



## Pilot clinical trial of gabapentin to decrease postoperative delirium in older patients

**Abstract**—In this randomized pilot clinical trial, the authors tested the hypothesis that using gabapentin as an add-on agent in the treatment of postoperative pain reduces the occurrence of postoperative delirium. Postoperative delirium occurred in 5/12 patients (42%) who received placebo vs 0/9 patients who received gabapentin,  $p = 0.045$ . The reduction in delirium appears to be secondary to the opioid-sparing effect of gabapentin.

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J.M. Leung, MD, MPH; L.P. Sands, PhD; M. Rico, BS; K.L. Petersen, MD; M.C. Rowbotham, MD; J.B. Dahl, MD; C. Ames, MD; D. Chou, MD; and P. Weinstein, MD

Postoperative delirium is strongly related to the severity of pain, and probably to the CNS effects of opioid analgesics.<sup>1</sup> Accordingly, we sought to develop a protocol to test the hypothesis that postoperative delirium could be reduced by addition of gabapentin to conventional therapy for postoperative pain. Gabapentin has been approved for treatment of epilepsy and postherpetic neuralgia, and recent evidence showed it might also reduce postoperative pain and the need for opioids.<sup>2-4</sup>

The goal of this trial was to assess safety and feasibility to enable a subsequent larger trial to be conducted to compare the incidence of postoperative delirium in patients given gabapentin vs placebo and to determine if the rates of delirium vary with differences in pain severity and opioid consumption in patients given gabapentin vs placebo.

**Methods.** This double-blind, placebo-controlled, randomized trial was approved by the Institutional Review Board for human research and informed consent was obtained preoperatively from

each study patient. The study was conducted in 2005 at the University of California, San Francisco Medical Centre, an academic hospital. Inclusion criteria were consecutive patients who were  $\geq 45$  years of age, undergoing surgery involving the spine, requiring general anesthesia, and expected to remain in the hospital postoperatively for  $\geq 72$  hours. Exclusion criteria were patients who could not complete the delirium testing, already taking preoperative gabapentin, or with sensitivity to gabapentin.

Intraoperative anesthetic for all patients was standardized to IV anesthetics and a low dose inhalational agent. Postoperatively, all patients received on-demand patient controlled analgesia (PCA) with IV hydromorphone.

A computerized random number list was created by one of the coinvestigators (L.S.) to designate the two treatment groups. This list was given to the research pharmacist who prepared and delivered the designated drug to each study patient according to the randomized allocation. Either gabapentin 900 mg or placebo was administered by mouth 1 to 2 hours before surgery and anesthesia. This dose was continued for the first 3 postoperative days. For patients with reduced renal function, the actual dosages of gabapentin were adjusted according to the Cockcroft and Gault Equation. We targeted the first 3 postoperative days for treatment given our previous findings that the incidences of postoperative delirium and pain levels were highest during this period. We used the lowest clinical dose (900 mg) for our patients based on our previous study which demonstrated that this dose of gabapentin was well tolerated by older patients with herpes zoster and was effective in reducing the median pain level from baseline by  $>50\%$ .<sup>5</sup>

Patients rated their pain using the 11-point verbal version of the visual analog scale at various time points: at rest, as well as average, minimum, and maximum pain during the last 24 hours. Ratings were collected once preoperatively, and daily postoperatively for the first 3 days between by research personnel blinded to the drug assignment.

Potential covariates of postoperative delirium were measured which included age, sex, race, and preoperative comorbid conditions, preoperative medication types including opioid and dose. Screening of depression was performed preoperatively using the 15-question Geriatric Depression Scale (GDS).<sup>6</sup> Other covariates included the American Society of Anesthesiologists physical classification surgery duration, risk and type, daily doses of all opioid analgesics used, and all medications with CNS effects were measured.

A trained interviewer (M.R.) blinded to the study drug assignment measured the occurrence of delirium using the Confusion Assessment Method Rating Scale (CAM)<sup>7</sup> which was developed as a screening instrument based on operationalization of Diagnostic and Statistical Manual of Mental Disorders-III-R criteria for use by nonpsychiatric clinicians in high-risk settings. This method has

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From the Departments of Anesthesia & Perioperative Care (J.M.L., M.R.), Neurology (K.L.P., M.C.R.), and Neurological Surgery (C.A., D.C., P.W.), University of California, San Francisco; Purdue University (L.P.S.), School of Nursing, West Lafayette, IN; and Glostrup University Hospital (J.B.D.), Glostrup, Denmark.

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Address correspondence and reprint requests to Dr. Jacqueline M. Leung, University of California, San Francisco, Department of Anesthesia and Perioperative Care, 521 Parnassus, San Francisco, CA 94143-0648; e-mail: leungj@anesthesia.ucsf.edu

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**Table 1** Demographics; medical, functional, and cognitive status; and surgical data

	Gabapentin group (n = 9)	Placebo group (n = 12)	p Value
Age, y, mean ± SD	57.2 ± 10.3	61.4 ± 11.3	0.39
Sex			0.67
Male	4	7	
Female	5	5	
Race			0.17
White	7	12	
Nonwhite	2	0	
History of stroke	0	2	0.49
History of vascular disease	0	1	0.37
Independent in 5 ADLs	8	12	1.0
Independent in 7 IADLs	6	7	0.43
TICS score (mean ± SD)	33.6 ± 2.6	34.5 ± 3.0	0.47
GDS score (mean ± SD)	3.9 ± 2.3	6.2 ± 4.9	0.18
Highest level of education			1.0
High school or less	0	1	
High school graduation and greater	9	11	
Alcohol intake	3	6	0.66
ASA classification			1.0
1–2	5	6	
3–4	4	6	
Charlson Comorbidity Index (mean ± SD)	1.2 ± 1.9	0.5 ± 1.0	0.28
No. preoperative comorbid conditions (mean ± SD)	2.3 ± 1.5	1.8 ± 1.2	0.40
Preoperative opioid use	5	8	0.60
Surgical risk*			1.0
Low	0	0	
Intermediate	8	11	
High	1	1	
Surgical duration (min)	347 ± 106	356 ± 128	0.86
Intraoperative blood loss (mL)	1,036 ± 1,575	450 ± 512	0.24
Intraoperative blood transfusion	2	3	1.0
Intraoperative hypotension†	1	5	0.18
Intraoperative fentanyl dose (µg)	681 ± 381	593 ± 648	0.72
Intraoperative propofol dose (mg)	586 ± 596	1,172 ± 1,529	0.29

\* Surgical risk was estimated using the guidelines from the American College of Cardiology and American Heart Association update for the perioperative cardiovascular evaluation for noncardiac surgery.<sup>10</sup>

† Intraoperative hypotension was defined as systolic blood pressure decrease of >30% over preoperative baseline for >10 min.

ADL Scale = Katz basic Activities of Daily Living Scale; IADL Scale = Lawton-Brody Instrumental Activities of Daily Living Scale; TICS = Telephone Interview for Cognitive Status; GDS = Geriatric Depression Scale; ASA classification = American Society of Anesthesiologists physical status classification.

a sensitivity of 94 to 100% and a specificity of 90 to 95% and has a high interobserver reliability, and has convergent agreement with four other mental status tests. All delirium data were validated by a second investigator (L.S.) who was also blinded to the drug assignment.

Any potential adverse events related to the use of gabapentin such as sedation, dizziness, ataxia, and nystagmus were measured daily by the research team and validated by the principal investigator (J.M.L.).

Bivariate associations were tested using  $\chi^2$  tests or Fisher exact test for categorical variables and Mantel-Haenszel  $\chi^2$  tests for trend were used for ordinal variables. Repeated measures analyses of variance were used to examine group differences in change in postoperative pain and opioid use.

**Results.** Twenty-one patients were enrolled. There was no significant difference in demographic information,

**Table 2** Postoperative use of PCA hydromorphone

	Day of surgery (n = 21)	POD 1 (n = 21)	POD 2 (n = 20)	POD 3 (n = 17)	*p Value (time x drug)
Placebo	3.32 ± 3.95	13.54 ± 25.31	7.88 ± 15.20	1.02 ± 2.35	
Gabapentin	2.68 ± 2.24	2.78 ± 2.26	2.47 ± 3.65	1.84 ± 2.73	0.37 ± 2.26

The postoperative PCA hydromorphone doses are shown (mean ± SD, in mg).

\* The p value refers to a test for differences between the two groups in the change in dose over the four assessments.

PCA = patient-controlled analgesia; POD = postoperative day.

**Table 3** Preoperative and postoperative self-reported pain scores

	Preoperative (n = 21)	POD 1 (n = 21)	POD 2 (n = 20)	POD 3 (n = 17)	* <i>p</i> Value (time x pain severity)
Resting VAS					0.28
Placebo	4.8 ± 2.8	4.8 ± 2.6	5.1 ± 2.6	4.2 ± 1.8	
Gabapentin	4.1 ± 3.3	5.2 ± 1.9	4.2 ± 1.9	4.6 ± 1.5	
Average VAS					0.11
Placebo	5.0 ± 1.9	5.4 ± 2.1	5.5 ± 2.1	5.6 ± 1.7	
Gabapentin	5.7 ± 2.2	6.3 ± 1.8	5.1 ± 1.2	5.6 ± 1.4	
Min VAS					0.02
Placebo	2.3 ± 2.1	2.6 ± 2.4	3.3 ± 2.3	3.4 ± 1.7	
Gabapentin	3.2 ± 3.0	4.6 ± 2.5	2.1 ± 2.0	3.3 ± 1.7	
Max VAS					0.97
Placebo	7.7 ± 2.6	8.2 ± 2.7	7.8 ± 2.2	7.9 ± 2.2	
Gabapentin	8.2 ± 2.3	8.1 ± 1.8	8.0 ± 2.1	8.0 ± 1.7	

\* The *p* value refers to a test for differences between the two groups in the change in pain levels over the 3 postoperative days after statistically adjusting for preoperative level of pain. Since four statistical tests were used to measure the change in pain levels, the Bonferroni correction was used, which lowered the level of significance to 0.0125.

POD = postoperative day; VAS = visual analog scale; min = minimal pain in the last 24 hours; max = maximal pain in the last 24 hours.

general health status, baseline cognitive function, and functional status between patients who received gabapentin vs placebo (table 1). Similarly, the mean surgical duration, intraoperative blood loss and blood transfusion, and intraoperative doses of anesthetics were not significantly different between the gabapentin vs the placebo groups (table 1).

After surgery, there was a trend toward a reduced use of IV PCA hydromorphone in the gabapentin group for the first two postoperative days (table 2). Despite the trend toward less postoperative opioid consumption, the pain levels were not higher in the gabapentin group (table 3). The use of other analgesics or other medications with CNS effects was not different between the two groups (*p* = 0.997 for both).

The incidence of postoperative delirium was higher in the placebo than in the gabapentin groups (5/12 = 42% vs 0/9 = 0%, *p* = 0.045 by Fisher exact test). None of the patients had agitated delirium as defined by the Richmond agitation-sedation score.<sup>8</sup> Two patients (one in each group) had postoperative sedation reported. No patient had dizziness, nystagmus, or ataxia.

**Discussion.** In this small study, gabapentin was safe and was associated with a significantly lower incidence of postoperative delirium.

In surgical pain models and in clinical studies of inflammatory pain that produce allodynia and hyperalgesia, gabapentin and its analogs improve pain. These findings suggest that sensitization of dorsal horn neurons may be an important mechanism for pain in the early postoperative period. In addition, antihyperalgesic drugs could improve postoperative analgesics, as they may block pathologic pain while leaving other protective nociceptive mechanisms intact.<sup>9</sup>

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