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Injections during labor and intrapartum-related hypoxic injury and mortality in rural southern Nepal

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Abstract

Objective—To estimate the association between unmonitored use of injections during labor and intrapartum-related neonatal mortality and morbidity among home births.

Methods—Recently delivered women in Sarlahi, Nepal, reported whether they had received injections during labor. Data on breathing and crying status at birth, time to first breath, respiratory rate, sucking ability, and lethargy were gathered. Neonatal respiratory depression (NRD) and encephalopathy (NE) were compared by injection receipt status using multivariate regression models.

Results—Injections during labor were frequently reported (7108 of 22 352 [31.8%]) and were predominantly given by unqualified village "doctors." Multivariate analysis (excluding facility births and complicated deliveries) revealed associations with intrapartum-related NRD (relative risk [RR] 2.52; 95% CI, 2.29–2.78) and NE (RR 3.48; 95% CI, 2.46–4.93). The risks of neonatal death associated with intrapartum-related NRD (RR 3.78; 95% CI, 2.53–5.66) or NE (RR 4.47; 95% CI, 2.78–7.19) were also elevated.

Conclusion—Injection during labor was widespread at the community level. This practice was associated with poor outcomes and possibly related to the inappropriate use of uterotonics by unqualified providers. Interventions are required to increase the safety of childbirth in the community and in peripheral health facilities.

Parent trial registered at clinicaltrials.gov (NCT00 109616).

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Conflict of interest
The authors have no conflicts of interest.

Keywords

Home births; Injections; Neonatal encephalopathy; Neonatal mortality; Nepal

1. Introduction

Intrapartum-related (IPR) hypoxic injury accounts for 2 million neonatal deaths and stillbirths per year worldwide [1]. Progress in reducing the rate of infection-related deaths has increased the proportion of neonatal deaths attributable to IPR events, which are now the second-most common cause of neonatal mortality [2]. Poor access to and low quality of obstetric services are factors contributing to the high burden of IPR maternal, fetal, and neonatal deaths. In South Asia, where a large proportion of mothers deliver without skilled attendants, inappropriate use of injections during labor is widespread [3–7], and might substantially increase the risk of poor intrapartum outcomes for mother and child.

Injections during labor can include the non-medically indicated or unmonitored use of uterotonics such as oxytocin. Such injections could potentially result in uterine hyperstimulation and reduce oxygen supply to the fetus, leading to stillbirth, neonatal respiratory depression (NRD), neonatal encephalopathy (NE), and death [8]. In the USA, oxytocin is “the drug most commonly associated with preventable adverse perinatal outcomes” and is among the drugs listed by the Institute for Safe Medication Practices as “bearing a heightened risk of harm” [9]. A recent systematic review of injectable uterotonic use in low-resource settings found oxytocin was commonly used to accelerate labor in home deliveries, especially in South Asia, with frequency estimates ranging from 21% to 69% [10]. In Uttar Pradesh, India, use during home deliveries exceeded 48%, and two-thirds of those who received injections reported the receipt of multiple injections [3]. Injections during delivery may be provided by traditional birth attendants or, more often, by unqualified local providers (“doctors”) [3,4,6]; the injections are often demanded by the laboring woman and/or family members.

Small studies in low-resource settings have demonstrated links between the receipt of oxytocin during labor and poor late fetal and early neonatal outcomes, including death [11,12]. Such associations may be spurious, given that such outcomes are strongly associated with complicated deliveries, especially prolonged labor, and uterotonic injections are used to augment non-progressing or difficult labor. However, a multi-site facility-based study of normal, uncomplicated deliveries in West Africa [13] demonstrated a significantly increased risk of stillbirth and neonatal resuscitation among women receiving oxytocics.

Given recent global interest in expanding extra-facility interventions to prevent postpartum hemorrhage, key policy debates are surfacing regarding the appropriate settings and healthcare cadres authorized to administer uterotonics at or around birth [8,14–18]. Large-scale population-based research is urgently needed to better understand the possible risks. The present study aimed to quantify the association between reported exposure to injections during labor and observed IPR hypoxic morbidity and mortality among more than 20 000 home and peripheral health facility deliveries in rural southern Nepal.

2. Materials and methods

The data for the present study were collected during a previously described [19,20] community-based cluster-randomized trial of the impact of chlorhexidine cleansing interventions on neonatal mortality and morbidity. Between September 1, 2002, and January 31, 2006, 23 662 live-born infants in Sarlahi District, Nepal, were eligible to participate. Their mothers were approached at mid-pregnancy, the study procedures were explained, and

oral informed consent was obtained. All women received iron supplements, deworming treatment, clean birthing kits, and basic counseling on nutrition and prenatal and postnatal care. Data on household socioeconomic status, parental education, and birth history were collected. Locally resident female staff were notified of the births, and the infants were visited as soon as possible and throughout the neonatal period on a standard schedule (days 1–4, 6, 8, 10, 12, 14, 21, 28). The gestational age was defined as time since last menstrual period, estimated by maternal report. The infants were followed until study completion at 28 days, out-migration, or death. The study was approved by the Nepal Health Research Council (Kathmandu, Nepal) and Johns Hopkins University Bloomberg School of Public Health (Baltimore, MD, USA).

The aim of the study was to understand the possible association between injections of any type received by the mother during labor (“exposure”) and neonatal outcomes (“outcome”). Information on exposure was collected at the time of the birth assessment visit, which was conducted only for live births, defined as infants that moved or cried after birth based on parental report. Questions related to pregnancy, labor, and delivery included: “Was anything done to help the baby come out?” (women could select up to 3 responses). Exposure to injection during labor was defined as a positive response to this question and an indication that the specific action taken was provision of an injection.

The primary outcomes of interest were IPR hypoxic events, ranging in severity from relatively mild (NRD at birth) to more severe (NE). These events were defined on the basis of clinical signs. Development of these definitions involved the use of information collected at the first assessment after birth and at subsequent home visits during the first month of life, as described previously [21]. For the current purpose (to understand possible links between these outcomes and the receipt of injections during labor), the analysis was limited to: (1) NRD at birth, defined as NRD among live-born infants who failed to cry at birth, experienced delayed onset of breathing, or required assistance to initiate breathing; (2) IPR-NRD, defined as NRD among full-term infants (at least 37 weeks), and excluding those with a major congenital malformation; and (3) IPR-NE, defined as IPR-NRD resulting in death or seizures and 2 of the following: lethargy, poor suck, or respiratory rate less than 40 breaths per minute, observed anytime during the first 7 days after birth among full-term infants. In addition, deaths within 28 days related to these morbidities were examined as separate outcomes (IPR-NRD-specific and IPR-NE-specific mortality rates per 1000 infants).

The relative risk (RR) and 95% confidence interval (CI) of each outcome by injection receipt status was calculated using binomial regression with a log link function; Poisson regression was used if the model failed to converge. In addition, 2 multivariate models were used: in the first model, the risk was adjusted for location of delivery (health facility versus home), prolonged labor (“labor pains” more than 24 hours for nulliparous women and more than 12 hours for multiparous women), prolonged rupture of membranes (more than 24 hours before birth), self-reported maternal fever, vaginal bleeding, and/or convulsion at any time in the 7 days before delivery; the second model excluded women who had any of these complications or delivered in a facility (to account for reverse-causality bias). All multivariate models were adjusted for sex, gestational age at birth, maternal age, maternal and paternal literacy, parity, chlorhexidine receipt status, ethnic group, and caste. All analyses were conducted using Stata 12.0 (StataCorp, College Station, TX, USA). Comparative risk estimates were considered significant if 95% CIs did not include unity.

3. Results

Between September 1, 2002, and January 31, 2006, 23 662 infants were born alive in the study area and exposure data were available for 22 352 (94.5%). Missing data resulted

mainly from administering a shortened version of the birth assessment module to more efficiently manage workloads during periods immediately following week-long holidays. Most respondents (16 237 [72.6%]) reported specific actions were taken to help the child come out (Table 1). Injection during labor (prior to delivery of the infant) was reported among 7108 (31.8%) mothers of the 22 352 live births. Among 13 847 normal, uncomplicated deliveries at home, receipt of injection was reported in 3153 (22.8%) cases. Injections were more common among deliveries in health facilities and/or with reported complications (3995/8505 [46.5%]), and among younger, nulliparous women (Table 2).

Attendants at delivery were mainly family members (18 701 [84.3%]) and neighbors (11 125 [49.9%]), followed by traditional birth attendants (6400 [28.7%]) and unqualified "doctors" (generally untrained local providers without a medical license; 4377 [19.7%]). Auxiliary nurse midwives were less commonly reported to assist deliveries (1934 [8.7%]). Injections were uncommon among the 15 073 women who delivered without assistance or with assistance from family members, neighbors, or traditional birth attendants only (1018 [6.8%]), but were reported 83.7% (6090/7279) of the time when attendants included someone outside this local circle. The local informal health providers ("doctors") assisted with 56.6% (3998/7061) of deliveries where injections were reported prior to delivery, compared with only 2.5% (379/15218) of deliveries for which no injections were reported (RR 22.7; 95% CI, 20.5–25.2).

The total number of cases for each type of neonatal outcome, the incidence rate (per 1000 infants), and the case fatality are shown in Table 3. The number of infants available for the estimation of NRD outcomes (n=22 179) exceeds that for the estimation of NE outcomes (n=21 474) because the latter required direct examination of the infant within 7 days, and this did not occur for all infants.

The neonatal outcomes were strongly associated with the injection receipt status of the mother (Table 4). Children born to mothers receiving injections during labor were more than twice as likely to experience NRD or moderate–severe NE. The magnitude of the association was substantially elevated when only IPR events were considered.

Application of the adjusted model resulted in slightly reduced comparative risk estimates (Table 5). When the analysis was further restricted to home-born infants without any labor complications (excluding mothers reporting any of the previously mentioned complications; Table 5), the relationships between NRD/NE outcomes and the receipt of injections during labor remained statistically significant, with slight increases in magnitude.

The IPR-NRD-specific mortality rate among newborns whose mothers reported the receipt of injections during labor was 16.1 per 1000 (113 deaths among 7012 live births); for unexposed infants, the rate was 4.5 per 1000 (69 deaths among 15 167 live births) (RR 3.54; 95% CI, 2.63–4.77). Similarly, the IPR-NE-specific mortality rate was 3.63 (95% CI, 2.56–5.14) times higher among exposed infants (12.4 per 1000; 84 of 6796 live births) than among unexposed ones (3.4 per 1000; 50 of 14 678 live births). When infants born at a health facility and those with maternal labor complications were excluded, the estimates were slightly increased: RR 3.78 (95% CI, 2.53–5.66) and 4.47 (95% CI, 2.78–7.19) for the mortality risks associated with IPR-NRD and IPR-NE, respectively.

4. Discussion

The present data demonstrate that administration of injections during labor to help deliver the child is common in this rural South Asian setting and suggest an association between injections during labor and subsequent poor neonatal outcomes. The large magnitude and statistical strength of the relationship, observed even after adjustment and after exclusion of

health-facility deliveries and/or deliveries with maternal intrapartum complications, indicate that a critically important proportion of IPR morbidity in newborns might be attributable to this practice.

Because of limitations in the present analysis, future research is strongly recommended to quantify this relationship more precisely. Perhaps most important among the study limitations is the absence of more specific information about the injections, including the type of injection, the number of injections received, the mode or location of administration, the specific timing of the injection(s) (how much time before delivery of the child), the provider of the injection(s), the specific reason why an injection was given, who made the decision to do give an injection (e.g. requested from mother/family member, advised by traditional birth attendant or another attendant), and whether the injection(s) were paid for by the women. The present measure of exposure more broadly captured injections of any type, and these might include oxytocin or other injectable uterotonics, antibiotics, vitamin B12, saline, and antipyretics. The true association (if any) between injections and the neonatal outcomes examined here likely varies across these injection types (and across other factors, such as dosage, potency, purity, frequency, and timing). The potential inclusion of injections other than uterotonics likely biases the observed associations toward the null.

The likelihood that an important, if not large, proportion of the injections reported here comprised oxytocin or another injectable drug with uterotonic effects should not be discounted. There is substantial evidence in both the medical and the social science literature [4,10] that oxytocin is widely used at home births, especially in South Asia and predominantly administered by unqualified local providers. That this may also apply to the present setting is strengthened by the observation that local “doctors” (unqualified providers) were most strongly associated with injection use, especially among home deliveries. Previous qualitative investigations [7,10] have highlighted the critical roles unqualified providers have in the inappropriate use of oxytocin and other uterotonic drugs.

Another important limitation that warrants caution in interpreting the present results is the possibility of residual reverse-causality bias. Because exposure to injections during labor may be more likely to arise among complicated, and especially non-progressing, deliveries, children born to exposed mothers may be at higher risk for the neonatal outcomes investigated in the present study, especially IPR hypoxia. Although an attempt was made to account for this possibility by repeating the analyses after exclusion of facility births or births with reported maternal complications, the potential for continued bias remains.

The present outcome definitions are sign-based and should be used cautiously given that symptoms required by the American College of Obstetricians and Gynecologists and the American Academy of Pediatrics [22] to establish intrapartum causality are not included. These symptoms include, among others, measures of metabolic acidosis, fetal heart rate, findings of brain imaging, and/or sentinel events monitored before and/or during labor. It was not possible to collect information on such symptoms in the present population-based cohort from a low-resource setting with a high proportion of home births.

Another limitation is that mothers of infants with poor outcomes might have recalled their injection receipt status differently from mothers of infants without poor outcomes. Additionally, although reporting of the delivery location (facility versus home) is assumed to be accurate, self-reporting of complications during delivery is not particularly accurate [23]. Finally, no extensive information was collected on the nutritional status (e.g. anemia) or morbidities (e.g. pre-eclampsia), and a complete picture of care-seeking throughout pregnancy was not gathered either; such covariates might have an important role in further refining the present estimates.

Each of the limitations discussed here arises from misclassification or omission: the type of injection was not specified, the neonatal outcome definitions may capture infants that are not severely ill or ill for reasons other than hypoxic injury, and the reported complications may not reflect true complications. For each of these, it is possible that misclassification leads to an underestimation of the magnitude of the true association between inappropriate use of injections (especially uterotonics) and neonatal outcomes. Associations of greater magnitude than those observed here have been reported from hospital-based studies. A case-control study in Kathmandu [12] estimated that the odds of induction with oxytocin were more than 9 times higher among mothers of infants with NE than among controls.

The overall negative impact of this practice may be substantially greater when one considers that stillbirths occur at elevated frequency if uterine hyperstimulation (uterine rupture, postpartum hemorrhage, vaginal/cervical tears) is present [8,24]. Stillbirths make up an important portion of perinatal death in this population [25], but the present study did not collect data on the receipt of injections for stillbirths.

In conclusion, the magnitude of the associations between injections and poor neonatal outcomes in the present population-based sample was large, even after exclusion of complicated deliveries. This result indicates an urgent need for further research into the widespread practice of injections during labor among deliveries occurring at home and at health facilities in South Asia. Further efforts are required to better characterize these injection practices (including investigation of the type of injection, mode of administration, frequency, reason for provision) and the relationship between injection exposure and maternal, fetal, and neonatal health outcomes. To inform policy dialog, data from rigorous studies are particularly needed to quantify the attributable fraction of stillbirths and adverse neonatal outcomes associated with these practices, and to clarify the specific role of unmonitored use of uterotonic injections. Urgent efforts are needed to develop interventions to increase the safety of deliveries both at the community level and at peripheral health facilities.

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Synopsis

Receipt of injections during labor in rural Nepal is associated with substantially higher rates of intrapartum-related respiratory depression, encephalopathy, and neonatal mortality.

Table 1

Actions taken to help the child come out during labor[a,b]

Action taken	First response (n=22 352)	Second response (n=8264)	Third response (n=1820)	Overall (n=22 352)
Nothing	6116 (27.4)	—	—	6116 (27.4)
External pressure applied	5463 (24.4)	59 (0.7)	11 (0.6)	5533 (24.8)
Massage	7608 (34.0)	4506 (54.5)	13 (0.7)	12 127 (54.3)
Child pulled out	63 (0.3)	95 (1.2)	50 (2.8)	208 (0.9)
Injection given	2834 (12.7)	3068 (37.1)	1206 (66.3)	7108 (31.8)
Cesarean delivery	131 (0.6)	58 (0.7)	33 (1.8)	222 (1.0)
Episiotomy	91 (0.4)	364 (4.4)	211 (11.6)	666 (3.0)
Home remedy (not specified)	46 (0.2)	114 (1.4)	296 (16.3)	456 (2.0)

[a] Women could select up to 3 responses.

[b] Values are given as number (percentage).

Table 2

Study population characteristics by exposure status[a]

Indicator [b]	No injection during labor	Injection during labor
Sex of child		
Male	7681 (50.6)	3731 (53.2)
Female	7486 (49.4)	3281 (46.8)
Preterm status, wk		
<37	2835 (18.7)	1125 (16.0)
≥37	12 324 (81.3)	5886 (83.9)
Maternal age, y		
<15	70 (0.5)	39 (0.6)
15–19	3344 (22.1)	2185 (31.2)
20–24	6088 (40.1)	2737 (39.0)
25–29	3501 (23.1)	1310 (18.7)
30–34	1483 (9.8)	530 (7.6)
≥35	676 (4.5)	207 (3.0)
Parity		
Nulliparous	2951 (19.5)	2729 (38.9)
1	3786 (25.0)	1555 (22.2)
2–3	5396 (35.6)	1754 (25.0)
4–5	2063 (13.6)	678 (9.7)
>5	971 (6.4)	296 (4.2)
Maternal literacy		
Yes	3318 (21.9)	2341 (33.4)
No	11 840 (78.1)	4668 (66.6)
Paternal literacy		
Yes	8086 (53.4)	4387 (62.6)
No	7065 (46.6)	2619 (37.4)
Ethnic group		
Pahadi	4436 (29.7)	1759 (25.5)
Madeshi	10 486 (70.3)	5129 (74.5)
Facility delivery		
Yes	397 (2.6)	1509 (21.5)
No	14 755 (97.4)	5500 (78.5)
Chlorhexidine receipt status [c]		
Chlorhexidine	9327 (61.5)	4479 (63.9)
Placebo	5840 (38.5)	2533 (36.1)
Prolonged labor		
Yes	3308 (21.9)	2757 (39.4)
No	11 803 (78.1)	4234 (60.6)
Prolonged rupture of membranes		
Yes	759 (5.0)	760 (11.0)

Indicator [b]	No injection during labor	Injection during labor
No	14 290 (95.0)	6166 (89.0)
Maternal fever		
Yes	485 (3.2)	329 (4.7)
No	14 661 (96.8)	6671 (95.3)
Convulsions		
Yes	63 (0.4)	38 (0.5)
No	15 086 (99.6)	6963 (99.5)
Vaginal bleeding		
Yes	520 (3.4)	332 (4.7)
No	14 617 (96.6)	6674 (95.3)

[a] Values are given as number (percentage).

[b] Missing data for these covariates was as follows: sex of child, 0 (0.0%); preterm status, 9 (<0.1%); maternal age, 9 (<0.1%); parity, 0 (0.0%); maternal literacy, 12 (<0.1%); paternal literacy, 22 (<0.1%); ethnic group (366; 1.7%); facility delivery, 18 (<0.1%); chlorhexidine receipt status, 0 (0.0%); prolonged labor, 77 (0.4%); prolonged rupture of membranes, 204 (0.9%); maternal fever, 15 (<0.1%); convulsions, 32 (0.1%); vaginal bleeding, 36 (0.2%).

[c] The chlorhexidine intervention was deemed protective by the Data Safety and Monitoring Board for the parent trial in January 2005 [19], and was subsequently provided to all newborns from March 8, 2005, to January 31, 2006.

Table 3

Incidence and case fatality of neonatal respiratory depression and encephalopathy

Outcome	Total no. of live births	No. of cases	Rate per 1000 (95% CI)	No. of deaths	Case fatality rate, %
Neonatal respiratory depression	22 179	4364	197 (192–202)	347	8.0
Intrapartum-related neonatal respiratory depression	22 179	3465	156 (151–161)	182	5.3
Moderate–severe neonatal encephalopathy	21 411	527	24.6 (22.6–26.8)	35	6.6
Intrapartum-related moderate–severe neonatal encephalopathy	21 474	290	13.5 (12.0–15.1)	134	46.2

Table 4

Unadjusted risk of poor neonatal outcomes among infants whose mothers received an injection during delivery

Outcome	No injection during labor			Injection during labor			RR	95% CI
	Total no. of live births	No. of cases	Rate per 1000	Total no. of live births	No. of cases	Rate per 1000		
Neonatal respiratory depression	15 167	2135	140.8	7012	2229	317.9	2.26	2.14–2.38
Intrapartum-related neonatal respiratory depression	15 167	1633	107.7	7012	1832	261.3	2.43	2.28–2.58
Moderate–severe neonatal encephalopathy	14 655	317	21.6	6756	210	31.1	1.44	1.21–1.71
Intrapartum-related moderate–severe neonatal encephalopathy	14 678	109	7.4	6796	181	26.6	3.59	2.83–4.54

Abbreviations: CI, confidence interval; RR, relative risk.

Table 5

Adjusted risk of poor neonatal outcomes among infants whose mothers received an injection during delivery

Outcome	Multivariate model [a]			Multivariate model excluding facility births and complicated deliveries [b]		
	Total no. of live births	RR	95% CI	Total no. of live births	RR	95% CI
Neonatal respiratory depression	21 512	2.06	1.94–2.19	13 582	2.35	2.18–2.53
Intrapartum-related neonatal respiratory depression	21 512	2.18	2.03–2.33	13 582	2.52	2.29–2.78
Moderate–severe neonatal encephalopathy	20 787	1.27	1.04–1.54	13 183	1.34	1.02–1.76
Intrapartum-related moderate–severe neonatal encephalopathy	20 846	2.92	2.23–3.82	13 246	3.48	2.46–4.93

Abbreviations: CI, confidence interval; RR, relative risk.

[a] Adjusted for sex of child, preterm status, maternal age, parity, maternal and paternal literacy, caste, ethnic group, facility delivery, chlorhexidine receipt status, and complications (prolonged labor, prolonged rupture of membranes, maternal fever, convulsions, or vaginal bleeding).

[b] Adjusted for sex of child, preterm status, maternal age, parity, maternal and paternal literacy, caste, ethnic group, and chlorhexidine receipt status.