

Risk factors for labor epidural conversion failure requiring general anesthesia for cesarean delivery

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Abstract

Background and Aims: To evaluate the rate and risk factors of labor epidural conversion failure requiring general anesthesia for Caesarean delivery (CD).

Material and Methods: Pregnant patients requiring conversion from labor to CD with a pre-existing labor epidural at our institution from 2009 to 2014 were identified. Through a retrospective review, we compared successful epidural conversion with those who required general anesthesia for CD. Patient characteristics were analyzed to identify risk factors for failed epidural conversion for CD.

Results: A total of 673 patients were included in the study. The rate of epidural conversion failure was 21%. Main risk factors for epidural conversion failure requiring general anesthesia included: younger maternal age (95% CI 0.94, $P = 0.0002$) and supplementation of intravenous fentanyl (95% CI 0.19, $P < 0.0001$) or midazolam (95% CI 0.26, $P = 0.0008$) during CD. A higher risk of conversion failure was also associated with a more urgent CD (CD category 1, 2, and 3 vs category 4).

Conclusion: Consistent with previous reports, young age and the urgency of CD increases the likelihood of epidural conversion failure. While conversion failure is likely multifactorial and complex, many of these factors are suggestive of inadequate and poorly functioning labor epidurals prior to CD. Prospective studies to further evaluate these factors are necessary, and the best prevention of epidural conversion failure is diligent diagnosis and evaluation of ineffective labor epidural analgesia prior to impending CD.

Keywords: Cesarean delivery, conversion rates, general anesthesia, labor epidural, obstetric anesthesia

Introduction

Epidural analgesia is the most effective method used to relieve labor pain. On the occasion that a laboring patient requires Caesarean delivery (CD), a previously placed labor epidural may be utilized to provide surgical analgesia.

However, not all labor epidurals are successfully converted to provide adequate analgesia for CD. The reported incidence of failure to convert an existing labor epidural to epidural anesthesia for CD varies largely depending on the criteria to define "failure".^[1]

In the event an epidural is unsuccessful in providing adequate surgical analgesia, the conversion to general anesthesia is often required. While the use of general anesthesia for obstetric patients is acceptable in these circumstances, certain risks do exist for both the patient and fetus. Some of these risks include airway manipulation and possible difficult intubation, aspiration, and exposure of mother and fetus to inhaled and intravenous anesthetics and analgesics.

The purpose of our study was to evaluate obstetric patients with labor epidurals who required CD, and our primary objective

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was to determine the incidence of failed epidural conversions for CD requiring general anesthesia at our institution. In addition, we evaluated potential characteristics that may be significant for increased epidural conversion failure.

Material and Methods

Following Institutional Review Board (IRB) approval on December 9, 2014, a retrospective chart review was performed at the Penn State Health Milton S. Hershey Medical Center, Hershey, Pennsylvania, United States. Subjects were all patients who received an epidural for labor analgesia and underwent CD from November 2009 through September 2014. The patients who received an epidural catheter for a scheduled C-section delivery without spontaneous or induced labor were excluded from the study.

We collected the following patient characteristics: age (years); weight (kg); body mass index; parity (nulliparous or multiparous); gestation; CD urgency; number of epidural attempts; interspinous level of the epidural catheter placement; depth of loss of resistance achieved on epidural placement (cm); epidural catheter length at skin (cm); epidural catheter length in epidural space (cm); use of combined spinal-epidural technique (yes or no); use of initial epidural bolus on placement (yes or no), initial epidural bolus medication type and amount (0.125% bupivacaine with fentanyl 2 mcg/ml [ml], 0.25% bupivacaine [ml], and fentanyl 50 mcg/ml [mcg]); initial epidural infusion rate (<8 ml/h or ≥ 8 ml/h), time of epidural infusion discontinuation prior to CD (<1 h or ≥ 1 h), epidural infusion rate at the time of discontinuation prior to CD (ml/h); duration of epidural infusion from initiation to discontinuation for CD (min); type and amount of local anesthetic for epidural bolus for CD conversion (lidocaine 2% [ml], bupivacaine 0.25% [ml], and bupivacaine 0.5% [ml]); adjuvant medications administered in epidural bolus for CD conversion (sodium bicarbonate, epinephrine, and fentanyl); and intravenous supplemental medications administered during CD (ketamine, fentanyl, and midazolam).

We defined epidural conversion failure as the requirement for general endotracheal anesthesia at any time prior to the start or during the surgical CD. Anesthesiology residents in our program participate in obstetric patient care, and typically perform the epidural procedure and manage the catheter infusion under supervision of a faculty anesthesiologist. The majority of epidural catheters are placed with the patient in a sitting position and using a midline technique. We use a standard epidural infusion for obstetric patients consisting of 0.125% bupivacaine with fentanyl 2 mcg/ml. The epidural

infusion is provided based upon patient-controlled epidural analgesia (PCEA) dosing, which includes a basal rate, bolus dose, lockout interval, and hourly maximum. An initial bolus dose of local anesthetic after the standard test dose mixture of lidocaine 1.5% with 1:200,000 epinephrine is typically administered by the anesthesiology team.

If emergent CD is necessary during labor, the anesthesiology team will discontinue the epidural infusion and provide a catheter bolus for surgical analgesia. In the event that the epidural does not provide adequate surgical analgesia, general endotracheal anesthesia is performed.

The urgency of C-section was classified by the obstetric team into the following categories: 1) immediate threat to life of mother or fetus, 2) maternal or fetal compromise not immediately life-threatening, 3) an early delivery necessary with no maternal or fetal compromise, 4) no maternal or fetal compromise and delivery can occur at any suitable time.^[2]

Statistical analysis

Logistic regression was used to analyze each potential characteristic as a risk factor for conversion of epidural to general anesthesia for CD. Results were quantified using odds ratio (OR) and 95% confidence interval (CI). All hypothesis tests were two-sided and conducted using SAS software version 9.4 (SAS Institute Inc., Cary, NC, United States).

Patient characteristics with multiple levels and large distributions were collapsed into binary variables for the analysis. Each CD urgency category 1–3 was independently compared to the least urgent category 4. The interspinous lumbar level of epidural catheter placement was compared independently to the lowest level of placement at L4-L5. The epidural infusion rate of the local anesthetic mixture was compared between an hourly basal rate of <8 ml/h and ≥ 8 ml/h, as 8 ml/h is a typical basal infusion rate used at our institution.

Results

A total of 678 charts were reviewed and 673 were included in the statistical analysis. Five patients were excluded due to incomplete information in the medical record. We found that 21% ($n = 142$) of labor epidurals used for CD during the study period at our institution required conversion to general anesthesia. During labor, all patients received a continuous epidural infusion solution containing 0.125% bupivacaine with fentanyl 2 mcg/ml, with an average basal rate of 8 ml/h. The descriptive statistics and results of the logistic regression analysis for patient characteristics can be found in Table 1. The results for binary epidural treatment characteristics are

in Table 2, and those for continuous epidural characteristics are in Table 3.

Women receiving labor epidural catheters within our institution, during the study time frame, ranged in age from 16 to 47 years. Younger age was associated with higher epidural conversion failure and requirement of general anesthesia for CD [Table 1], as the odds of requiring general anesthesia decreased by 6% for every 1-year increase in age ($P = 0.0002$, OR 0.94, [CI 0.90, 0.97]).

The degree of CD urgency correlated with the risk of epidural conversion failure to general anesthesia, with categories 1, 2, and 3 having higher rates than category 4. A comparison of interspinous levels of epidural placement found that less general anesthetic occurred for CD using the L3-L4 interspace when compared to the L4-L5 interspace [Table 2].

The local anesthetic type or bolus amount on initial catheter placement was not found to be significant for epidural failure requiring general anesthetic conversion. However, a catheter bolus for CD conversion with either 0.2% lidocaine ($P = 0.0046$, OR 0.57, [CI 0.38, 0.84]) or 0.5% bupivacaine ($P = 0.0269$, OR 0.57, [0.35, 0.94]) was associated with an increased epidural conversion failure to general anesthesia. In addition, adjuvant medications added to the local anesthetic epidural bolus for CD conversion were found to be independently significant, including fentanyl ($P = 0.0001$, OR 0.47 [CI 0.32, 0.69]) and epinephrine ($P = 0.0157$, OR 0.28, [CI 0.10, 0.79]), [Table 2].

The administration of supplemental intravenous medications to the mother during CD, including midazolam ($P = 0.0008$, OR 0.26, [CI 0.12, 0.57]) and fentanyl ($P = <0.0001$, OR 0.19, [CI 0.10, 0.35]), were significant for increased epidural conversion failure to general anesthesia.

Discussion

The etiology of epidural conversion failure and inadequate surgical analgesia is likely complex and multifactorial.^[1] At present, there is no consensus on definitive risk factors

making epidural conversion failure for CD more likely. An understanding of these risk factors may help increase the efficacy of epidurals for CD analgesia and decrease the risk of exposure for obstetric patients to general anesthesia.

The incidence of epidural conversion failure for CD at our institution was higher than reported by others. Previous studies, including both retrospective and prospective ones, have reported epidural conversion failure rates as low as 1.7% and up to 19.8%.^[3-7] This wide range may represent varying patient populations between institutions and database studies, as well as variable definitions of “failure of conversion.” Such a wide range of epidural conversion failure is also supportive of complex multifactorial mechanisms leading to inadequate analgesia.

In our study, we were able to identify several characteristics significant to increased epidural conversion failure for CD, and one among these was younger age. A 6-month prospective study previously reported that younger age was associated with higher epidural conversion failure.^[5]

The urgency classification of CD was found to be significant for increased epidural conversion failure for each category 1, 2, and 3, when compared to the least urgent category 4. This is consistent with a previous prospective audit in which the highest epidural conversion failure was found in category 1 urgency,^[4] as well as several systematic reviews that indicate increased urgency of CD is associated with higher epidural conversion failure.^[8,9] The more urgent the CD, the less time is expected for fetal delivery to ensure safety of the fetus and mother. Therefore, less time is available for the anesthesiologist to bolus the epidural catheter with local anesthetic for CD and wait for adequate surgical anesthesia, making general anesthesia a more rapid choice.

Interestingly, we also found that the interspinous level of epidural catheter placement was associated with higher incidence of epidural conversion failure, with level L3-L4 more likely for failure when compared to L4-L5. This has not been reported previously and supports the choice for a lower lumbar level, L4-L5, for epidural placement. The selection of interspinous spaces is determined typically by palpation and

Table 1: Patient characteristics

Variable	Failed Epidural Conversion Requiring General Anesthesia				Odds Ratio	P
	No		Yes			
	n	Mean (SD)	n	Mean (SD)		
Age (years)	531	29.01 (5.73)	142	26.99 (5.13)	0.94	0.0002
Weight (kg)	529	89.75 (39.69)	142	88.19 (22.20)	1.00	0.6580
Body Mass Index (kg/m ²)	494	33.65 (6.37)	134	33.36 (7.06)	0.99	0.6434

Legend: n=Number, SD=Standard Deviation

Table 2: Binary treatment characteristics

Variable	Subtype	Frequency	Odds Ratio	P
CD Urgency Classification (n=638) *Compared to Urgency Class 4	Category 1	8 (1%)	16.62	0.0007
	2	32 (5%)	9.23	<0.001
	3	199 (31%)	1.7	0.0132
	4	399 (63%)		
Parity (n=667)	Nulliparous	552 (83%)	1.47	0.1039
	Multiparous	115 (17%)		
Gestation (n=668)	<37 weeks	36 (5%)	0.80	0.5732
	≥37 weeks	632 (95%)		
Number of Epidural Attempts (n=669)	1	633 (95%)	1.95	0.681
	>1	36 (5%)		
Interspinous Level of Catheter (n=644) *Compared to L4-L5 Level	L1-L2	10 (1%)	0.69	0.7325
	L2-L3	103 (16%)	1.59	0.2120
	L3-L4	423 (66%)	1.87	0.0377
	L4-L5	108 (17%)		
CSE Technique (n=662)	Yes	652 (98%)	0.42	0.4095
	No	10 (2%)		
Initial Epidural Bolus (n=671)	Yes	499 (74%)	1.22	0.3691
	No	172 (26%)		
Initial Bolus Medication (n=490)	Bupivacaine 0.125% with Fentanyl 2 mcg/ml	314 (64%)	1.32	0.1430
	Bupivacaine 0.25%	123 (25%)	0.83	0.4709
	Fentanyl 50 mcg/ml	53 (11%)	0.98	0.9492
Initial Epidural Infusion Rate (n=659)	<8 ml/h	118 (18%)	1.10	0.7015
	≥8 ml/h	541 (82%)		
Time Infusion Discontinued Prior to CD (n=557)	<1 Hour	492 (88%)	1.40	0.2767
	≥1 Hour	65 (12%)		
Local Anesthetic Bolus for CD (n=713)	Lidocaine 2%	486 (68%)	0.57	0.0046
	Bupivacaine 0.25%	76 (11%)	1.39	0.2381
	Bupivacaine 0.5%	151 (21%)	0.57	0.0269
Adjuvants Added to Local Anesthetic Bolus for CD (n=496)	Sodium Bicarbonate	97 (17%)	1.45	0.1381
	Epinephrine	54 (9%)	0.28	0.0157
	Fentanyl	345 (60%)	0.47	0.0001
Placement of Spinal Prior to CD (n=663)	Yes	112 (17%)	0.36	0.0024
	No	551 (83%)		
Supplemental IV Medications During CD (n=315)	Ketamine	32 (10%)	0.24	0.0517
	Fentanyl	187 (59%)	0.19	<0.0001
	Midazolam	96 (31%)	0.26	0.0008

Legend: CD=Caesarean Delivery, n=Number, CSE=Combined Spinal-Epidural Technique, IV=Intravenous

Table 3: Continuous epidural characteristics

Variable	General Anesthesia Conversion				Odds Ratio	P
	No		Yes			
	n	Mean (SD)	n	Mean (SD)		
Loss of Resistance During Placement (cm)	508	5.96 (1.17)	136	5.92 (1.15)	0.97	0.7591
Catheter at Skin (cm)	508	11.09 (1.32)	136	11.08 (1.31)	0.99	0.9286
Catheter Length in Epidural Space (cm)	508	5.13 (0.65)	134	5.16 (0.57)	1.07	0.6787
Initial Bolus Dose of 0.125% Bupivacaine with Fentanyl 2 mcg/ml (ml)	239	6.93 (2.65)	73	6.82 (2.65)	0.98	0.7476
Initial Bolus Dose of 0.25% Bupivacaine (ml)	96	7.70 (2.52)	23	6.98 (2.59)	0.89	0.2210
Initial Bolus Dose of Fentanyl (mcg)	42	87.48 (25.56)	10	67.80 (40.36)	0.98	0.0723
Infusion Rate Prior to CD (ml/h)	512	8.08 (1.59)	134	8.32 (2.89)	1.06	0.2061
Duration of Infusion Prior to CD (min)	419	38.89 (43.93)	98	33.21 (26.71)	1.00	0.2237
Lidocaine 2% Bolus Dose Prior to CD (ml)	396	14.71 (5.78)	89	14.54 (5.69)	0.99	0.8054
Bupivacaine 0.25% Bolus Dose Prior to CD (ml)	55	9.05 (3.67)	19	7.11 (3.51)	0.84	0.0531
Bupivacaine 0.5% Bolus Dose Prior to CD (ml)	124	9.67 (5.55)	22	8.18 (2.48)	0.92	0.1957

Legend: n=Number, SD=Standard Deviation, CD=Caesarean Delivery

anatomical landmarks, and it is possible that providers may be choosing a space above or below the space they actually desire.^[10] For this reason, it would be reasonable to choose a

lower space to avoid a level closer to the spinal cord, which typically ends at L1 in adults,^[11] but can end even lower, at L2, in a subset of adults.^[12]

The use of either lidocaine 2% or bupivacaine 0.5% as an epidural catheter bolus dose for CD conversion was found to increase epidural conversion failure to general anesthesia. Both lidocaine 2% and bupivacaine 0.5% are common local anesthetics for epidural analgesia and are used widely by anesthesiologists for labor epidural conversion to CD.^[3,13] Interestingly, a meta-analysis found that the use of bupivacaine 0.5% was associated with increased intraoperative supplementation for analgesia when compared to lidocaine 2% and ropivacaine 0.75% during CD.^[14] This might be explained by potential local anesthetic tachyphylaxis from continuous epidural during labor, thus, requiring a higher concentration of local anesthetic bolus for adequate surgical analgesia during CD.^[14,15] While this may explain the higher incidence of epidural conversion failure with either lidocaine 2% or bupivacaine 0.5% bolus for CD, we did not find that the volume (ml) of the local anesthetic administered for CD conversion was associated with epidural failure. This indicates that the concentration of local anesthetic is less likely a direct contributor to epidural conversion failure, making the suggestion that the epidural catheters in question were more likely to poorly functioning prior to CD.

Moreover, the prompt diagnosis and treatment of breakthrough pain and inadequate labor epidural analgesia are thought to be a key in the successful use of epidural conversion for C-section.^[1,16] Thus, patients with breakthrough pain, or requiring increased epidural bolus doses during labor, are more likely to experience epidural conversion failure.^[3,6] This may indicate that an epidural catheter is less likely to provide complete surgical analgesia required for C-section.

The use of either intrathecal fentanyl or epinephrine as an adjunct to the epidural local anesthetic bolus for CD conversion was associated with increased epidural conversion failure. It was previously reported that the use of epidural fentanyl as an adjunct in local anesthetic for CD conversion was not preventative for epidural failure. Therefore, it was suggested that maximal epidural opioid analgesic effects may already be obtained during labor epidural catheter infusion with fentanyl admixture.^[17] Thus, the use of adjunct medications with the local anesthetic bolus for CD conversion may imply an already poorly functioning labor epidural. As a result, anesthesiologists may attempt to supplement the epidural bolus with fentanyl or epinephrine prior to imminent CD conversion.

Another consideration is the use of supplemental intravenous medications during CD and risk of epidural conversion failure. We found that the use of intravenous fentanyl and midazolam to be associated with a higher incidence of epidural conversion failure. During CD, surgical manipulation and uterus externalization may increase visceral pain and

require analgesic supplementation.^[1] However, the use of intravenous fentanyl and midazolam may also be indicative of an inadequate epidural catheter for analgesia or emotional distress and psychologic factors that may require general anesthesia.

Interestingly, we did not find that BMI was associated with increased epidural conversion failure. Mixed results linking BMI as a positive predictor of epidural conversion failure have been reported.^[3,5] Epidural insertions may be more difficult in patients with higher BMI, and perhaps the anesthesiology team may take more care at insertion with a lower threshold to replace a non-working epidural early in delivery for these patients. This may explain why BMI was not associated with increased epidural conversion at our institution.

There are several limitations to our study, including its retrospective design. Our study was not designed to analyze emotional factors such as anxiety and distress during labor and CD, which may contribute to epidural conversion failure requiring general anesthesia. In addition, outside of the urgency classification of CD, we did not examine surgical influences that may increase the likelihood of epidural conversion failure, such as the degree of uterine externalization. Uterine externalization is routinely used in our institution, thereby contributing to an increased incidence of visceral pain during CD. This may explain a higher rate of epidural conversion failure at our institution, and requires more investigation. More prospective studies to further examine the causes of epidural conversion failure for CD are warranted.

In conclusion, we identified several factors associated with increased labor epidural conversion failure for CD requiring general anesthesia. While it is clear from our study and previous reports that the urgency classification of CD is a significant risk for epidural conversion failure, we report several newly identified risk factors for consideration. The actual mechanism of epidural conversion failure is likely multifactorial and complex, and many factors that we have identified are also suggestive of an inadequate or poorly functioning labor epidural prior to CD. While further prospective research is still necessary, we agree with previous investigators that the best prevention of epidural conversion failure for CD is the aggressive diagnosis and treatment of inadequate labor epidural analgesia prior to the impending need for CD.^[1,16]

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Conflicts of interest

There are no conflicts of interest.

References

1. Portnoy D, Vadhera RB. Mechanisms and management of an incomplete epidural block for cesarean section. *Anesthesiol Clin North Am* 2003;21:39-57.
2. Lucas DN, Yentis SM, Kinsella SM, Holdcroft A, May AE, Wee M, *et al.* Urgency of caesarean section: A new classification. *J R Soc Med* 2000;93:346-50.
3. Halpern SH, Soliman A, Yee J, Angle P, Ioscovich A. Conversion of epidural labour analgesia to anaesthesia for Caesarean section: A prospective study of the incidence and determinants of failure. *Br J Anaesth* 2009;102:240-3.
4. Lee S, Lew E, Lim Y, Sia AT. Failure of augmentation of labor epidural analgesia for intrapartum cesarean delivery: A retrospective review. *Anesth Analg* 2009;108:252-4.
5. Orbach-Zinger S, Friedman L, Avramovich A, Ilgiaeva N, Orvieto R, Sulkes J, *et al.* Risk factors for failure to extend labor epidural analgesia to epidural anesthesia for Cesarean section. *Acta Anaesthesiol Scand* 2006;50:793-7.
6. Paech MJ, Godkin R, Webster S. Complications of obstetric epidural analgesia and anaesthesia: A prospective analysis of 10,995 cases. *Int J Obstet Anesth* 1998;7:5-11.
7. Rafi MA, Arfeen Z, Misra U. Conversion of regional to general anaesthesia at caesarean section: Increasing the use of regional anaesthesia through continuous prospective audit. *Int J Obstet Anesth* 2010;19:179-82.
8. Bauer ME, Kountanis JA, Tsen LC, Greenfield ML, Mhyre JM. Risk factors for failed conversion of labor epidural analgesia to cesarean delivery anesthesia: A systematic review and meta-analysis of observational trials. *Int J Obstet Anesth* 2012;21:294-309.
9. Mankowitz SK, Gonzalez Fiol A, Smiley R. Failure to extend epidural labor analgesia for cesarean delivery anesthesia: A focused review. *Anesth Analg* 2016;123:1174-80.
10. Whitty R, Moore M, Macarthur A. Identification of the lumbar interspinous spaces: Palpation versus ultrasound. *Anesth Analg* 2008;106:538-40, table of contents.
11. Chin KJ, Karmakar MK, Peng P. Ultrasonography of the adult thoracic and lumbar spine for central neuraxial blockade. *Anesthesiology* 2011;114:1459-85.
12. Preeti MC. MRI Study of level of termination of spinal cord (Conus Medullaris). *Int J Sci Res* 2016;5:122-4.
13. Regan KJ, O'Sullivan G. The extension of epidural blockade for emergency Caesarean section: A survey of current UK practice. *Anaesthesia* 2008;63:136-42.
14. Hillyard SG, Bate TE, Corcoran TB, Paech MJ, O'Sullivan G. Extending epidural analgesia for emergency Caesarean section: A meta-analysis. *Br J Anaesth* 2011;107:668-78.
15. Mogensen T, Hjortso NC, Bigler D, Lund C, Kehlet H. Unpredictability of regression of analgesia during the continuous postoperative extradural infusion of bupivacaine. *Br J Anaesth* 1988;60:515-9.
16. Bauer ME, Mhyre JM. Active management of labor epidural analgesia is the key to successful conversion of epidural analgesia to cesarean delivery anesthesia. *Anesth Analg* 2016;123:1074-6.
17. Malhotra S, Yentis SM. Extending low-dose epidural analgesia in labour for emergency Caesarean section-A comparison of levobupivacaine with or without fentanyl. *Anaesthesia* 2007;62:667-71.