Covenant Health

Covenant Health Research Centre (CHRC)

CHRC Final Report

Study Information	
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HERO # **Pro00024506**; CHRC Study # **1300**	
Research Project Title: **Is epidural analgesia in labor associated with respiratory distress in term and near-term neonates? – A case-control study**	

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Executive Summary
Background: **See attached publication**
Purpose:
Method:
Results:

Summary of Knowledge Translation (KT) Activities:
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Please describe all KT activities completed or currently underway for this study.
Poster of research findings presented in annual meetings of Canadian Pediatric Society (2013) and Society for Pediatric Research (2013). Research finding published in a reputed pediatric journal.

Implications and Recommendations for Policy
Please describe all implications and recommendations for institution and organization-level administrators, system-level policy makers…
The study shows an association between exposure to epidural analgesia in labour and the occurrence of respiratory distress in the immediate neonatal period. Further well-designed studies should be conducted to validate the finding of this study.

Implications and Recommendations for Best-Practice
Please describe all implications and recommendations for practitioners and educators…
Clinicians need to be aware of potential respiratory side-effects of epidural analgesia in immediate newborn period.

Strategic Impact at Covenant Health	
Please indicate which strategic objectives your study impacts at Covenant Health (check all that apply)	
☐ 1.1 Deepen our commitment to our mission, values and ethical framework	☐ 1.2 Strengthen our accountability through improved planning, implementation, monitoring and reporting processes
☑ 1.3 Develop capacity & resources to sustain and grow our mission	☐ 2.1 Fosters a highly skilled and effective team
☐ 2.2 Create a safe work environment for staff, physician & volunteers	☐ 2.3 Excel in employee and physician engagement
☑ 3.1 Ensure safe care: reduce harm	☐ 3.2 Strengthen patient, resident & family centered care
☐ 3.3 Exceed performance expectations on standards and best practice	☑ 3.4 Enhance our culture of quality & safety
☐ 4.1 Identify and respond to community needs	☐ 4.2 Enable innovation and leverage our expertise

through programs and services in urban acute and rural health	to be of greater service in: Seniors Care, Addiction & Mental Health Services, Palliative and End of Life Care
☐ 5.1 Develop an understanding of our strategic contribution to the health care system with AHS, AHW, key partners and the public	

Strategic Targets at the Covenant Health Research Centre	
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☐ Study focuses on vulnerable populations and responding to those in need	**x**☐ Study is multi-disciplinary
☐ Study is driven by new researchers	**x**☐ Study is funded in part or wholly by the CHRC grant or seed funding

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Epidural analgesia in labour and neonatal respiratory distress: a case-control study

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Arch Dis Child Fetal Neonatal Ed published online October 29, 2013
doi: 10.1136/archdischild-2013-304933

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ADC-FNN Online First, published on October 29, 2013 as 10.1136/archdischild-2013-304933

Epidural analgesia in labour and neonatal respiratory distress: a case-control study

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Received 24 July 2013
Revised 27 September 2013
Accepted 30 September 2013

ABSTRACT

Background Epidural analgesia is the commonest mode for providing pain relief in labour, with a combination of bupivacaine and fentanyl most often used in practice.

Objective To test whether late-preterm and term neonates exposed to opioids in epidural analgesia in labour are more likely to develop respiratory distress in the immediate neonatal period.

Methods A case-control study was conducted of singleton infants born during January 2006 to December 2010. *Cases* were neonates ≥34 weeks gestation, who developed respiratory distress within 24 h of life requiring supplemental oxygen ≥2 h and/or positive pressure ventilation in the neonatal intensive care unit. *Controls* were gestation and site-matched neonates who did not develop any respiratory distress within the same period. The information on *exposure* to epidural analgesia and on potential confounding variables was obtained from the standardised delivery record, routinely filled out on all women admitted to the labour wards.

Results In our study, 206 cases and 206 matched controls were enrolled. Exposure to epidural analgesia was present in 146 (70.9%) cases as compared with 131 (63.6%) of the controls. The association between exposure to epidural analgesia and respiratory distress in neonates was statistically significant upon adjustment for all potential confounders (adjusted OR: 1.75, 95% CI 1.03 to 2.99; p = 0.04). When data was separately analysed for term and late-preterm infants, the results were consistent across these subpopulations, showing no interaction effect.

Conclusions Late-preterm and term infants exposed to maternal epidural analgesia in labour are more likely to develop respiratory distress in the immediate neonatal period.

What is already known on this topic

- Epidural analgesia in labour is associated with prolongation of labour, decreased rates of spontaneous vaginal delivery, intrapartum fever and increased rates of sepsis evaluation in neonates.
- Opioids used for epidural analgesia in labour diffuse freely across the placenta.

What this study adds

- We found an association between the exposure to epidural analgesia used in labour and the occurrence of respiratory distress in the immediate neonatal period in late-preterm and term infants.
- Clinicians need to be aware of these potential side-effects of epidural analgesia.

BACKGROUND

Epidural analgesia has become the most common mode for providing analgesia in labour in North America. Compared to parenteral opioids, the epidural route has been shown to provide better quality of analgesia to the women in labour and is recommended as the preferred option where sufficient resources are available.[1] Approximately 50–70% of women admitted to a birthing centre have epidural analgesia as a primary mode of pain relief.[2 3] Although the practice started with the use of a local anaesthetic agent alone, the addition of an opioid was later recognised to enhance the onset of analgesia and provide better pain relief with decreased motor blockade.[4] Currently, a combination of bupivacaine (a local anaesthetic) and fentanyl (an opioid) is most often used to achieve adequate pain relief.[1]

It is generally perceived that the use of epidural analgesia in labour is unlikely to cause respiratory depression in newborns as the drug is contained at the site of administration. However, contrary to this widely held belief, pharmokinetic studies have shown that fentanyl diffuses freely from the epidural space into the maternal blood and across the placenta due to its high lipid solubility.[5 6] Neonates are also known to be more prone to respiratory effects of opioids due to the immaturity of their respiratory centre.[7] Additionally, the respiratory side-effects from the opioid agents could arise up to several hours after exposure due to the longer terminal half-life of fentanyl in neonates and from the secondary peaks in plasma drug concentration reported.[7–9]

Cases of neonatal respiratory depression following epidural fentanyl analgesia have been reported in observation studies and in small clinical trials.[10–13] However, other studies have failed to show such effects on newborn respiration.[14–16] We have previously published the limitations of existing literature in this area, that is, the studies lacked statistical power to detect a significant difference in the outcome of respiratory distress.[11] Additionally, most studies have primarily focussed on the neonatal outcomes in the delivery room, ignoring the possibility of late effects.[17 18]

Our objective was to determine an association between the exposure to epidural opioid analgesia

To cite: Kumar M, Chandra S, Ijaz Z, *et al*. *Arch Dis Child Fetal Neonatal Ed* Published Online First: [*please include* Day Month Year] doi:10.1136/archdischild-2013-304933

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in labour and the occurrence of respiratory distress in the immediate neonatal period, through an adequately powered case-control study.

METHODS

Study design: A case-control study was conducted.

Participants and the settings. Subjects were singleton babies of ≥34 weeks' gestation, born between 1 January 2006 and 30 December 2010, at the Grey Nuns' and Misericordia Hospital sites in Edmonton. *Cases* were neonates who developed respiratory distress within 24 h of life, defined as one or more of the following: need for supplemental oxygen ≥2 h and/or positive pressure ventilation (via nasal continuous positive airway pressure (CPAP) or endotracheal intubation) following admission to neonatal intensive care unit (NICU). Exclusions were major congenital malformations known to be associated with respiratory distress in newborn or aneuploidy (diagnosed on antenatal investigations or following delivery), culture proven sepsis diagnosed within 72 h of birth or delivery by elective caesarean section (as the practise of obstetrical analgesia differs significantly in the latter situation). *Controls* were neonates, matched for gestational age (in completed weeks) and hospital site of birth, which did not develop any respiratory distress within the same period or did not require use of an opioid antagonist to establish effective respiration. If more than one neonate qualified for being a control, the one with closest hospital number to the corresponding case was selected. Similar exclusion conditions, as listed for cases, applied.

Potential subjects were identified through electronic search of database of hospital records. Relevant medical information for confirmation of cases and controls were obtained from primary newborn admission charts. These charts also contained a copy of standardised 2-page delivery record, routinely filled out by the labour-room nurses for all deliveries, which provided data for *exposure* to epidural analgesia and potential confounding variables. The information was extracted on a standardised computer-based case report form that was developed for the study in REDCap database software[19] and pilot tested before actual use.

Statistical analyses

The sample size for this study was calculated based on the following desired parameters: ά-error (two-sided) 0.05, power of 80%, ratio of cases to controls of 1:1 and minimum OR of 2. With the baseline incidence of epidural analgesia in women delivering through vaginal route near 70% in our setting, the required sample size was 404 subjects (202 in each group).[20] Continuous variables were analysed using the two-sample t tests if they appeared normally distributed, or by the Mann–Whitney U tests if not normally distributed. Categorical variables were analysed using χ^2 test or Fisher exact test, as appropriate. We conducted the following logistic regression analyses to adjust for the impact of potential confounders. In the multiple logistic regression analysis, we planned a priori to adjust for selected antenatal and intrapartum variables considered to be independent predictors for respiratory distress in newborn (ie, maternal diabetes, pregnancy induced hypertension, antenatal steroids, oligohydroamnios, opioids provided in labour via other routes, delivery route and meconium in amniotic fluid) and for infant's sex . Additionally, we planned to adjust for other antenatal and intrapartum variables if they were significant in the univariate logistic regression analysis at a p value of 0.1. All statistical analyses were conducted using STATA software, V.12 (SAS Institute, Cary, North Carolina, USA).

RESULTS

We enrolled 412 subjects (206 in each group). The baseline characteristics of the cases and the controls are shown in table 1. The groups were comparable in terms of gestation, however, cases were of slightly higher birth weight (mean difference=122.5 g, p=0.06) and had higher proportion of female infants (52.4% vs 47.6%, p=0.06). In terms of maternal variables, the groups were comparable for maternal age, maternal hypertension, use of antenatal steroids, and the proportion with spontaneous onset of labour and prolonged rupture of membranes. Cases were more likely to be associated with maternal history of diabetes, oligohydroamnios, meconium in amniotic fluid, delivery by caesarean section (following the onset of labour) or assisted vaginal delivery. Cases were also noted to have lower 1 and 5 min Apgar scores, and a greater need for resuscitation after birth.

Table 2 shows description of pain management strategies employed in labour among the cases and the controls. Overall, the cases were associated with more likely use of some form of analgesia in labour (87.9% vs 80.1%, p=0.03). However,

Table 1 Baseline characteristics of the case and the control groups

	Cases (n=206)	Controls (n=206)	p Value
Gestational age in weeks (mean±SD)	37 (2.4)	37 (2.4)	0.95
▶ Term	100	98	
▶ Preterm	106	108	
Birth weight (mean±SD)	3057 (727 g)	2934 (604 g)	0.06
Sex (M : F)	89/117	98/108	0.06
Hospital site			1.00
▶ Site#1 (Grey Nuns)	159	159	
▶ Site#2 (Misericordia)	47	47	
Maternal age in years (mean±SD)	28.74 (5.25)	28.01 (5.9)	0.19
Antenatal factors			
▶ Assisted conception	3 (?%)	2 (?%)	1.00
▶ GDM	13	7	0.17
▶ Any diabetes	16	7	0.05
▶ PIH	16	19	0.60
▶ Any hypertension	16	19	0.60
▶ Oligohydramnios	8	3	0.10
▶ Antenatal steroids	7	5	0.56
Intrapartum factors			
▶ Labour (spontaneous/induced)	52/154	57/149	0.58
▶ PROM (>18 h)	41	42	0.92
▶ Antibiotics in labour	99	97	0.84
▶ Meconium in amniotic fluid (none/thin/thick)	176/11/19	197/6/3	0.001
▶ Presentation in labour (cephalic/breach)	197/8	200/5	0.70
▶ Delivery (vaginal/c-section)	152/54	174/32	0.008
▶ Vaginal delivery description (spontaneous/vacuum/forceps)	122/11/19	158/8/8	0.017
1 min Apgar [median±IQR]	7 [5–8]	9 [8–9]	<0.001
5 min Apgar [median±IQR]	8 [7–9]	9 [9–9]	<0.001
Resuscitation after birth (y/n)*	116/90	22/184	<0.001

*defined as need for any one of the following after birth – bag and mask ventilation, ETT, chest compression or resuscitation drugs.
GDM, gestational diabetes mellitus; PIH, pregnancy-induced hypertension; PROM, prolonged rupture of membranes.

Table 2 Description of pain management in labour among the cases and the controls

	Case (206) n (%)	Control (206) n (%)	p Value
No analgesia used	25 (12.1)	41 (19.9)	0.03
Intravenous/ per oral narcotics	22 (10.7)	31 (15.1)	0.018
Spinal	24 (11.7)	7 (3.4)	0.001
Epidural	146 (70.9)	131 (63.6)	0.11
Inhalation	13 (6.3)	24 (11.6)	0.058
Others (as follows)	3 (1.5)	7 (3.4)	0.34
▶ Local	2	3	
▶ Pudendal block	0	3	
▶ General	0	1	
▶ Acetaminophen	1	0	

exposure to intravenous and oral opioids in labour (most commonly intravenous morphine or Demerol) or inhalational analgesia was more common in the control group in infants.

Table 3 shows the results from the multiple logistic regression analysis for exposure to epidural analgesia in the two study groups along with the analyses for the adjustment for confounders. As seen in the table, 70.9% of the cases as compared with 63.6% of the controls were exposed to the epidural analgesia in labour (unadjusted OR=1.42; 95% CI (0.92 to 2.17, p=0.11). The difference between the groups was significant following adjustment for potential confounders in the multiple logistic regression analysis, with the cases more likely to be exposed to the epidural analgesia in labour than the controls (adjusted OR=1.75; 95% CI 1.03 to 2.99, p=0.04). When the analysis was restricted to adjustment for a priori identified variables of clinical importance (as listed in methods section), the OR was 1.85 (95% CI 1.11 to 3.08, p=0.02). The results were consistent when data was analysed separately for term and late-preterm infants, showing no interaction effect.

DISCUSSION

Our study demonstrates an association between the use of maternal epidural analgesia in labour and the outcome of respiratory distress in late-preterm and term infants occurring on the day of birth. The subgroup analysis revealed that this association was noted irrespective of the maturity of the babies enrolled in this study. We chose babies born at ≥34 weeks of gestation at birth for our investigation, as below this gestation, surfactant deficiency is considered to be the primary cause of respiratory distress in immediate neonatal period.

To our knowledge, this is the largest study to date that systematically looked for the effects of epidural analgesia in labour on neonatal respiratory outcomes. Epidural analgesia in labour has been shown to be associated with a lower rate of spontaneous vaginal delivery, a higher rate of instrumental vaginal delivery, prolongation of labour and intrapartum fever, and the exposed infants are more likely to be evaluated and treated for suspected sepsis.[18] Additionally, infants born to mothers with epidural-related fever have been shown to be hypotonic at birth with lower 1 and 5 min Apgar scores.[21] However, the effects of maternal epidural analgesia on neonatal respiration, beyond the outcomes in the delivery room, are not well described to date. The likely reason for these delayed effects of fentanyl noted on neonatal respiration could be because of its much larger volume of distribution in steady-state in neonates, resulting in much longer terminal elimination half-life lasting several hours.[7]

Our results differ from the negative results of a few published small RCTs,[14–16] which is likely due to the fact that none of these trials were powered for the outcome of neonatal respiratory distress. These trials, in total, reported outcomes on 106 infants (majority ≥36 weeks' gestation) exposed to maternal epidural analgesia. With a low baseline risk for developing respiratory distress in immediate neonatal period in this subpopulation, these trials, combined, had only a 10–20% chance of finding an association even if it truly existed.[20] Contrary to the negative findings of these trials, several studies have documented cases of respiratory depression in neonates after birth following use of epidural analgesia in labour.[10–13] We chose a case-control design knowing the limitations of the existing negative studies and adequately powered our study to avoid the possibility of a β-error (ie, missing the association with the exposure of interest, if it truly existed).

The results of our study have important clinical implications. Respiratory distress requiring either oxygen or ventilatory support occurs in 5–15% of the near-term infants and 2–5% of the term infants,[22 23] resulting in the infant's admission to the NICU on the site of delivery or transport to an advanced neonatal centre. Provision of healthcare services to this group of infants takes up a considerable amount of neonatal resources.[24] Current neonatal resuscitation guidelines do not take into account the possibility of significant neonatal respiratory distress occurring beyond the delivery room from exposure to maternal epidural analgesia.[25] The positive association as demonstrated in this study, if validated in further studies, would potentially impact clinical practice in terms of consideration for use of opioid antagonists in some of these exposed infants in the period following initial stabilisation in the delivery room, particularly to avoid the need for ventilatory support. This could potentially reduce transfers of some neonates to the advanced-level NICUs. However, we believe that the results of this study are unlikely to impact the current practice of obstetrical analgesia, as the epidural mode is considered to provide better quality of analgesia in parturient as compared with the use of parenteral opioids.[1] Thus, it is likely to remain as the most common mode of obstetrical analgesia.

Our study has several potential limitations. First, we could not find exact gestational matched controls for five of our cases. We chose the nearest gestational age control from the same

Table 3 Relationship between respiratory distress and exposure to epidural analgesia: results from the multiple logistic regression

	Cases (n=206)	Controls (n=206)	Crude OR (95% CI)	Adjusted OR† (95% CI)
All infants	146 (70.9%)	131 (63.6%)	1.42 (0.92 to 2.17)	1.75 (1.03 to 2.99)*
Term (≥37 weeks GA)	82/100	75/98	1.46 (0.72 to 2.96)	1.59 (0.62 to 4.04)
Preterm (<37 weeks GA)	64/106	56/108	1.45 (0.85 to 2.50)	2.03 (1.00 to 4.12)**

*p Value 0.04; **p value 0.048.
†Adjusted for the following variables in the multiple logistic regression analysis: infant's sex, maternal diabetes, maternal hypertension, antenatal steroids, type of delivery, opioids provided in labour via other routes, inhalational analgesia, oligohydroamnios and meconium in amniotic fluid.

hospital site for these cases (four within ±1 week difference and one control 2 weeks apart). We believe, this is unlikely to confound our results as the two groups remained similar in terms of mean gestational age and its SD. Second, we did not adjust for postnatal factors, such as Apgar scores or need for resuscitation in the delivery room, as we considered them as intermediary variables which could have been affected by the exposure of interest.[26 27] Third, there could have been confounding from temporal changes in clinical practice in terms of use of epidural analgesia over the duration of the study. We reduced the possibility of this bias in our study by choosing corresponding controls as closest hospital number to the enrolled case (majority were within a week of each enrolled case). Thus, the ratio of cases to controls was proportionate for each study year. Fourth, there could have been a risk for bias in terms of determining the status of exposure and confounders among the study subjects. We tried to avoid this bias by obtaining the majority of our information about these variables from a standardised delivery record that is routinely completed in real time by the labour and delivery nurses for every patient admitted in a labour room. However, we were unable to obtain the exact doses of narcotics obtained by each study subject from those records which might have resulted into some residual bias. Last, although we adjusted for known confounders in our regression analyses, our results may still be biased because of one or more hitherto unknown confounders, a risk inherent to all observational studies.

CONCLUSION

In summary, the findings of this case-control study show a positive association between exposure to maternal epidural analgesia and respiratory distress in the immediate neonatal period, in late-preterm and term infants. The clinicians should be aware of these potential side-effects of the epidural analgesia used in labour on newborn respiration. Further well-designed studies should be conducted to validate the finding of this study.

Acknowledgements The authors are grateful to Heather Rylance (Research Nurse) at Women & Children's Health Research Institute (WCHRI) at the University of Alberta, Edmonton, who helped in coordinating this project. The authors are also thankful to Pam Marples and Rick Watts, members of Clinical Research Informatics Core (CRIC) at WCHRI, for their help with REDCap database for this study.

Contributors MK was involved with all stages of this study, wrote the first draft of the manuscript and approved the final manuscript. SC helped with the planning of the study, provided her inputs for manuscript writing and approved the final manuscript. ZI was involved in the planning of the study, data collection, reviewing of the manuscript and approved the final manuscript. Also, ZI received stipend support from Alberta Innovates-Health Solutions (AIHS) as a summer studentship award. AS was involved in the planning of the study, provided statistical support to the project, helped with data analysis and approved the final manuscript.

Funding The study (Study #1300) received funding from Covenant Health, Alberta. The authors have no competing interests (AIHS is a government body that provides summer studentship awards to hundreds of students each year without any restrictions).

Competing interests None.

Ethics approval The study was approved by the Health Research Ethics Board at the University of Alberta.

Provenance and peer review Not commissioned; externally peer reviewed.

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