2016

Does Oral Gabapentin Administered Prior to Scheduled Cesarean Delivery Decrease Pain With Movement in Adult Women at 24 Hours as Compared to Placebo?

Ashley E. Boller
Philadelphia College of Osteopathic Medicine, ashleybol@pcom.edu

Does Oral Gabapentin Administered Prior to Scheduled Cesarean Delivery Decrease Pain with Movement in Adult Women at 24 Hours as Compared to Placebo?

Ashley E. Boller, PA-S

A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

In Partial Fulfillment of the Requirements For

The Degree of Master of Science

In

Health Sciences – Physician Assistant

Department of Physician Assistant Studies

Philadelphia College of Osteopathic Medicine

Philadelphia, Pennsylvania

December 18, 2015

ABSTRACT

OBJECTIVE: The objective of this selective evidence based medicine review is to determine whether or not oral gabapentin administered prior to scheduled cesarean delivery decreases pain with movement in adult women at 24 hours postpartum as compared to placebo. DESIGN: Review of three English language, peer-reviewed, primary studies published after 2000. SOURCES: Three randomized, placebo-controlled trials comparing the efficacy of oral gabapentin to a lactose placebo in adult women undergoing elective cesarean delivery. Sources were selected from PubMed, Medline, Ovid, and the Cochrane Database to include all studies matching the keywords that were published in peer-reviewed, English language journals after 2000 and included only women over 18 years of age. OUTCOMES MEASURED: Primary outcome measured was patient reported pain perception on a 0-100mm Visual Analog Scale (VAS - 0 = no pain, 100 = worst possible pain) measured 24 hours post cesarean section. Satisfaction with pain management, as measured by a numerical rating scale (0-10) was considered secondarily. RESULTS: Two of the three studies found significant improvement in post-cesarean delivery analgesia and satisfaction with analgesia with adjunctive gabapentin therapy at doses of 600mg and 300mg respectively. A third study investigated both dosages, but found no clinical benefit to either. CONCLUSIONS: Evidence is inconclusive as to whether oral gabapentin administered prior to scheduled cesarean delivery decreases pain with movement in adult women at 24 hours postpartum as compared to placebo.
KEY WORDS: Gabapentin, Pregnancy, Cesarean Section, Cesarean Delivery.

INTRODUCTION

Cesarean delivery is the most commonly performed surgical procedure in the United States and accounts for roughly 30% of all deliveries.[1] While traditionally indicated for high-risk pregnancies in which vaginal delivery would result in increased maternal or fetal mortality, it has become increasingly common in recent decades as women without medical indication request the procedure. Estimates of prevalence for cesarean delivery by maternal request are as high as 18% of all deliveries worldwide and 2.5% in the United States.[1,2] Patient reported reasons for elective cesarean delivery include convenience of scheduled delivery, fear of pain and childbirth, as well as poor past experiences with spontaneous vaginal delivery.[2] Additionally, elective cesarean delivery proffers a number of medical benefits to both the mother and fetus, including decreased risk of pelvic floor injury, fetal shoulder dystocia, maternal-fetal transmission of herpes simplex virus and human immunodeficiency virus, and late-term still birth.[2]

Despite the benefits, cesarean delivery also presents a number of unique risks to both mother and fetus. Studies indicate that patients are most concerned about intra- and post-operative pain from cesarean delivery, and for good reason; one of the most commonly reported complications from cesarean delivery is pain.[3] The mechanism for this is not well understood. Contributing factors may include unopposed central sensitization of nociceptors, neuropathic sensitization following nerve entrapment, and incision type.[4] Access to the abdomen and uterus is typically gained via a Pfannenstiel-type incision, which may result in entrapment of the iliohypogastric and ilioinguinal nerves and chronic pelvic pain months after the procedure.[4,5]

Cesarean section pain is typically managed with a combination of anesthetics and analgesics. Intra-operative bupivacaine is most commonly employed for spinal anesthesia, while lidocaine with epinephrine is most commonly employed in epidural anesthesia; both may be used

with adjunctive opioids or fentanyl to provide analgesia for 18-24 hours.[6] Post-operative analgesia is typically achieved with a multimodal approach including patient-controlled IV morphine, non-steroidal anti-inflammatory drugs, and acetaminophen.[6]

Opioid analgesia, however, poses many potential risks and may be inappropriate in patients who are opioid naïve, have allergies to opiates, or suffer from an opiate addiction.[7,8] Morphine products like Astramorph/PF, Infumorph, and Duramorph, carry warnings for overdose and resuscitation in the setting of epidural/intrathecal administration, and their use post-operatively have been noted to negatively affect the heart rate of the fetus and result in respiratory depression of the breastfeeding newborn.[7] These findings are supported by studies demonstrating a longer time to first interaction between mother and baby, longer times to breast feeding, decreased ability to breast feed, decreased maternal-fetal bonding, and decreased satisfaction with the birthing experience associated with opioid pain management following cesarean delivery.[3,8,9]

Furthermore, chronic pain following cesarean delivery has substantial impact on the cost of healthcare. In 2008, cesarean delivery with complications, such as prolonged pain, resulted in an additional two days hospitalization over vaginal delivery (mean 4.5 days vs. 2.6 days) and accounted for 46% of hospital delivery costs.[10] Of those deliveries with complications, it is estimated that 12.3% specifically result in debilitating pain that affects infant care within the first 6 months postpartum, accounting for $3.1 billion of hospital delivery costs.[10]

With the number of adverse effects and the overwhelming costs of care associated with chronic, debilitating pain following cesarean delivery, alternative methods of pain control are essential. Gabapentin, a centrally-acting calcium channel alpha 2-delta ligand used in the management of neuropathic pain, is a relatively safe alternative that has been shown to be

effective in decreasing acute post-surgical pain in similar procedures, such as total hysterectomy.[8] Although classified as pregnancy category C, studies have yet to demonstrate increased maternal-fetal risk from gabapentin exposure within hours of delivery. Gabapentin is excreted in breast milk at a rate of 1 mg/kg/day; the effect that this has on newborns is unknown.[7]

OBJECTIVE

The objective of this selective EBM review is to determine whether or not oral gabapentin administered prior to scheduled cesarean delivery decreases pain with movement in adult women at 24 hours postpartum as compared to placebo.

METHODS

Three studies were included in the analysis. All studies were randomized, double-blind, placebo-controlled trials investigating the efficacy of oral gabapentin administered prior to delivery compared to a visually-matched, lactose placebo in adult women undergoing elective cesarean delivery. The primary outcome measured was pain with movement at 24 hours post-operation. Studies also measures satisfaction with pain management. [8,11,12]

Sources were queried from PubMed, Medline, Cochrane Database, and OVID to include English-language studies of adult women in peer-reviewed journals published after 2000. Articles were selected by the author based on their relevance to the clinical question. Articles were excluded if they were published outside of the search window, were not published in a peer-reviewed publication, were not in English, or included women younger than 18 years of age. Additionally, articles were excluded if they had appeared in prior meta-analyses or

systematic reviews of similar clinical inquiries. Key words included gabapentin, pregnancy, cesarean delivery, and cesarean section.

OUTCOMES MEASURED

The primary outcome for all three studies was patient reported pain perception with movement as measured by a 0-100mm Visual Analog Scale (VAS - 0 = no pain, 100 = worst possible pain) 24 hours post cesarean section. [8,11,12] Moore et al[8] and Short et al[12] further defined primary outcomes as VAS scores 6, 12, and 48 hours post-cesarean section with movement and at rest, as well as at three months post-operatively. Anaraki et al[11] also defined primary outcomes as time to first request for supplemental analgesia and total dose of supplemental analgesia required.

Secondary measures varied by study. All three studies measured patient satisfaction with intra- and post-operative analgesia. [8,11,12] Moore et al[8] and Anaraki et al[11] utilized a 0-10 numerical rating scale (NRS). Short et al[12] used a 0-100 VAS (0 = not satisfied, 100 = completely satisfied). Safety and tolerability were assessed by Moore et al[8] and Short et al[12] using a patient reported numerical rating scale of 0-3 for level of sedation, nausea, vomiting, dizziness, and pruritus. Anaraki et al[11] do not explicitly monitor for safety and tolerability, but report nursing assessments of nausea, sedation, and pruritus.

RESULTS

Study Designs and Subject Selection

Study subjects were enrolled from either an internationally-regarded Canadian tertiary care hospital[8,12] or a Middle-Eastern teaching hospital.[11] Subjects were English-speaking women

over 18 years of age presenting at term for elective cesarean delivery on an inpatient basis. Gravity and parity were null factors in subject selection in two studies;[8,12] the third excluded all multiparous women.[11] Patients were excluded from participation if they had moderate to severe systemic illness as evidenced by an ASA Physical Status Score of 3 or greater; infectious diseases, including HIV and hepatitis; uncontrolled hypertension or diabetes mellitus; contraindications to neuraxial anesthesia/study medications; or had taken pain medications one week prior to surgery. Patients were also excluded if they were known IV drug users or were carrying fetuses with known congenital abnormalities. All three studies utilized a demographically-matched placebo-controlled group.[8,11,12]

Dosing of gabapentin varied by study, with Moore et al[8] dosing 600mg orally, Anaraki et al[11] dosing 300mg orally, and Short et al[12] dosing both 600mg and 300mg orally. The variable dosing accounts for the lack studies demonstrating replicable therapeutic levels of gabapentin for peri-operative pain and attempts to find the minimum necessary therapeutic dosage.[6,7,12] One study administered gabapentin two hours pre-operatively[11] and the other two studies administered the study drug one hour pre-operatively.[8,12] Compliance was 100%, as only one dose was required and was administered by study staff prior to surgery.

Intra-operative anesthesia was managed similarly across studies and consisted of either 0.75% bupivacaine [8,12] or 0.5% bupivacaine.[11] Moore et al[8] and Short et al[12] augmented the anesthesia with 10μg fentanyl and 100μg morphine, per hospital protocol, for all subjects, regardless of study arm. Anaraki et al[11] additionally administered 10μg fentanyl intrathecally to the control group only to mitigate pain. In all studies, subjects were able to request additional opioid analgesia post-operatively to augment pain management.

A summary of selected studies is presented in Table 1.

Moore et al[8]

A total of 46 subjects were distributed evenly to each arm of the study, with two excluded from analysis in the gabapentin group due to unblinding and spontaneous vaginal delivery. VAS scores were compared using a repeated measures analysis of variance (ANOVA). Categorical data, such as satisfaction and adverse event severity, were analyzed by χ^2, Fisher exact test, or Mann-Whitney *U* test. At 24 hours post cesarean delivery, the gabapentin group showed significantly less pain with movement than the placebo group, with mean VAS scores (95% CI) of 21mm (13-29) and 41mm (32-51), respectively (P = 0.001). Subjects in the gabapentin group were also significantly more satisfied with their pain management than the subjects in the placebo group at 24 hours (NRS, p=0.02). 5 subjects in each group requested supplemental morphine. There was no significant difference in the amount of supplemental morphine dosed. Mean total supplemental morphine (95% CI) for the gabapentin group was 4.2mg (1.1-7.2) and 3.2mg (1.0-5.4) for the placebo group (p=0.58).

Short et al [12]

A total of 132 subjects were distributed evenly to each arm of the study, with 6 excluded from analysis for failed spinal (3), protocol breach (2), or postponed procedure (1). VAS scores were compared using a repeated measures analysis of variance (ANOVA) with Bonferroni correction (pairwise $\alpha = 0.05 / 3$ comparisons $= 0.016$) for multiple comparisons across the three treatment groups. Categorical data, such as adverse event severity and NICU admission, were analyzed by Fisher exact test or nonparametric Kruskal-Wallis tests.

At 24 hours post cesarean delivery, there were no significant differences between groups in pain scores with movement (overall p=0.61). Comparison of the 600mg gabapentin group to the 300mg gabapentin group revealed improved pain control with the lower dose that was not significant (mean difference = 5mm with 95% adjusted CI = -7 to 17). Comparison of 300mg to placebo reveals a non-significant improvement in pain control (mean difference = -2mm with 95% adjusted CI = -14 to 10). 38 total subjects requested supplemental morphine. There was no significant difference in the amount of supplemental morphine dosed. Mean total supplemental morphine (95% CI) for the gabapentin 300mg group was 5.7mg (1.3-10.2), 6.7mg (4.7-8.8) for the gabapentin 600mg group, and 7.9mg (5.9-9.9) for the placebo group (p=0.46).

Anaraki et al [11]

A total of 78 subjects were distributed evenly to each arm of the study, with one excluded from analysis in the gabapentin group due to failure of the spinal block. VAS scores, maternal satisfaction, and supplemental morphine usage were analyzed by χ^2 or Mann-Whitney *U* test. At 24 hours post cesarean delivery, the gabapentin group showed significantly less pain with movement than the placebo group, with mean VAS scores (95% CI) of 24mm (13-30) and 38mm (24-56), respectively (P = 0.001). Subjects in the gabapentin group were also significantly more satisfied with their pain management than the subjects in the placebo group at 24 hours (NRS mean (range) = 7 (4-10) gabapentin, 5 (1-9) placebo; p=0.001). Authors did not report how many subjects in each group required supplemental morphine; however, in those subjects who did receive supplemental morphine, the time to first dose was significantly longer in the gabapentin group compared to placebo (mean hours (SD) = 4.59 (1.63) gabapentin, 2.65 (0.92) placebo; p=0.000). Subjects in the gabapentin group requesting supplemental morphine also requested

less than the placebo group. Mean total supplemental morphine (SD) for the gabapentin group was 7.18mg (3.26) and 12.62mg (5.16) for the placebo group (p=0.000).

Safety and Tolerability

A well reported side effect of gabapentin use is sedation.[7,12] The selected studies provide further evidence for this effect. Moore et al[8] demonstrate a significant difference in incidence of severe sedation between gabapentin and placebo groups (19% vs. 0%, p=0.04) and note that severe sedation occurred early, as there were no reports of sedation after 24 hours. Severe sedation was not correlated with VAS pain ratings or satisfaction scales, although R values are not reported.

Short et al[12] refutes this claim, finding no increase in maternal sedation with either 600mg of gabapentin or a reduced dose of 300mg. They posit that the findings of the 2011 study were the result of researcher bias. However, Anaraki et al[11] document increased sedation at a dose of 300mg compared to the placebo group (p=0.012).

Independent analyses of the combined reported adverse events in these three studies supports this data (Table 2). The most deleterious adverse event encountered was nausea (NNH = 27.2). Comparatively, sedation was relatively mild (NNH = 488.48) and pruritus least likely (NNH = 767.96).

Neonatal outcomes were similar for all participants in all studies (Table 3).

DISCUSSION

Two of the three studies found significant improvement in post-cesarean delivery analgesia and satisfaction with analgesia with adjunctive gabapentin therapy at doses of 600mg

and 300mg respectively. [8,11] Dose finding studies in other surgical situations indicate that a typical dose of 300-1200mg pre-operatively may be effective.[12] Short et al varied the doses accordingly, studying both 300 and 600mg doses, but found no clinical benefit.[12]

Gabapentin is capable of potentiating the effect of morphine, leading to prolonged analgesia and marked CNS depression.[7] While the included studies demonstrated relative safety of the drug during labor and delivery and in the immediate postpartum period, patients must be counseled about, and monitored for, common side effects of gabapentin administration, including increased sedation, angioedema, multi-organ hypersensitivity (DRESS syndrome), and suicidal ideation.[7] Additionally, providers should use gabapentin with caution in patients with impaired renal function, as gabapentin is renally-excreted.[7]

Moreover, care providers should take into consideration cost and coverage of drugs used during labor and delivery. The wholesale cost for the dosages of gabapentin used in the included studies are $252.62 per 100 tablets ($2.53/dose) for gabapentin 600mg and $133.20 per 100 tablets ($1.33/dose). This is in adjunct to the standard opiate analgesia, which is not inexpensive ($3.30 for 3mg epidural morphine; $0.11 for 100mcg intrathecal morphine).[7]

Limitations

Further research is warranted to address a number of issues among the studies. With a limited sample size, the generalizability of the results to other women requesting cesarean delivery is questionable. Although all three studies recorded the amount of supplemental morphine administered per patient request, in depth analyses of these patients as their own sub-group were not conducted. None of the studies included women undergoing cesarean delivery on a non-elective or emergent basis. Future study is warranted to evaluate the effects of oral gabapentin in the management of these populations before routine use can be recommended.

CONCLUSION

Evidence is inconclusive as to whether oral gabapentin administered prior to scheduled cesarean delivery decreases pain with movement in adult women at 24 hours postpartum as compared to placebo.

At the time of writing, recent publication of new data from Monks et al[13] aims to clarify many of these issues and finds that one pre-operative dose of gabapentin followed by 6 post-operative doses over two days produces modest improvement in pain scores and satisfaction with pain management over control. This improvement comes at the expense of marked sedation, casting the role of gabapentin in a multimodal approach to pain management for cesarean delivery in doubt.

Table 1 - Demographics & Characteristics of Selected Studies

Study	Type	# pts	Age (y)	Inclusion	Exclusion	W/D	Interventions
Moore (2011)	Double-blind RCT	46	>18y (mean = 34)	• Full-term pregnant women undergoing scheduled cesarean delivery •>18 years	• ASA Physical Status Score of ≥3 • Contraindications to neuraxial anesthesia • History of HIV, hepatitis, uncontrolled hypertension, or diabetes mellitus • Known IVDU • Women with fetuses having known congenital abnormalities • Women having taken pain medications one week prior to surgery	2	Experimental: 600mg gabapentin PO 1 hour before surgery Control: Lactose placebo
Short (2012)	Double-blind RCT	132	>18y (mean = 34.8)	• Full-term women with singleton pregnancies undergoing scheduled cesarean delivery •>18 years	• ASA Physical Status Score of ≥3 • Contraindications to neuraxial anesthesia • History of epilepsy, central nervous system or mental disorders, chronic pain, drug abuse, or use of neuropathic analgesics or antiepileptic drugs • Women with fetuses having known congenital abnormalities	6	Experimental: - 600mg gabapentin PO 1 hour before surgery; - 300mg gabapentin PO 1 hour before surgery Control: Lactose placebo
Anaraki (2014)	Double-blind RCT	78	>18y (mean = 27)	•Full term, primiparous women undergoing scheduled cesarean delivery •>18 years	• ASA Physical Status Score of ≥3 • Contraindications to neuraxial anesthesia • History of smoking, hepatitis, chronic use of gabapentin or opioids, psychological problems, severe preeclampsia, and diabetes mellitus • Women with fetuses having known congenital abnormalities	1	Experimental: 300mg gabapentin PO 2 hour before surgery Control: Lactose placebo PO and 10ug fentanyl IV

Table 2. Safety and Tolerability of Gabapentin versus Lactose Placebo					
	CER (N)	**EER (N)**	**RRI**	**ARI**	**NNH**
NAUSEA					
Cumulative	**46 (107)**	**49 (105)**	**0.09**	**0.04**	**27.2**
Moore 2011[†]	8 (23)	12 (21)	0.64[‡]	0.22	4.47
Short 2012, 600mg	19 (42)	19 (42)	0	0	0
Short 2012, 300mg	19 (42)	18 (42)	-0.05	-0.02	-42
Anaraki 2014	--	--	--	--	--
VOMITING					
Cumulative	**28 (145)**	**26 (143)**	**-0.06**	**-0.01**	**-88.61**
Moore 2011	3 (23)	5 (21)	0.83	0.11	9.29
Short 2012, 600mg	10 (42)	7 (42)	-0.30	-0.07	-14
Short 2012, 300mg	10 (42)	10 (42)	0	0	0
Anaraki 2014	5 (38)	4 (38)	-0.22	-0.03	-34.47
SEDATION					
Cumulative	**65 (107)**	**64 (105)**	**0.003**	**0.002**	**488.48**
Moore 2011	17 (23)	17 (21)	0.10	0.07	14.21
Short 2012, 600mg	24 (42)	23 (42)	-0.04	-0.02	-42
Short 2012, 300mg	24 (42)	24 (42)	0	0	0
Anaraki 2014	--	--	--	--	--
PRURITUS					
Cumulative	**86 (145)**	**85 (143)**	**0.002**	**0.001**	**767.96**
Moore 2011	22 (23)	16 (21)	-0.20	-0.19	-5.14
Short 2012, 600mg	32 (42)	33 (42)	0.03	0.02	42
Short 2012, 300mg	32 (42)	36 (42)	0.13	0.1	10.5
Anaraki 2014	0 (38)	0 (38)	0	0	0

[†] Moore 2011 – Gabapentin 600mg; Short 2012- Gabapentin 600mg; Anaraki 2014 – Gabapentin 300mg

[‡] Results rounded for simplicity of presentation. Calculations done without rounding.

Table 3. Neonatal Outcomes Across Studies							
	Moore et al[8]		**Short et al[12]**			**Anaraki et al[11]**	
	Gaba	**Placebo**	**Gaba 300mg**	**Gaba 600mg**	**Placebo**	**Gaba**	**Placebo**
N	*21*	*23*	*42*	*42*	*42*	*38*	*39*
Weight (g)[a]	3520	3341	3429	3505	3382	--	--
1-minute Apgar[b]	9	9	9	9	9	10	10
5-minute Apgar[b]	9	9	9	9	9	10	10
Umbilical artery pH[a]	7.26	7.29	7.29	7.28	7.28	--	--
NICU admission[c]	1	0	2	1	2	--	--

[a] – Mean (SD) [b] – Median (range) [c] – Count

References

1. Beckman CRB, Ling FW, Herbert WNP, et al. *Obstetrics and Gynecology*. 7th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2014
2. Norwitz ER. Cesarean delivery on maternal request. In: UpToDate, Post TW (Ed), UpToDate, Waltham, MA. (Accessed on November 30, 2015.)
3. Carvalho B, Cohen SE, Lipman SS, Fuller A, Mathusamy AD, Macario A. Patient preferences for anesthesia outcomes associated with cesarean delivery. *Anesth Analg* 2005;101:1182–7. doi:10.1097/01.sa.0000234693.69247.48
4. Landau R, Bollag L, Ortner C. Chronic pain after childbirth. *Int J Obstet Anesth*. 2013;22:133–145. doi: 10.1016/j.ijoa.2013.01.008
5. Loos MJ, Scheltinga MR, Mulders LG, Roumen RM. The Pfannenstiel incision as a source of chronic pain. *Obstet Gynecol,* 2008;111:839–46. doi: 10.1097/AOG.0b013e31816a4efa.
6. Grant GJ. Anesthesia for cesarean delivery. In: UpToDate, Post TW (Ed), UpToDate, Waltham, MA. (Accessed on November 30, 2015.)
7. Lexicomp Online, Pediatric & Neonatal Lexi-Drugs, Hudson, Ohio: Lexi-Comp, Inc.; January 29, 2015. Accessed November 30, 2015.
8. Moore A, Costello J, Wieczorek P, Shah V, Taddio A, Carvalho JC. Gabapentin improves postcesarean delivery pain management: A randomized, placebo-controlled trial. *Anesth Analg*. 2011;112(1):167-173. doi: 10.1213/ANE.0b013e3181fdf5ee.
9. Dimatteo M, Morton S, Lepper H, et al. Cesarean childbirth and psychological outcomes: A meta-analysis. *Health Psychology.* 1996:15(4):303-314. doi:10.1037/0278-6133.15.4.303

10. Statistical Brief #110: Hospitalizations related to childbirth, 2008. Agency for Healthcare Research and Quality, Healthcare Cost and Utilization Website. https://www.hcup-us.ahrq.gov/reports/statbriefs/sb110.jsp Published April 2011. Accessed October 2015.
11. Anaraki AN, Mirzaei K. The effect of gabapentin versus intrathecal fentanyl on postoperative pain and morphine consumption in cesarean delivery: A prospective, randomized, double-blind study. *Arch Gynecol Obstet*. 2014;290(1):47-52. doi: 10.1007/s00404-014-3152-5.
12. Short J, Downey K, Bernstein P, Shah V, Carvalho JC. A single preoperative dose of gabapentin does not improve postcesarean delivery pain management: A randomized, double-blind, placebo-controlled dose-finding trial. *Anesth Analg*. 2012;115(6):1336-1342. doi: 10.1213/ANE.0b013e31826ac3b9.
13. Monks DT, Hoppe DW, Downey K, Shah V, Bernstein P, Carvalho JC. A perioperative course of gabapentin does not produce a clinically meaningful improvement in analgesia after cesarean delivery. *Anesthesiology*. 2015;123(2):320-6. doi:10.1097/aln.0000000000000722.