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Epidural analgesia associated with low-dose oxytocin augmentation increases cesarean births: A critical look at the external validity of randomized trials

Andrew J. Kotaska, MD,[a] Michael C. Klein, MD,[b] Robert M. Liston, MD[a]

Department of Obstetrics and Gynaecology,[a] Department of Family Practice,[b] University of British Columbia, Vancouver, British Columbia, Canada

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KEY WORDS
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Objective: Randomized controlled trials suggest epidural analgesia (EA) does not increase the frequency of cesarean births compared with opioid analgesia. We analyzed trials comparing EA with opioid analgesia to determine their external validity in contemporary North American practice.

Study design: Randomized controlled trials comparing EA with opioid analgesia were identified from the Cochrane database and Medline and included if they reported labor outcomes and management protocols. Labor management was then compared with current obstetric practice determined from surveys of North American teaching maternity units and clinical practice guidelines.

Results: Of 19 trials identified, 8 were included. Seven trials used Active Management of Labor protocols that used high-dose oxytocin; each demonstrated no epidural-related increase in cesarean births. One trial that used low-dose oxytocin demonstrated a marked increase in cesarean births. Most large North American obstetric units use low-dose oxytocin.

Conclusion: Randomized trials showing no effect of EA on cesarean section (CS) rate lack external validity in much of North American practice. The limited data available suggest EA and low-dose oxytocin used together increase the CS rate. Early detection of dystocia and high-dose oxytocin augmentation should be considered for women receiving EA; those delivering in low-dose oxytocin settings should be advised of a probable increase in the likelihood of CS.

The strengths of randomized controlled trials (RCTs) have vaulted them to the status of gold standard among research methodologies. Nonetheless, generalizability of their results to individual patients and practice settings remains a concern.[1,2] RCTs and systematic reviews have evolved sophisticated methods of assessing and reporting the internal validity of trials, while largely neglecting issues of external validity.[1] A trial must be internally valid to be external valid, but internal validity alone does not ensure generalizability. Assessing external validity requires a comparison of trial conditions and subjects with real-world clinical settings and populations. Such assessments are rare in the literature, leaving

Reprints not available from the authors. Address correspondence to Andrew J. Kotaska, University of British Columbia, Department of Obstetrics & Gynaecology 2H30, B. C. Women's Hospital, 4490 Oak Street, Vancouver, B. C. V6H3V5, Canada

E-mail: Kotaska@bulkley.net

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Table I Randomized trials comparing EA with opioid analgesia: Trial characteristics and analgesia regimens

Study	n			Cross-over		Bupivicaine	Fentanyl	Meperidine	
	O	E	% P_0	O→E	E→O	Conc.	Conc.	Dose (mg)	PRN Interval
Bofill et al[3]	51	49	100	24%	4%	0.125%	1.5 μg/mL	*	q1-2 h
Clark et al[4]	162	156	100	52%	3%	0.125%	1 μg/mL	50-75 IV	q90 min
Howell et al[9]	185	184	100	28%	N/A	0.25%	—	50-100 IM	N/A
Loughnan et al[5]	310	304	100	56%	14%	0.125%	—	100 IM	q2 h × 3
Ramin et al[6,†]	437	432	56	—	—	0.125%	2 μg/mL	50 IV	Max 200/4 h
Ramin (ITT)	666	664	52	15%	N/A	0.125%	2 μg/mL	50 IV	Max 200/4 h
Sharma et al[7]	357	358	54	2%	1%	0.125%	2 μg/mL	50 IV PCA	10-15 mg q10 min
Sharma et al[8]	233	226	100	6%	N/A	0.0625%	2 μg/mL	50 IV PCA	15 mg q10 min
Thorp et al[16]	45	48	100	2%	0	0.125%	—	75 IV	q90 min

O, Opioid; *E,* epidural; *P_0,* nulliparous; *IV,* intravenous; *IM,* intramuscular; *ITT,* intention to treat analysis; *PCA,* patient controlled analgesia.

* Butorphanol 1-2 mg IV q1-2 h.

† Protocol-compliant subjects only.

most decisions regarding the external validity of evidence up to individual practitioners.

The effect of epidural analgesia (EA) on labor progress and delivery outcome has been controversial for decades. Early retrospective reports showing increased cesarean section (CS) rates associated with EA have since been refuted by RCTs.[3-9] The current Cochrane meta-analysis comparing EA with opioid analgesia found no increase in CS rate and better analgesia with EA. However, EA prolonged labor, increased fetal malposition, oxytocin augmentation and instrumental delivery, and was associated with more maternal fever and hypotension, but no difference in neonatal outcome.[10]

Additional systematic reviews have reached similar conclusions, leading to consensus within obstetric and anesthesia circles that EA does not increase the risk of CS.[11,12] The American College of Obstetricians and Gynecologists (ACOG) committee opinion on pain relief during labor reflects this belief: EA provides the best pain relief during labor and a woman's request for one is indication enough to provide it.[13] Accordingly, from 1981 to 1997, epidural usage increased from 22% to 66% of all US births.[8] Paralleling the sharp rise in epidural usage has been a rise in CS rate. The discrepancy between high contemporary CS rates and the low CS rates reported in trials forming the Cochrane meta-analysis prompted us to examine the external validity of published RCTs in contemporary North American practice.

Material and methods

All RCTs comparing EA with parenteral opioid analgesia in labor were identified from the 2003 Cochrane meta-analysis and Medline (1966-2003). Trials involving low-risk singleton cephalic term pregnancies were included if they described labor management practices and reported labor outcomes, including the incidence of CS. Information on subject parity, labor management, oxytocin augmentation, and delivery method were summarized. Trial research methodology was reviewed, but our focus was on external rather than internal validity. The University of British Columbia's Research Ethics Board approved the study.

Questionnaires were sent to the Obstetrics and Gynecology department chairs of all 17 Canadian medical schools. Data on labor management practices, oxytocin protocols, EA availability, and CS rates were requested, and incomplete responses were followed up by telephone. A convenience sample of 10 large US maternity units was determined from a geographically broad but otherwise nondirected Internet search of academic department and hospital Web sites. Similar information was obtained by telephone or email from attending, resident, or nursing staff; however, information on CS rates and Active Management of Labor (AML) use were not reliably available. ACOG and Society of Obstetricians and Gynaecologists of Canada (SOGC) dystocia and labor management guidelines were reviewed.[14,15] Labor management practices in academic North American practice were then compared with those found within RCTs comparing epidural with opioid analgesia.

Results

Of 19 randomized trials identified, 8 were included: 5 from the 2003 Cochrane review[3,4,6,7,16] and 2 from Medline.[5,8,9] Eleven trials were excluded because labor management and/or outcome data were lacking (8), because they were subsets of other trials (1), or because they were in abstract form only (2). Included trials are summarized in Tables I and II. All 8 trials, except Ramin et al, reported an intention-to-treat analysis. Intention-to-treat data for Ramin has since been published and is included separately.[17] All trials required women to be in active labor before analgesia was administered and included only