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Conflicting Results in Clinical Research: Is the Proof in the *P* Value, the Study Design, or the Pudding?

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In this issue of *Regional Anesthesia and Pain Medicine*, Williams and colleagues present data from a previously-published clinical investigation in which subjects undergoing outpatient anterior cruciate ligament reconstruction (ACLR) received 1 of 3 postoperative treatments in a randomized, double-masked fashion: (1) a femoral "block" with saline followed by a continuous femoral infusion also of saline; (2) a femoral block with levobupivacaine (0.25%) followed by a continuous femoral infusion of saline; and (3) a femoral block with levobupivacaine (0.25%) followed by a continuous femoral infusion of levobupivacaine (0.25%).[1] In the present report, the authors retrospectively analyze prospectively-collected data and conclude, "the addition of a femoral nerve block to the described multimodal technique was not associated with NVR [nausea, vomiting, retching] or quality of sleep-restfulness."[2] As noted by the authors, this lack of association is the *opposite* finding of multiple previously-published randomized, double-masked, placebo-controlled investigations involving ambulatory continuous peripheral nerve blocks (CPNB) that *did* find a strong association between CPNB and decreased nausea/vomiting and sleep disturbances.[3-5] *With differing conclusions, what should practitioners expect for their patients with CPNB—in essence, what is the "take-home" message from this newly reported data?*

Nausea and Vomiting

There are many possible explanations for the proposition that a local anesthetic CPNB decreases nausea and vomiting.[6] However, the overwhelmingly prominent hypothesis is that the CPNB produces potent analgesia, thereby decreasing use of supplemental opioid analgesics and, subsequently, opioid-induced side effects such as nausea and vomiting.[6;7] If the CPNB does not decrease opioid use, there is little reason to expect that side effects such as nausea and vomiting will decrease as well.[7] In the original published study by Williams and colleagues there were no clinically or statistically significant differences in reported opioid use among the three treatment groups (Table 1), except for the minor difference noted on postoperative day one.[1] Was this lack of observed difference in supplemental opioid use truly a reflection of similar pain experienced among the three treatment groups? The evidence does not suggest

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this is the case since patients with a femoral levobupivacaine infusion reported lower pain scores that were both clinically and statistically significant.[1] Therefore, what explains the lack of difference in opioid use among the treatment groups?

In this study all subjects were instructed to take immediate-release oxycodone for breakthrough pain, and *at least* 10 mg of sustained-release oxycodone (Oxycontin) twice daily, "even if NRS [Numeric Rating Scale] scores were zero."[1] In effect, the study design *required* all treatment groups to receive a relatively high dose of opioids around-the-clock until postoperative day (POD) 4, regardless of analgesic requirements. This protocol ensured that even subjects with*out* supplemental analgesic requirements still received relatively high doses of opioids—to such a degree that there were almost no differences in opioid use among the three treatment groups (Table 1). Most likely, *it is this lack of difference in opioid use mandated by the study design that accounts for the lack of difference in nausea, vomiting, and retching*.

Sleep Quality

The required use of sustained-release oxycodone can also at least partially explain the lack of association between a levobupivacaine femoral block/CPNB and sleep quality. Without sustained-release oxycodone, subjects lacking a femoral block/CPNB may have been awakened by pain when their short-acting, immediate-release opioids wore off. They may not have achieved the same level of potent analgesia without the combination of sustained- and immediate-release oxycodone. Therefore, subjects in the current study who received a placebo block/CPNB possibly experienced fewer sleep disturbances and higher sleep quality than patients in other investigations who did not have access to sustained-release oxycodone.

"Appropriate" Clinical Practice

Of course, there are multiple other possible explanations for the differences in findings between the Williams and colleagues' study and previous investigations, such as extracting responses from a health-related quality-of-life instrument (QoR-40), decreasing sensitivity by "pooling" Likert-type QoR-40 responses into dichotomous variables, knee innervation from nerves not covered by the femoral block/CPNB, lack of patient-controlled CPNB-administered bolus doses, etc. Each of these could serve as the topic for an editorial and is beyond the scope of the current article. However, the study methodology requiring relatively high doses of mandatory opioids is—*alone*—more than enough to account for the lack of effect of CPNB found in the Williams and colleagues study.[2] The authors acknowledge that the analgesic protocol used in their study does not accurately reflect current common and "appropriate" postoperative opioid administration as they explain, "…it is unlikely that controlled-release oxycodone can be currently considered a mainstay in postoperative analgesia for various medicolegal reasons."[1] They add, "*In clinical practice… a more appropriate opioid analgesic plan would be to dose only on a symptomatic basis* (as opposed to a regular dosing schedule), in which case NVR rates may be further reduced [emphasis added]."[2]

The authors explain that the study protocol was designed in 1999 and mandatory opioids were "used (and required by our institutional review board) to offset the risks of significant postoperative pain in the placebo nerve block catheter treatment group."[1] However, whether or not the opioid dosing algorithm used by the investigators provided the optimal study protocol is not at issue here—although that topic is also deserving of editorial comment—*but rather the effect of the analgesic protocol upon the data reported by the authors and their proposed conclusions*.

Rebound Pain Scores

Williams and colleagues have published an additional article in this month's journal also based on their previously-published ACLR study which compared the “rebound pain scores” of the two groups receiving a levobupivacaine (0.25%) femoral block and subsequently receiving either a femoral saline or levobupivacaine femoral infusion.[8] They conclude that “based on our data, 33 additional hours of nerve block duration are required to lower Rebound Pain NRS scores by a *mere* one point on a zero-to-10 scale [emphasis added].”[8] The authors acknowledge that “There may be several factors that attenuated RPS [rebound pain scores] in our study. One may have been our multimodal analgesic protocol…”[8] We would suggest that the study design —the mandatory use of high-dose opioids and relatively short infusion duration following the initial block resolution (22 hours)—not only “attenuated” the rebound pain scores, but decreased both groups' to such a degree that the results provide little practical information for clinicians utilizing a more current and “appropriate” postoperative analgesic protocol.

Take-Home Message

The Editorial Board of *Regional Anesthesia and Pain* Medicine decided it was it legitimate to publish the results of the Williams and colleagues' retrospective studies. But considering the opioid protocol of the original study on which the subsequent investigations are based, what should clinicians do with the newly-published information? There are significant problems with drawing conclusions from retrospectively-analyzed data, and the issue is complex enough to lie outside the scope of this editorial and is therefore addressed separately.[9] Such *post hoc* analysis of data that was originally collected to address a completely different hypothesis should be viewed as pilot data and used primarily to design future investigations. In this context, the presented data suggest that there is not a strong relationship between CPNB, sleep quality, opioid use, opioid-related side effects, and “rebound pain scores” *when consumption of high-dose opioids is mandated.* However, if CPNB is provided with opioids on an as-needed basis —a scenario the authors themselves declare to be preferable in clinical practice—then the data from the new Williams and colleagues' articles offer little relevant information for practitioners when compared with previous studies that utilize a more current and clinically-relevant opioid dosing protocol.

To the journal's readership, awareness of Williams and colleagues' data is both good and bad. Good because it suggests to future *investigators* that further study appears unwarranted using the combination of CPNB and mandatory high-dose opioid administration. The articles may also help to increase awareness of other important endpoints/outcomes besides simple pain scores and “pill-counts” as well as evaluative instruments (e.g. health-related quality-of-life questionnaires) that deserve prospective investigation. However, publication may be bad because they may unduly influence *clinicians*' practice and patient care both because of the opioid protocol, and because negative (or positive) findings that result from the *post hoc* analysis of data are of limited use in the clinical arena.[9] This is especially true when data from previous investigations provide very strong evidence that following moderate-to-severely painful surgery, adding a CPNB to a multimodal analgesic regimen in the ambulatory environment—with opioids used as needed—*is* associated with decreased opioid requirements, opioid-related side effects, sleep disturbances, and post-infusion “rebound” pain.[3-5;10;11]

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Table 1

Daily oxycodone consumption

POD	Placebo Block & 50 h Placebo Infusion	Levobupivacaine Block & 50 h Placebo Infusion	Levobupivacaine Block & 50 h Levobupivacaine Infusion
1	42 (37-47)*	33 (29-37)	30 (26-34)
2	27 (23-31)	28 (24-32)	25 (22-28)
3	21 (17-25)	20 (17-24)	19 (16-22)
4	14 (10-18)	13 (10-16)	14 (10-17)

Values are reported mean (95% confidence interval) and include both immediate- and sustained-release oxycodone [the source document by Williams and colleagues did not separate immediate-release oxycodone from sustained-release oxycodone use, and therefore these two different formulations cannot be presented individually in this table]

POD: Postoperative Day

There were no statistically significant differences among the groups other than for postoperative day 1

*P<0.001 for the Placebo/Placebo group compared with the other two treatment groups Adapted from Table 2, Williams and colleagues[1]

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