing a neonate with jaundice [10]. Several previous studies have investigated whether the use of NSAIDs (ibuprofen) for closing the ductus arteriosus in premature newborns displaces bilirubin from albumin or not. However, the results were controversial [11,12]. Moreover, there has been no previous study on the interaction between neonatal hyperbilirubinaemia and NSAID use in breastfeeding mothers. Thus, this study aimed to investigate whether postpartum analgesics can affect neonatal hyperbilirubinaemia.

Materials and methods

Study population

Mothers who gave birth in the Tri-Service General Hospital between January 2017 and December 2017 were included in our study population. Those who were not exclusively breastfeeding,

who had a preterm delivery, who had undergone a caesarean section, and whose infants had abnormalities such as an imperforated anus, diaphragmatic hernia, or ovarian tumour were excluded (Fig. 1). The study was approved by the institutional review board (IRB) of Tri-Service General Hospital, National Defense Center, Taipei, Taiwan (TSGHIRB no. 1-107-05-176). The patient data was de-identified prior to data collection and was collected from the medical records. Therefore, the need for informed consent was waived by the ethic committee.

Study design

Through a medical record review, we documented the baseline characteristics of the mothers and their newborns (Table 1). Mothers were divided into 2 groups based on the type of painkiller received postpartum: acetaminophen users and NSAID (flurbiprofen) users.

The infants' serum total bilirubin concentration was checked within 48 h obtained post-delivery via capillary blood sampling through heel stick puncture and measurement using nonchemical photometric devices. The serum total bilirubin of flurbiprofen group infants was obtained as maternal medicine intake as least 3 dosage of flurbiprofen and 24 h apart of acetaminophen. Infants whose serum total bilirubin concentration >95th percentile for age in hours were considered to have hyperbilirubinaemia.

Statistical analyses

Multivariable logistic regression was adopted to estimate the risk of developing hyperbilirubinaemia with the use of different kinds of painkillers.

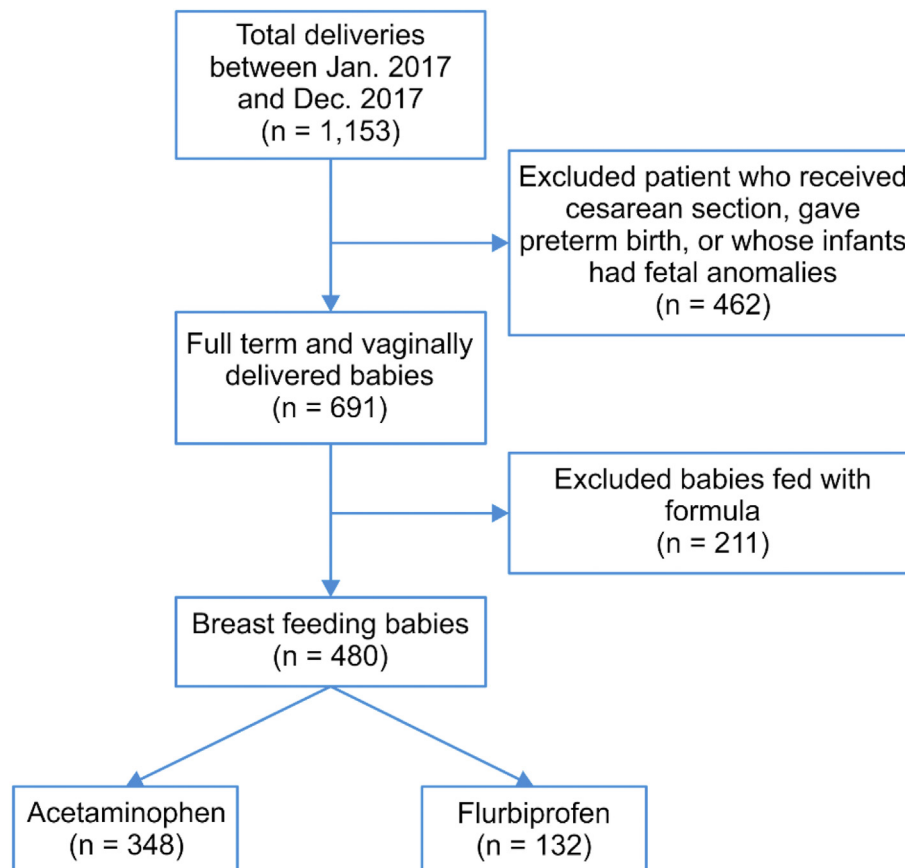


Fig. 1. Flow diagram showing selection of babies for the study.

Table 1
Perinatal characteristics of the study population.

	Acetaminophen (N = 348)	Flurbiprofen (N = 132)	p-value
<i>Intrapartum and maternal characteristics</i>			
Age (Means, SD)	31.97 (4.87)	32.05 (4.53)	0.8902
BMI	25.78 (3.52)	25.27 (3.62)	0.1598
Parity			0.0012
0 previous live birth	170	90	
≥1 previous live births	178	42	
Hypertension	6	4	0.5192
Pre-eclampsia	1	1	0.5192
GDM	28	12	0.6923
Instrumental delivery	30	11	0.9401
<i>Infant characteristic</i>			
Gestational age (week)	39.24 (0.99)	39.26 (0.98)	0.8902
Gender			0.3560
Male	191	66	
Female	157	66	
Birthweight(g)	3110 (319.7)	3093 (301.8)	0.5875

BMI: body mass index, GDM: gestational diabetes mellitus.

Results

A total of 1153 mothers gave birth in our hospital during the study period. After applying the exclusion criteria, 480 mothers were included in our final analyses. Among them, 348 (72.67%) and 132 (27.33%) mothers received acetaminophen and flurbiprofen as their painkillers, respectively. Seven (2.01%) newborns had hyperbilirubinaemia among the acetaminophen users, whereas there was only 1 (0.76%) newborn with hyperbilirubinaemia among the flurbiprofen users (Table 2). The risk of developing hyperbilirubinaemia in infants whose mothers received the NSAID as the painkiller was not significantly different from that in infants whose mothers received acetaminophen (adjusted odd ratio = 0.50, 95% confidence interval = 0.06–4.50, p-value = 0.4552).

Discussion

Our study demonstrated that the risk for severe hyperbilirubinemia was not significantly different between breastfeeding mothers receiving flurbiprofen and those receiving acetaminophen (adjusted odd ratio = 0.50, 95% confidence interval = 0.056–4.498, p-value = 0.4552). If the infants with serum total bilirubin level of more than the 75th percentile are included in calculation, 57 (16.24%) newborns will be included among the acetaminophen users, whereas, 8 (6.06%) newborns will be included among the flurbiprofen users (Table 2). The risk of developing hyperbilirubinemia among infants whose mothers received the NSAID as the painkiller was even significantly lower than that of those whose mothers received acetaminophen (adjusted odd ratio = 0.33, 95% confidence interval = 0.15–0.72, p-value = 0.0062). The results demonstrate that the NSAID (flurbiprofen) did not displace bilirubin.

Bilirubin is a product of haeme catabolism that is transported to the liver by attaching to albumin. Bilirubin detaches from the albumin and is then absorbed by hepatocytes, where it is processed for excretion. Uridine diphosphoglucuronate glucuronosyltransferase 1A1(UGT1A1) breaks down the conjugation of bilirubin with

hepatocytes. The activity of UGT in term infants is approximately 1% of that in the adult liver at seven days of age and reaches adult levels at 14 weeks of age. Owing to the reduced activity of UGT1A1 in term infants, bilirubin clearance is usually decreased in newborns [13,14].

The NSAID families are acidic and have low lipid solubility, which are features that reduce their transfer into breastmilk, which is also acidic compared to plasma; thus, milk to plasma ratios of NSAIDs are generally <1 [15]. However, such ratios cannot give information about the exposure of the infant to drugs that are transferred into breastmilk. If the estimated absolute infant dose of a drug from breastmilk is established (by measurement of breastmilk concentration and estimation of the volume of milk ingested), the relative infant dose expressed as a percentage of the maternal dose can be calculated. Flurbiprofen is the drug used in our hospital during the postpartum period, which has been well evaluated and is known to transfer into breastmilk at <0.1% of the maternal dose [16]. NSAIDs are also known as high protein binding (>90%) drugs. High protein binding and restricted gastrointestinal tract absorption reduce systemic infant exposure to the drug from the ingested breastmilk. Other considerations that may affect infant exposure to a drug include the drug's duration of administration, its pharmacokinetics, the changes in breastmilk composition and volume that occur in the first few days of lactation, and the neonatal oral bioavailability. If the relative infant dose of a drug is <10% and without significant toxic effects, the drug is considered unlikely to be harmful to a breastfed infant, in spite of the immaturity of the neonatal metabolic pathways [16].

NSAIDs, as well as bilirubin, are well known to have a relatively high human serum albumin binding affinity, which improves their solubility and increases the half-life of NSAIDs [17]. Previous crystal structure analyses have demonstrated that there are two main drug-binding sites on HSA, which are located in subdomains IIA and IIIA [18] and named as sites I and II [19]. The drug binding was site-specific and drugs bound to site I did not interfere with other drugs or compounds bound to site II [17,20]. Different interaction reactions may occur between drugs and HSA, such as independent binding, co-operative binding, anti co-operative binding, and competitive binding. The competitive interaction between two drugs to one binding site on HSA may remarkably displace the distribution of both drugs [20]. Bilirubin is confirmed to be a strong site I binding compound. On the other hand, NSAID families can be divided into two groups according to their binding sites: NSAIDs with hydrophobic structures are classified as site I binding drugs (e.g. iodipamide) and NSAIDs with aromatic carboxylic acid as site II binding drugs (e.g. ibuprofen, flurbiprofen) [21,22]. Therefore, flurbiprofen will not compete with bilirubin in albumin binding.

NSAIDs may also interfere with bilirubin catalysis. As mentioned earlier, bilirubin is cleared by UGT1A1 and decreased in newborns. The families of UGT1A1 play an important role in NSAID elimination. However, flurbiprofen is catalysed mainly by UGT2B7 but not by UGT1A1 [23], which may explain the less competitive interaction in catalysis between flurbiprofen and bilirubin.

The main strength of this study is that we exclude the mothers who received caesarean section because the anaesthetic drugs are also catalysed by the liver enzymes and the need for more postpartum analgesics may have interfered with the serum bilirubin.

Table 2
Incidence and adjusted odds ratios of neonatal hyperbilirubinaemia.

	Total, n = 480	Bilirubin > 95%	aOR (95% CI)	p-value	Bilirubin > 75%	aOR (95% CI)	p-value
Drug		n (%)			n (%)		
Acetaminophen	348	7 (2.01)	1		57 (16.37)	1	
Flurbiprofen	132	1 (0.76)	0.501 (0.06–4.50)	0.4552	8 (6.06)	0.333 (0.15–0.73)	0.0062

Moreover, the neonatal serum bilirubin was routinely collected within the same period after birth and with the same method. Therefore, total serum bilirubin of neonates was relatively objective. However, there are several limitations in this study. First, the postpartum mothers were routinely administered acetaminophen initially and then shifted to flurbiprofen if there was no pain relief. Second, the period of postpartum analgesic use was usually short. Third, the breastfeeding mothers may lack adequate breastfeeding skills, which may have resulted in suboptimal breastmilk intake of infants; these were missed out from our medical record review. Hence, we were not able to adjust this variable. Further studies are warranted to confirm our results.

Conclusion

Flurbiprofen use in breastfeeding mothers does not increase the risk of neonatal hyperbilirubinemia in infants compared to acetaminophen use.

Declarations of competing interest

The authors declare that there is no financial and conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.tjog.2020.09.015>.

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