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Retrospective analysis on transient tachypnea of the newborn: is it associated with spinal anesthesia after cesarean section?

Yenidoğan geçici takipnesinin retrospektif analizi: sezaryende spinal anestezi ile ilişkili midir?

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Abstract
We investigated whether maternal gestation, newborn gender, delivery times and cord blood gas and pH might play a role in the increased risk of transient tachypnea of the newborn (TTN) after cesarean section (C/S). Data from 114 term parturients scheduled for elective C/S under spinal anesthesia were retrospectively analyzed according to having a newborn with TTN or not. Presence of TTN, neonatal Apgar scores, umbilical artery (UA) and umbilical venous (UV) blood gas analysis and pH, total amount of fluid and ephedrine administered, time intervals related to delivery were documented. TTN was observed in 15 out of 114 cases (13.2%). No significant differences were observed in gestation age, Apgar scores, newborn gender, amount of ephedrine and fluid administered between newborns with or without TTN. Mean UA PO_2 tensions of TTNs were significantly lower than in newborns without TTN (p=0.043). Time interval from spinal block to skin incision was significantly longer in newborns with TTN than without TTN (p=0.046). In conclusion, TTN might be associated with spinal anesthesia for C/S. Therefore, reducing the time interval from spinal block to onset of surgery might be one of the important factors to decrease the incidence of TTN after elective C/S under spinal anesthesia.
Keywords: Cesarean section; spinal anesthesia; transient tachypnea of the newborn (TTN)

Özet
Sezaryenden sonra görülen yenidoğan geçici takipnesi (YGT) riskindeki artışta gebelik haftası, yenidoğan cinsiyeti, doğum süreleri ve kord kan gazı ve pH'nın rolünü gözden geçirdik. Spinal anestezi altında elektif sezaryen uygulanan 114 term gebe, YGT'li yenidoğanı olanlar ya da olmayanlar olarak retrospektif incelendi. YGT bulunması, neonatal Apgar skorları, umbilikal arter (UA) ve umbilikal ven (UV) kan gazı incelemesi ve pH, uygulanan toplam sıvı ve efedrin miktarları, doğum ile ilişkili süreler incelendi. YGT, 114 olgunun 15'inde tespit edildi (%13,2). Gebelik haftası, Apgar skorları, yenidoğan cinsiyeti, efedrin ve sıvı uygulama miktarları bakımından YGT olan ve olmayan yenidoğanlar arasında anlamlı fark yoktu. YGT bulunanlarda ortalama UA PO_2 düzeyleri YGT bulunmayanlardan anlamlı derecede düşüktü (p=0.043). Spinal blok ile cilt insizyonu arasındaki süre, YGT bulunanlarda YGT bulunmayanlara göre daha uzundu (p=0.046). Sonuç olarak, YGT sezaryende uygulanan spinal anestezi ile ilişkili olabilir. Bu nedenle, spinal blok ile cerrahiye başlama arasındaki süreyi azaltmak, spinal anestezi altındaki elektif sezaryenlerden sonra görülen YGT insidansını azaltmadaki önemli faktörlerden biri olabilir.
Anahtar kelimeler: Sezaryen; spinal anestezi; yenidoğan geçici takipnesi (YGT)

Introduction

Transient tachypnea of the newborn (TTN) is a self-limiting parenchymal lung disorder characterized by pulmonary edema (1). The underlying mechanism is generally explained by the delayed resorption of the lung fluid (2). Some other pathophysiological factors in the etiology of TTN include mild degree of pulmonary immaturity in the expression of epithelial sodium channel, absence of the effects of catecholamines and steroids, genetic variations of beta adrenergic receptor encoding genes can lead to retention of fluid in air spaces, slight and transient surfactant deficiency or myocardial left-heart failure due to asphyxia, resulting in pulmonary interstitial edema (2,3). In addition to these perinatal factors, several potential risk factors like negative amniotic fluid phosphatidylglycerol, Apgar score <7 and male gender have been reported for TTN (4). However, clinical factors that might be related to cesarean section (C/S) during spinal anesthesia have not been thoroughly investigated yet. Therefore, the aim of this study is to elucidate retrospectively whether TTN might be associated with any of the factors including maternal gestation, newborn gender, delivery times, Apgar scores and umbilical cord blood gas analysis and pH measurements after C/S under spinal anesthesia.

Material and methods

After approval of IRB, clinical data from newborns and ASA I or II parturients with singleton vertex pregnancy underwent elective C/S under spinal anesthesia in a recent 6-month period were retrospectively analyzed. Data from non-elective cases, parturients with weight greater than 100 kg and height less than 150 cm and

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taller than 180 cm, multiple gestations and high risk pregnancies were not included.

The diagnosis of TTN was established by pediatricians based on the criteria described (1). Onset of tachypnea (respiratory rate exceeding 60/min) within 6 hours after birth, persistence of tachypnea at least 12 hours, at least one of the chest radiography findings (prominent central vascular markings, widened interlobar fissures of pleural fluid, symmetrical perihilar congestion, hyperaeration), and exclusion of either known respiratory (meconium aspiration, respiratory distress syndrome, pneumonitis, congenital cardiac diseases) or non-respiratory disorders (hypocalcemia, persistent hypoglycemia, polycythemia).

Primarily, incidence of TTN was determined. Then, demographic properties of the parturients (age, weight, height, gravidity, parity and gestation age) and newborns (weight and gender), Apgar scores at 1 and 5 minutes, results of umbilical artery and venous (UA and UV) blood gas analysis (PO_2 and PCO_2) and pH measurements were recorded. The time intervals from spinal block (onset of anesthesia) to skin incision (onset of surgery), and from skin incision to uterine incision and umbilical cord clamping (delivery of the newborn) were documented in the parturients assigned to two groups as newborn with (TTN group) or without TTN (non-TTN group) for statistical comparison.

All parturients underwent elective C/S under spinal anesthesia who were enrolled in this retrospective study had a standard anesthesia and surgical care. According to the records, after overnight fasting all parturients received preload of Ringer's lactate (RL) solution intravenously through a 16 G cannula within a 15 min period before spinal block. All women received aspiration prophylaxis with intravenous (iv) ranitidine 50 mg and metoclopramide 10 mg half an hour before the operation. Routine monitorization included heart rate, ECG, mean arterial pressure (MAP) and peripheral oxygen saturation. Spinal anesthesia was performed with a 25 G pencil point spinal needle using hyperbaric bupivacaine 12 mg + morphine 100 µg + fentanyl 10 µg in the sitting position by midline approach. Aortocaval decompression was provided by tilting the operating table to 15º left in all patients to avoid supine hypotension. Hypotension which had been defined by more than 20% decrease from baseline MAP was treated with 10 mg of iv bolus ephedrine. After delivery of the newborn, parturients received iv infusion of synthetic oxytocin 20 IU in 1000 ml RL solution. Apgar scores at 1 and 5 min that was used to assess neonatal outcome by pediatricians were noted. The surgical technique was uniform including exteriorization of the uterus for all parturients.

The diagnosis of TTN was made by neonatologists during fraction of inspired oxygen >0.21.

Statistical analysis

Results were expressed as mean±standard deviation (SD), range or n where appropriate. Mann Whitney-U test followed by post hoc LSD was used to elucidate difference in all parameters except newborn gender and frequency of TTN. Newborn gender and the frequency of TTN were compared by Chi-square test. A p value less than 0.05 was considered as statistically significant.

Results

Fifteen out of 114 (13.2%) newborns suffering from TTN were admitted to neonatal intensive care unit and they were not discharged until they recovered. Regarding the delivery times, mean time interval from spinal block to skin incision in the TTN group was significantly longer than that of the non-TTN group (p= 0.046), while the time intervals from skin incision to uterus incision and umbilical cord clamping were comparable (p>0.05).

The results of the UA and UV blood gas analysis except UA PO_2 did not differ significantly between the groups. Mean UA PO_2 tension of the TTN group was significantly lower than that of the non-TTN group (p=0.043) (Table 1).

Table 1. Demographics and clinical data according to TTN versus non-TTN groups.

	TTN Group (n=15)	Non-TTN Group (n=99)	P value
Maternal age (year)	30.9±6.5	30.1±5.0	0.096
Maternal weight (kg)	77.9±9.6	76.5±9.6	0.687
Maternal height (cm)	165.3±3.9	163.5±4.0	0.555
Gestation (week)	38.38±0.93 (37.0-41.0)	38.63±0.77 (37.4-42.3)	0.145
Amount of fluid infused (ml)	1240±335.5	1199±324.8	0.817
Amount of ephedrine used (mg)	48.33±15.03	45.06±12.82	0.287
Time interval from spinal block to skin incision (min)	10.73±2.89	9.24±2.98	0.046
Time interval from skin incision to uterus incision (min)	2.87±1.50	2.64±1.24	0.526
Time interval from skin incision to umbilical cord clamping (min)	4.40±2.06	3.93±1.50	0.500
UA pH	7.35±0.076	7.35±0.056	0.377
UA PO_2 (mmHg)	23.26±4.90	28.21±8.33	0.043
UA PCO_2 (mmHg)	45.90±10.14	46.44±8.21	0.637
UV pH	7.40±0.054	7.38±0.049	0.082
UV PO_2 (mmHg)	35.32±4.51	37.06±8.51	0.363
UV PCO_2 (mmHg)	37.87±5.22	39.39±7.11	0.375
Apgar score at 1 min	8.7±0.5 (8-9)	8.9±0.4 (7-10)	0.157
Apgar score at 5 min	9.9±0.4 (9-10)	9.9±0.3 (9-10)	0.204
Newborn gender (Male/Female) (n)	5/10	50/45	0.165

TTN: Transient tachypnea of the newborn. All data except newborn gender were expressed as mean ± standard deviation (SD) and compared with Mann Whitney-U test. Newborn gender was presented as n and chi square test was used for statistical comparison of the groups. Additionally, range and median were also given in brackets for gestation and Apgar scores (at 1 and 5 min), respectively.

However, there were no significant differences in the newborn gender and maternal gestation, amount of RL infused to parturients before spinal anesthesia to prevent spinal anesthesia associated hypotension and ephedrine

administered to treat hypotension between the groups (Table 1). Additionally, the mean pH measurements in UA and UV samples and Apgar scores at 1 and 5 minutes were comparable when the TTN and the non-TTN groups were compared ($p>0.05$) (Table 1).

Discussion

In the present study, we have demonstrated that mean time interval from spinal block to skin incision was significantly longer and UA PO_2 tension was significantly lower in the TTN group versus non-TTN group after elective C/S under spinal anesthesia. These findings could be explained by either cesarean delivery related factors or some of the standard treatments and approaches used for parturients scheduled to undergo elective C/S under spinal anesthesia. Since demographic and clinical factors including maternal gestation age, amount of fluid and ephedrine administered to the parturients, newborn gender, Apgar scores and umbilical cord pH measurements were comparable between the groups, they might not seem to contribute to the increased risk of TTN after elective C/S under spinal anesthesia. But as far as longer time interval from spinal block to skin incision and lower UA PO_2 levels were concerned, the increased risk of TTN could be associated with these factors.

Transient tachypnea of the newborn is a clinical syndrome associated with respiratory distress that develops shortly after birth but resolves within 2 to 5 days (1). In a review of 33289 term deliveries between 37 to 42 weeks' gestation, the prevalence of TTN was 5.7 per 1000 births (5). In another case-control study of 110 neonates with TTN versus 110 newborn controls, the frequency of TTN was 2% (6). However, 15 out of 114 (13.2%) newborns suffered from TTN in the present study which was surprisingly higher than the documented data in the above mentioned studies.

Several clinical factors might be associated with the increased risk of TTN after C/S. Transient tachypnea of the newborn has been reported to occur more frequently in preterm births and male infants (1,4). It has been suggested that negative amniotic fluid phosphatidylglyserol, prematurity (<38 weeks) and Apgar score (at 1-minute) less than 7 made an independent contribution to the overall characterization of infants at increased risk for TTN (4). Additionally, TTN has been observed in infants born after cesarean delivery without labor because of the inadequate mechanism to reabsorb lung fluid (1). When infants are delivered near-term (births at ≥34 and <37 weeks), especially by C/S (repeat or primary) before the onset of spontaneous labor, the fetus is often deprived of the hormonal changes, making the neonatal transition more difficult (4). In the present study, the gestation age of all the parturients were between 37 to 42 weeks and the mean gestation week did not differ between TTN and non-TTN groups. Since both groups included term parturients and they were comparable with respect to newborn gender and Apgar scores, it seems that none of these factors might contribute to the increased of TTN, but cesarean delivery without labor could have the greater risk.

Spinal anesthesia provides a fast and profound, sympathetic, sensory and motor block in parturients undergoing C/S, but severe hypotension due to spinal anesthesia can cause serious risks to both mother and baby if untreated (7,8). Therefore, prophylactic measures to prevent or minimize that complication are of interest, because concomitant reduction in the uteroplacental blood supply associated with maternal hypotension has deleterious effects such as fetal acidosis (7). One of the conventional strategies to prevent hypotension is the infusion of fluid which is called as maternal preloading (7). Another strategy is to use ephedrine which is a non-specific adrenergic agonist that increases blood pressure mainly by increasing cardiac output (8). Regarding these strategies, prophylactic iv fluid administration prior to spinal anesthesia for C/S is still an accepted standard practice in our institution. When we compared the amount of RL infused before spinal anesthesia to prevent hypotension, we found that it was not significantly different between TTN and non-TTN groups. Moreover, therapeutic use instead of prophylactic administration of ephedrine was preferred and we have not found any significant difference in the amount of ephedrine when groups were compared. Although ephedrine that crosses the placenta might have resulted in increased fetal catecholamine concentrations correlated with decreasing pH in previous studies (8,9), no significant differences were recorded in the pH measurements between the groups in the current study. The reason for obtaining better pH results might be due to the less need for ephedrine in both groups.

The Apgar score quantifies a newborn's medical condition at birth and is also an indirect measure of fetal well-being (10). In a study examining infants delivered vaginally at 37 weeks or later, TTN has been reported in newborns with low Apgar score at 1 min (11). Although it was suggested to be the greatest risk factor for TTN in that study, the mean Apgar scores at 1 and 5 minutes were comparable and the median Apgar score at 1 min was not less than 7 in both groups in our study. The lowest values were 7 and 8 for TTN and non-TTN groups, respectively.

The determination of umbilical cord blood gas analysis is another indicator of perinatal asphyxia and TTN. Umbilical cord blood gas and pH analysis should be used in neonates with low Apgar scores to distinguish metabolic acidosis from hypoxia or other causes that might result in low Apgar scores. Recent reviews have determined the mean value of umbilical arterial blood pH to be greater than 7.25 for normal term newborns. Classically, a cord arterial pH cut-off value of less than 7.20 has been used for defining pathologic fetal acidemia (12). In our study, there were no significant differences in the UA and UV pH measurements between the groups and they were not less than 7.25. We have only determined a slightly significant reduction in the mean UA PO_2 tension of the TTN group with respect to the non-TTN group. That finding seemed to be well

correlated with the slightly significant longer time interval between onset of spinal anesthesia and surgery noted in the TTN group. Studies investigating the time intervals related to delivery during elective or emergency C/S under different types of anesthesia techniques were mostly focused on the fetal oxygenation (13-16). However, TTN was not documented in none of these studies. In this regard, our study has been the first to suggest that TTN was associated with significantly longer time interval from spinal block to skin incision. That higher incidence of TTN might have resulted from longer exposure of fetus to hypotension episodes.

According to a meta-analysis that compares different anesthesia modes on fetal/neonatal outcome, cord pH was found to be significantly lower with spinal than with both general and epidural anesthesia (16). Although all parturients received spinal anesthesia in the present study, cord pH measurements were not only within normal clinical range but also similar between the groups. On the contrary to the previously mentioned studies, these factors did not play a role in the occurrence of TTN in infants delivered by C/S under spinal anesthesia since neither Apgar scores at 1 min nor cord pH measurements were not significantly different between the groups.

The limitation of the present study might be the evaluation of only elective cesarean deliveries retrospectively within a very short period of time. Since recognition of recently increased frequency of TTN in our institution stimulated us to look over all the parameters related to anesthesia and/or surgery, we tried to find out anesthesia and/or surgery dependent direct or indirect contributing factors. But we could have had the chance of documenting only a casual relationship between TTN and other variables from such a retrospective analysis. Therefore, further prospective studies comparing regional and general anesthesia techniques can be designed to elucidate factors that contribute to the development of TTN which delays discharge of baby, so does the mother.

In conclusion, TTN might be associated with spinal anesthesia for elective cesarean delivery. Also, the longer time interval from spinal block to skin incision and the lower UA PO_2 might affect the risk of TTN. As a matter of fact, reducing the time interval from spinal block to onset of surgery might be one of the important measures to decrease the incidence of TTN after elective cesarean deliveries under spinal anesthesia.

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