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Labor induction by transcervical balloon catheter and cerebral palsy associated with umbilical cord prolapse

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Running foot: Transcervical balloon catheter & cord prolapse

Abstract

Objective: To determine whether the use of transcervical balloon catheter (TCBC) for induction of labor (IOL) is a risk factor for cerebral palsy (CP) associated with umbilical cord prolapse (UCP-CP) in singleton pregnancies with cephalic presentation.

Study design: Among all 102 infants with CP who were determined preliminary as caused by antenatal and/or intrapartum hypoxemia by the Japan Council for Quality Health Care until April 2012, all 56 infants who met all of the following criteria were studied: cephalic singleton pregnancy, reassuring fetal status on electronic cardiotocogram at time of admission to obstetric facilities for labor pains, ruptured fetal membranes, and/or IOL, and hypoxic-ischemic encephalopathy at birth. Clinical backgrounds were compared between 6 infants with UCP-CP and the remaining 50 infants with CP not associated with UCP (non-UCP-CP).

Results: Frequencies of IOL (83% [5/6] vs. 32% [16/50], $P = 0.0236$), use of TCBC (67% [4/6] vs. 10% [5/50], $P = 0.0044$), and amniotomy (67% [4/6] vs. 24% [12/50], $P = 0.0494$) were significantly higher in the UCP-CP than the non-UCP-CP group. Only TCBC was a risk factor significantly associated with UCP-CP after logistic regression analysis, yielding odds ratio of 18.0 (95% confidence interval, 2.6 – 124; $P = 0.003$). Saline volumes of 80 – 150 mL were used for TCBC inflation in the 4 UCP-CP patients.

Conclusion: Use of TCBC was a significant risk factor for UCP-CP.

Key words: cerebral palsy, induction of labor, transcervical balloon catheter, umbilical cord prolapse

Introduction

A transcervical balloon catheter (TCBC), including Foley catheter or metreurynter, inflated with 30 mL of more of sterilized normal saline (or water) is currently used for the induction of labor (IOL) in women with unfavorable uterine cervix in Western countries as well as in Japan [1 – 9]. Pharmacological agents, such as prostaglandin E2 gel for ripening of the cervix, are not available in Japan, and the Japan Society of Obstetrics and Gynecology (JSOG) recommends use of a TCBC with a saline volume of 150 mL or less to reduce the risk of umbilical cord prolapse (UCP) [7], because there have been reports that volumes of more than 150 mL have a possible increase risk of UCP [6 – 9].

On January 1, 2009, the Japanese government launched a new medical insurance system, the Japan Obstetric Compensation System for Cerebral Palsy, to compensate for cerebral palsy (CP) derived in principle from intrapartum hypoxia and to improve perinatal care and requested the Japan Council for Quality Health Care (JCQHC) to organize this system. The detail of this system was described previously [10]. In this system, a professional committee investigates the causative factors in CP carefully in each case and publishes a brief summary of each case together with the cause of CP in a form with privacy protection on their website [11]. Researchers can gain access to a more detailed report made by the committee after being approved by the JCQHC in this system.

UCP is regarded as an indication for emergency cesarean section and accounts for 8.0% of such cases with emergency (crash) cesarean sections [12]. UCP is a risk

factor of CP [13, 14]. Accordingly, we conducted this study to determine whether the use of TCBC for the IOL is a risk factor for cerebral palsy associated with umbilical cord prolapse (UCP-CP).

Materials and Methods

This study was conducted after being approved by the Ethics Committee of Hokkaido University Hospital. We were provided access by the JCQHC to 102 detailed reports made up to April 11, 2012, in which clinical courses of 102 infants born to 102 women and results of the investigations regarding the causes of CP were recorded. In these reports, personal information regarding the date of birth, including year and month, place of birth, and maternal age, were masked for privacy protection. However, all 102 infants were born in or after January 2009, because this compensation system was instigated on January 1, 2009. In addition, the JCQHC announced in May 2012 that a total of 171 infants born in 2009 were compensated for their CP until the end of March 2012.

These 102 reports were retrospectively reviewed focusing on clinical backgrounds and causes of CP. UCP was defined as descent of the umbilical cord in advance of the presenting fetal part in the presence of fetal membrane rupture.

Forty-six of the 102 patients with CP were excluded from the present analyses (Table 1): 38 infants who exhibited already non-reassuring fetal status at admission to the facilities due to various causes; 3 twin infants; 3 infants who exhibited neither depressed respiratory nor neurological activity at birth; one with breech presentation; and one infant in whom CP was caused by anesthetic accident during cesarean section. Among the 46 infants excluded from the present analysis, there were two infants born

after the use of transcervical balloon catheter (TCBC) or umbilical cord prolapse (UCP); one infant born after UCP that was found at admission to the obstetric facility and one breech infant born after TCBC use in whom abruptio placentae caused CP (Table 1). The present analyses were performed in all the remaining 56 infants born to 56 mothers with a cephalic singleton pregnancy and confirmed fetal wellbeing at the time of admission to obstetric facilities for labor pains, ruptured fetal membranes, and/or the IOL and exhibited hypoxic-ischemic encephalopathy at birth.

CP was reported as associated with UCP in 6 of the 56 infants (Table 2). Available information on clinical backgrounds was compared between the 6 infants with CP associated with (UCP-CP) and the 50 infants with CP not associated with UCP (non-UCP-CP).

All the data are presented as the means $\pm$ SD or frequency. Fisher's exact test was used for comparison of categorical data and Student's *t* test or Mann-Whitney U-test was used to compare median values. Factors that were significantly correlated with UCP-CP were determined using univariate and multivariate logistic regression analyses performed using IBM SPSS Statistics 18.0 software (SPSS Inc., Chicago, IL). In all analyses, $P < 0.05$ was taken to indicate statistical significance. We used Wald's selection method in logistic regression analysis.

Results

Only one infant with a birth weight of less than 2000 g was included in the 56 study subjects (Table 3). Three factors, i.e., IOL, use of TCBC, and use of amniotomy, were significantly associated with UCP-CP. The frequencies of these three factors were significantly higher in the UCP-CP group than the non-UCP-CP group (Table 3).

Therefore, we used these 3 factors in multivariate regression analyses. After selection of essential parameters, IOL and use of amniotomy were considered confounding factors. Then, only the use of TCBC was extracted as a risk factor significantly associated the UCP-CP after logistic regression analysis (odds ratio, 18.0; 95% confidence interval, 2.6 – 124; $P = 0.003$).

Volumes of 80 – 150 mL of saline were used for inflation of the TCBC in the 4 women with UCP-CP infants (Table 4). Only one infant was born within 30 min after recognition of UCP among the 6 infants with UCP-CP. Volumes of 40 – 160 mL of saline were used in the remaining 5 TCBC cases (40 mL, 80 mL, 100 mL, 120 mL, and 160 mL for one patient each) in the non-UCP-CP group.

Discussion

The present study suggested that the use of TCBC was a significant risk factor for UCP-CP. Although this suggests that the use of TCBC increases the risk of UCP, to our knowledge, there have been no previous reports of a statistically significant increased risk of UCP among users of TCBC with saline volume less than 150 mL to date, which may be due to the low frequency of UCP.

Several reports have raised concerns about a possible increased risk of UCP among TCBC users [6, 8, 9] or among women who undergo IOL with unspecified methods [15, 16]. In 1983, Hirashima et al. [6] suggested that the risk of UCP may increase with use of a larger TCBC in Japanese women: the incidence of UCP were 0.0% (0/320) and 0.7% (3/446) among 150-mL and 200 – 250-mL TCBC users, respectively ($P = 0.2693$). A recent study confirmed that the incidence of UCP was

significantly higher among 180 – 250-mL TCBC users than among 70 – 150-mL TCBC users (3.3% [2/61] vs 0.0% [0/662], $P = 0.00701$) [9]. Another study retrospectively examined the incidence of UCP among 15549 Japanese women with cephalic singleton pregnancies who attempted to give birth vaginally at or after 34 weeks of gestation between 1997 and 2010 [8]; the incidence of UCP was 1 in 753 women (0.13%) who underwent IOL using a 150-mL TCBC, while the incidence was 1 in the remaining 14796 women (0.007%) who did not undergo a TCBC procedure ($P = 0.095$). IOL in which TCBC may be used is implicated as a risk factor for UCP [15,16]: the risk of UCP is 1.6 per 1000 overall viable singleton pregnancies, while that for IOL using an unspecified method is 2.6 per 1000 viable singleton pregnancies, representing an increase of 40% – 50% over the rate of UCP in women showing spontaneous labor [15]; IOL using an unspecified method was an independent risk factor for UCP and had an odds ratio of 2.2 (95% confidence interval, 1.7 – 2.8) (7.0/1000 vs. 3.4/1000) after multiple regression analyses of 121227 women, including 5162 women with abnormal fetal presentation (such as breech or transverse lie) and 3542 women with twin pregnancies [16]. We speculated that women who underwent IOL using TCBC had an increased risk of UCP compared to those who underwent IOL not using TCBC in these studies [15,16], because neither the IOL, use of uterotonics, nor amniotomy was an independent risk factor for UCP-CP in the present study.

TCBC with a saline volume of 80 – 150 mL was used in the women who had UCP-CP infants in the present study. Theoretically, such a large TCBC with saline volume of 80 – 150 mL may be more dangerous with regard to UCP compared to TCBC with a saline volume of 60 mL or less. No UCP occurrence was recorded in 77 [1], 83

[2], 94 [4], and 412 [5] cases using 30-mL Foley catheters, in 1083 cases using 50-mL Foley catheters [3], or in 98 cases using 60-mL Foley catheters [4]. However, because data on the risk of UCP in women undergoing spontaneous labor at or near term with cephalic presentation is limited, available studies concerning the usefulness of TCBC for IOL [1 – 5] may be too small to draw conclusions about the risk of UCP, which may be inherent in the use of TCBC. Most previous studies dealing with UCP included women with IOL, preterm birth, breech presentation, and/or multifetal pregnancies, and reported varying incidences of UCP, ranging from 1.4 to 3.8 per 1000 women, and consistently indicated that IOL, breech presentation, preterm birth, and/or multifetal pregnancies are risk factors for UCP [13, 15 – 23]. Therefore, the risk of UCP in women undergoing spontaneous labor at or near term with cephalic presentation may be somewhat lower than the reported incidence of 1.4 – 3.8 per 1000. Therefore, we may need data on the risk of UCP in women undergoing spontaneous labor at or near term with cephalic presentation to confirm whether the use of 30 – 60 mL TCBC does or does not increase the risk of UCP.

The strength of our study was that the Japan Obstetric Compensation System for Cerebral Palsy is expected to collect information on the clinical courses of all patients with both CP and a birth weight > 2000 g in and after January 2009 in Japan and in whom intrapartum factors are possible causes of CP [10]. The number of patients with UCP-CP and non-UCP-CP presented here likely reflected the true number of CP patients that occurred in Japan during a certain period that we were unable to specify because the date of birth for each case was masked. This limitation hampered the estimation of absolute risk of UCP-CP in Japan, which has an annual birth rate of

approximately 1050000 infants with birth weight > 2000 g [Tabulation information released annually by the Japanese Ministry of Health, Labor, and Welfare].

Overall, there were 10 (9.8%) cases using TCBC and 7 (6.9%) UCP-CP infants among the 102 patients (Tables 1, 2). Four UCP-CP infants were born to TCBC users and 3 UCP-CP infants were born to non-TCBC users. The general frequency of TCBC use in Japan may have been somewhat lower than 9.8%, because the use of TCBC was a risk factor for CP as demonstrated in the present study. As IOL is a common obstetric intervention worldwide, 10% – 30% of deliveries are induced with pharmacological and/or mechanical methods in Western countries and Japan [3, 24 – 27]. Among women undergoing IOL, a considerable number undergo mechanical ripening of the unfavorable uterine cervix: a 50-mL TCBC was used in one third of 4122 women whose deliveries were induced in a hospital in Israel, accounting for 3.9% of all births [3]; and a 150-mL TCBC was used in 4.8% of all 15549 women at more than 33 gestational weeks in a hospital in Japan [8]. In May 2012, the JCQHC announced that a total of 171 infants born in 2009 were compensated for CP until the end of March 2012. Thus, the 102 study subjects accounted for 60% of all 171 infants with CP born in 2009, were expected to be born during a period of an approximately 7.2 months in 2009, and diagnosed with CP before the end of 2011. An absolute risk of UCP-CP was estimated based on the following two assumptions: 1) TCBC was used in 31500 (5.0%) of the 630000 (60% of annual births of 1050000) women who gave birth to infants with birth weight > 2000 g in a 7.2-month period; and 2) the 102 patients accounted for 60% of all CP infants with a birth weight > 2000 g originating from perinatal episodes in Japan 2009. These assumptions would yield absolute risks of

UCP-CP of 4/31500 (1 in 7875) for TCBC users and 3/598500 (1 in 199500) for non-TCBC users. Perinatal mortality rates ranging from 2.0% to 12.6% have been reported among infants with UCP [13, 18 – 20, 22]. Although the prevalence of CP among infants with UCP has not been studied extensively, one study indicated that major handicap occurred in 1 (0.8%) of 132 infants with UCP [13]. The additional assumption that 630 (0.1%) of the 630000 women experiencing UCP would yield a UCP-CP risk of 7/630 (1.1%, 1 in 90) for infants born after UCP, consistent with the value of 0.8% in a previous study [13].

Use of ultrasound has been suggested to be helpful for the avoidance of UCP [28, 29]. Three of the four infants with UCP-CP born to TCBC users underwent amniotomy soon or immediately before the occurrence of UCP. Careful performance of ultrasound before amniotomy may have detected cord presentation in some of these three cases, thereby leading to emergency cesarean section and avoidance of UCP-CP. In addition, decision-to-delivery interval was more than 30 minutes in 5 of the 6 UCP-CP infants, suggesting that delayed delivery contributed to the irreversible brain injuries.

In conclusion, the present study suggested that the use of TCBC was a significant risk factor for UCP-CP. However, it was possible to speculate that TCBC was more frequently used in women with a higher risk for UCP. Thus, we do not know whether TCBC itself induces UCP-CP. This issue has to be solved with prospective and well-designed controlled studies. A risk of fetal jeopardy increases with advancing gestation at and after a certain gestational week [30, 31]. In pregnancy at and after 41 weeks of gestation, IOL results in a lower rate of cesarean section than serial antenatal

monitoring with the rates of perinatal mortality and neonatal morbidity being similar to the serial antenatal monitoring [32]. In women with an unfavorable uterine cervix at term, the effectiveness of IOL with 30 mL TCBC is similar to IOL with prostaglandin E2 gel, with fewer maternal and neonatal side-effects [5]. Whether the use of TCBC increases overall number of infants with adverse outcomes remains to be studied.

Disclosure

All authors declare that they have no financial relationship with a biotechnology manufacturer, a pharmaceutical company, or other commercial entity that has an interest in the subject matter or materials discussed in the manuscript.

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Table 1. Forty-six infants excluded from the present study

1. Non-reassuring fetal status on admission	38
Abruptio placentae	18
Fetomaternal transfusion	2
Umbilical cord prolapse	1*
Uterine rupture	1
Congenital metabolic disorder	1
Others	15
2. Twin	3
3. Normal respiratory and neurological activity at birth	3
4. Breech presentation	1†
5. Anesthetic accident	1

*, This infant was born to a mother who presented with umbilical cord prolapse at 40 weeks of gestation; †, Trans-cervical balloon catheter was used only in this case among the 46 infants excluded from the present analysis. This case developed abruption placentae, but not UCP during parturition at 37 weeks of gestation. Of 46 infants, 15 were born preterm: 28 weeks ($n = 1$), 30 weeks ($n = 1$), 33 weeks ($n = 2$), 35 weeks ($n = 6$), and 36 weeks of gestation ($n = 5$).

Table 2. Proposed etiologies of cerebral palsy in the 56 study subjects

1. Umbilical cord prolapse	6 (10.7%)
2. Abruptio placentae	5 (10.0%)
3. Uterine rupture	3 (5.4%)
4. Shoulder dystocia	1 (1.8%)
5. Bleeding*	1 (1.8%)
6. Others	40 (71.4%)

All 56 infants were born to women with a cephalic singleton pregnancy and confirmed fetal wellbeing on electronic cardiotocogram at the time of admission to obstetric facilities for labor pains, ruptured fetal membranes, and/or the induction of labor and showed hypoxic-ischemic encephalopathy at birth; *, Bleeding from low-lying placenta during parturition. Others included cerebral palsy associated with difficult labors, inappropriate use of instrumental deliveries, and inappropriate management of labor with or without inappropriate interpretation of electronic cardiotocogram.

Table 3. Comparison of clinical backgrounds of the two groups (univariate analysis)

	UCP-CP	Non UCP-CP	<i>P</i> -value
Number of infants	6 (100%)	50 (100%)	
Ruptured fetal membranes*	1 (17%)	13 (26%)	> 0.999
Polyhydramnios	0 (0.0%)	0 (0.0%)	>0.999
Induction of labor	5 (83%)	16 (32%)	0.0236
Use of TCBC	4 (66.7%)	5 (10%)	0.0044
Use of amniotomy	4 (67%)	12 (24%)	0.0494
Use of oxytocin	3 (50%)	23 (46%)	> 0.999
Use of uterotonics¶	4 (67%)	25 (50%)	0.6708
Birth weight	3387 ± 662	3113 ± 502.9	0.2243
≥ 2,000 g	6 (100%)	49 (98%)	>0.999
≥ 2500 g	6 (100%)	46 (92%)	>0.999
≥ 3500 g	3 (50%)	11 (22%)	0.1579
Gestational week at delivery	40.0 ± 0.89	39.3 ± 1.60	0.2659
≥ 37 weeks	6 (100%)	48 (96%)	>0.999
≥ 40 weeks	4 (67%)	24 (48%)	0.6695
Emergency cesarean section	5 (83%)	26 (52%)	0.2097
After failed instrumental delivery	0 (0.0%)	8 (16%)	0.5781
Decision-to-delivery interval (min)	42.4 ± 8.47	37.0 ± 19.0	0.1542
<u>Instrumental vaginal delivery</u>	<u>1 (16.7%)</u>	<u>12 (24%)</u>	<u>>0.999</u>

UCP-CP, cerebral palsy associated with umbilical cord prolapse; Non-UCP-CP, cerebral palsy not associated with umbilical cord prolapse; *, Rupture of fetal membranes was confirmed at admission; TCBC, transcervical balloon catheter; ¶, Use of uterotonic drugs, including intravenous oxytocin, intravenous prostaglandin F2α preparation, and/or oral prostaglandin E1 preparation. Two preterm infants were born at 32 weeks and 36 weeks of gestation weighing 1542 g and 2192 g, respectively. Two other infants with birth weights of less than 2500 g were born at 37 and 39 weeks (weighing 2095 g and 2158 g, respectively).

Table 4. Detailed information on the 6 cases with UCP-CP

Case	GW	TCBC	Amniotomy	Time interval (min)		
				A	B	C
1	41	Yes (150 mL)	Yes	50	33	48
2	39	Yes (100 mL)	Yes	75	1	53
3	40	Yes (150 mL)	Yes	105	0	43
4	41	Yes (80 mL)	No	270	0	17†
5	40	No	No	N/A	5	35
6	39	No	Yes	N/A	0	33

UCP-CP, umbilical cord prolapse-induced cerebral palsy; TCBC, transcervical balloon catheter; GW, gestational week at delivery; A, Occurrence of cord prolapse after TCBC expulsion; B, Occurrence of cord prolapse after fetal membrane rupture; delivery after recognition of cord prolapse; †, instrumental vaginal delivery.