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# Research Priorities Regarding Multimodal Peripheral Nerve Blocks for Postoperative Analgesia and Anesthesia Based on Hospital Quality Data Extracted from Over 1,300 Cases (2011–2014)

Disclosure: Brian Williams led in the preparation of the manuscript. He led the design and conduct of the quality improvement data query (preparatory to research) and analyzed all data. James Ibinson assisted in the preparation of the manuscript. He reviewed the content of the quality improvement data query (preparatory to research) and contributed text and context to the narrative. Michael Mangione assisted in the preparation of the manuscript. He was central in the original quality improvement data query (preparatory to research) and reviewed all data presented. Robert Modrak actively participated in the formulation of the orthopedic portions of the described clinical pathway, with original text contributions in this context. Elizabeth Tonarelli contributed to the preparation of the manuscript. Her original contributions focused on the context of length-of-stay and discharge disposition in joint replacement patients before and after the start of the described program. Hulimangala Rakesh assisted in the preparation of the manuscript. He was an active participant in serial process changes in the described quality improvement initiative (preparatory to research) and contributed text and context to the narrative. Alissa Kmatz contributed to the preparation of the manuscript. Her original contributions focused on the context of block duration and rebound pain score determination. Peter Cohen actively participated in the formulation of the clinical pathway and design and conduct of the quality improvement data query (preparatory to research), with original text contributions in these contexts.

The use of additives with local anesthetics for peripheral nerve blocks has received considerable attention [1] due to the patient-centered goals of prolonging analgesic duration and possibly reducing local anesthetic-related toxicity. Applying such additives to single-injection nerve blocks also has the potential to reduce overhead [2] and disposables [3] costs, when compared with the costs related to continuous perineural infusions. Furthermore, recent research has elucidated *in vivo* animal sciatic nerve safety of the preservative-free combination of clonidine, buprenorphine, and dexamethasone (CBD) with the local anesthetic bupivacaine (BPV) [4]. Ropivacaine–CBD was previously demonstrated to be no more neurotoxic than plain ropivacaine to cultured primary sensory neurons harvested from rat dorsal root ganglia *in vitro* [5].

In our institution (Veterans Affairs Pittsburgh Healthcare System [VAPHS]), the lead author was in charged with creating a regional anesthesia (RA) and analgesia program for patients eligible for peripheral nerve blocks. For this new program, hospital administration was unable to budget resources for a perineural catheter-based acute pain service. Instead, the Medical Executive Board approved the lead author's recommendation to routinely use BPV–CBD off-label. These single-injection nerve block procedures are typically placed before surgery to provide postoperative analgesia and intraoperative anesthesia when feasible, and thus avoiding general endotracheal anesthesia (GETA). The Medical Executive Board tasked the lead author with per-patient quality assurance/quality improvement (QA/QI) data collection to evaluate comparative effectiveness (against historical controls) and outcomes (block duration and rebound pain [6,7], perineural complications, etc.). In accordance with Veterans Health Administration Handbook 1058.05, this manuscript was processed for authentication of nonresearch status of the activities prior to submission to this journal. Our institutional review board declared these clinical operations as "not research" at the time of program initiation (mid-2011) and annually since then during required reviews.

The objective is to describe the patient outcomes to date associated with our Multimodal Perineural Anesthesia/Analgesia (MMPNA) program, consisting primarily of BPV–CBD nerve blocks, *en route* toward hypothesis generation for future clinical research.

## Methods

### *Patient Selection for Data Analysis*

From July 1, 2011 through June 30, 2014, over 1,300 consecutive patients underwent MMPNA procedures at VAPHS. For the purpose of this analysis (to maximize case-to-case comparability), we are directing specific attention to the following subsets of nonrandomized consecutive patient cases: 1) group 1: N = 279 having undergone total knee arthroplasty (TKA) or total hip arthroplasty (THA) by the lead author using BPV–CBD nerve blocks with a protocolized spinal anesthesia and intraoperative propofol-ketamine sedation regimen for *perineural analgesia*; 2) group 2: N = 62 TKA patients who specifically underwent lumbar plexus and sciatic blocks (without spinal or GETA, and similar propofol-ketamine) for perineural surgical *anesthesia* and postoperative *analgesia*; and 3) group 3: N = 181 patients who underwent brachial plexus blocks for upper extremity perineural *anesthesia and analgesia* (without concomitant GETA). During this period, there were no cases entailing the use of BPV without the use of perineural CBD, so no comparisons against blocks with plain BPV were possible.

### *Multimodal Oral Pain Medication Regimen*

TKA–THA inpatients in groups 1 and 2 also received a standardized local infiltration protocol from the surgeons, as well as a standardized postoperative oral multimodal analgesic protocol. Multimodal oral analgesia began before surgery with sustained-release acetaminophen (1,300 mg PO) and sustained-release dextromethorphan (60 mg PO); these oral analgesics were continued every 12 hours postoperatively for the duration of the hospital stay. Postoperative oral analgesics entailed sustained-release morphine (15 mg) on the night of surgery and at bedtime on postoperative days 1–2, and in the morning of postoperative days 1–3, if certain pain score thresholds were met. Oxycodone 5–10 mg PO was prescribed for breakthrough pain every 3–6 hours (including every 2 hours before and/or after physical therapy, when requested by the patient). Intravenous opioids were available as needed when rebound pain was refractory to the described oral analgesics. Intravenous patient-controlled opioid devices were not prescribed. Inpatients were not restricted from any scheduled oral opioid dosing based on the absence of pain; rather, patients were encouraged to gradually take doses of the described opioids while the blocks were still providing analgesia, to facilitate transitional analgesia from perineural to systemic. This gradual oral opioid-loading was consistent with the research method in our previous publication that validated the concepts of nerve block duration and rebound pain score [6]. Group 3 primarily entailed outpatients, for whom the described multimodal oral analgesic protocol was not used (due to formulary nonavailability for veteran outpatients); again, there were no restrictions on when they were permitted to consume oral opioids in anticipation of the dissipation of nerve block analgesia.

### *Dose Adjustments in the Setting of Diabetes*

In the clinical pathway protocol, based on a recent dose-reduction suggestion for diabetics [8], the recommended BPV concentrations for perineural analgesic dosing were up to 20% lower for diabetics (e.g., 2 mg/mL for L2–L4 and 1 mg/mL for L4–S3) than they were for nondiabetics (2.5 mg/mL for L2–L4, 1.25 mg/mL for L4–S3). Similar dosing principles were applied for diabetics undergoing BPV–CBD blocks for surgical anesthesia (approximately 20% lower BPV concentrations for diabetics, e.g., 4 mg/mL, than for nondiabetics, e.g., 5 mg/mL).

### *Methods to Quantify Block Duration and Rebound Pain Scores*

As part of our QA/QI data, we tracked patient-reported baseline pain score data (at rest and with movement), and nurse or physical therapist-recorded peak rebound pain scores [6,7] with movement for inpatients. For outpatients (group 3), phone calls after surgery were used to determine the time at which patients noted their postoperative peak rebound pain score with movement. For all patients, rebound pain scores with movement in these QA/QI data were defined as the initial peak pain scores likely attributable to complete resolution of multimodal perineural analgesia (as opposed to peak pain score attributable to resolution of the spinal anesthetic, or resolution of "numbness" from perineural bupivacaine). Block duration (hour) [6,7] was calculated as the time of the peak rebound pain score, minus the time of peripheral block placement. When applying rebound pain methodology [6] to clinical practice, patients are assumed and expected to take oral analgesics on a regular schedule before the analgesic block effects dissipate. During the phone calls to outpatients, the scripted question was described to the patient as "the peak pain score with movement" (0–10 on a numeric rating scale) after surgery, with the clear description by the patient that indeed the nerve block was "no longer providing any meaningful pain relief." On the other hand, inpatients' peak pain scores were simply recorded from the medical records as recorded by the nurse or physical therapist at the time the peak pain score was recorded.

### *Data Analyses Regarding Block Duration and Rebound Pain*

Analgesic duration data from the multimodal block and rebound pain score data were tested for normal distributions. Appropriate statistics were applied. If significant, when there were multiple variables, regression analyses were used to test for factor interaction.

The drug dose thresholds used for these regression equations were as follows: buprenorphine: $>300\,\mu$g total perineural dose for lower extremity joint replacement and $\geq 200\,\mu$g dose for upper extremity surgery; clonidine: $\geq 80\,\mu$g total perineural dose for joint replacement, and dexamethasone: 2 mg total perineural dose for joint

replacement. All data were analyzed with IBM SPSS v21 statistical software (IBM SPSS®, Chicago, IL, USA).

**Results (Table 1)**

*Specific to TKA and THA*

Duration Effects

For MMPNA analgesic block patients after TKA–THA with spinal anesthesia (N = 279), the median block duration was 37 (interquartile range [IQR] 30–49) hours. The median rebound pain score (not adjusting for preoperative baseline pain scores) was 8 (IQR 6–9), on a scale of 0–10. Three factors influenced the associated rebound pain score: 1) higher preoperative pain scores with movement predicted higher associated rebound pain scores; 2) higher perineural dexamethasone dosing (4 mg total perineural vs 2 mg total) predicted *higher* associated rebound pain scores; and 3) higher perineural buprenorphine dosing (>300 μg as opposed to ≤300 μg) predicted *lower* associated rebound pain scores.

For TKA only, comparing lumbar plexus and sciatic *anesthetic* blocks (Lum-Sci, N = 62) against spinal anesthesia and femoral-sciatic *analgesic* blocks (Spi-Fem-Sci, N = 180), regression results can be described using the following narrative illustration: When nondiabetic veteran at our institution underwent a Lum-Sci block, the associated mean duration was 33 hours. If the patient instead had Spi-Fem-Sci blocks, the associated mean duration was significantly longer at 37 hours ($P = 0.023$). If the Lum-Sci patient was diabetic ($P = 0.012$), the associated mean duration was significantly longer (than

**Table 1** Data highlights regarding multimodal perineural anesthesia and analgesia (MMPNA)

| | | |
|---|---|---|
| Total hip/knee replacement (N = 279—spinal and L2–L4 and L4–S3 MMPNA analgesic blocks) | | |
| • Median block duration | | 37 hours (IQR 30–49 hours) |
| • Median rebound pain score | | 8 (on 0–10 scale; IQR 6–9) |
| ○ Factors influencing rebound pain score | | |
| ■ Positive correlation with higher baseline preop movement pain scores, $P = 0.002$ | | |
| ■ Positive correlation with 4 mg total perineural dexamethasone dosing (as opposed to 2 mg), $P < 0.001$ | | |
| ■ Negative correlation with >300 μg total perineural buprenorphine (as opposed to ≤300 μg buprenorphine), $P = 0.018$ | | |
| ■ Summary: higher preop pain with movement predicts a higher associated rebound pain. Using 4 mg perineural dexamethasone (2 mg per plexus) is associated with higher rebound pain scores (vs 1 mg per plexus). Using >300 μg total perineural buprenorphine (e.g., >200 μg buprenorphine per plexus) was associated with lower rebound pain scores (than was ≤150 μg per plexus). | | |
| Total knee replacement (comparison of spinal and L2–L4 and L4–S3 MMPNA analgesic blocks (N = 180) against lumbar plexus and sciatic (N = 62) MMPNA anesthetic blocks) | | |
| • Block duration constant of lumbar plexus–sciatic blocks: | | 33.3 hours (SEM = 1.6) |
| ○ Add 4.0 (1.8) hour if Spi-Fem-Sci (instead of Lum-Sci) | | $P = 0.023$ |
| ○ Add 4.2 (1.7) hour if patient is diabetic (N = 71) | | $P = 0.012$ |
| • Will rebound pain be less than preop pain score with movement (yes/no)? | | |
| ○ Odds ratio constant | 0.5 | $P = 0.022$ |
| ○ If buprenorphine >300 μg (N = 160) | 2.5 (1.4, 4.3) | $P = 0.001$ |
| ○ If dexamethasone = 2 mg (N = 199) | 2.1 (1.0, 4.3) | $P = 0.038$ |
| ○ Summary narrative interpretation: when perineural buprenorphine >300 μg (most commonly 300 μg per plexus) and perineural dexamethasone = 2 mg (i.e., exactly 1 mg per plexus), then five patients will have rebound pain less than preop pain score with movement before one patient enjoys similarly low rebound pain using less buprenorphine (≤300 μg perineural total) and more dexamethasone (4 mg perineural total) or no dexamethasone. | | |
| Upper extremity MMPNA blocks for anesthesia and analgesia | | |
| • Overall block duration (N = 181): | 33 (IQR 26–45) hours | |
| ○ If buprenorphine <200 μg (N = 55) | 29 (24–41) hours | |
| ○ If buprenorphine ≥200 μg (N = 126) | 35.5 (27–46) hours | $P = 0.01$ |

L2–L4: femoral nerve analgesic MMPNA blocks for knee replacement surgery, and lumbar plexus psoas compartment ("Lum") analgesic MMPNA blocks for hip replacement surgery, coadministered with spinal ("Spi") anesthesia.
L4–S3: gluteal approach sciatic nerve ("Sci") analgesic MMPNA blocks for knee replacement surgery, and parasacral plexus analgesic MMPNA blocks for hip replacement surgery, coadministered with spinal anesthesia.
IQR = interquartile range; SEM = standard error of the mean.

the 33 hours baseline) at 37.5 hours. No specific drug dose/mass threshold (for clonidine, buprenorphine, and/or dexamethasone) was specifically associated with any block duration differences for TKA patients; however, these data could be underpowered. It should be reemphasized that comparisons to plain perineural bupivacaine (i.e., *not including* CBD) were not sought (as plain bupivacaine was not used in this clinical pathway).

#### Rebound Pain Effects

The regression results (Table 1) further showed drug dose/mass differences leading to associated changes in rebound pain when a veteran at our institution underwent one of the described nerve blocks for total knee replacement (Lum-Sci or Spi-Fem-Sci). The effect of dexamethasone dosing was somewhat surprising: dexamethasone dosing other than 1 mg per plexus (i.e., a total perineural dexamethasone dosing either greater than or less than 2 mg) was associated with higher rebound pain than when exactly 2 mg total perineural dexamethasone was used ($P = 0.038$, Table 1). Meanwhile, perhaps not surprisingly, if the total perineural buprenorphine dose was $\leq$300 $\mu$g ($\leq$150 $\mu$g per nerve/plexus) the rebound pain was greater than when a higher perineural buprenorphine dose was used ($>$300 $\mu$g, $P < 0.001$, Table 1). Meanwhile, the following factors did not influence the likelihood of rebound pain exceeding baseline pain with movement: 1) diabetes; 2) Lum-Sci block vs Spi-Fem-Sci blocks; 3) perineural clonidine dose; and 4) block duration. There is the possibility that these specific rebound pain data were underpowered.

### *Specific to Upper Extremity Outpatient Surgery*

We pooled the analysis of axillary (N = 121) and interscalene (N = 60) blocks with particular attention directed toward differing block duration associated with perineural buprenorphine dosing. Upper extremity patients treated with buprenorphine $\geq$200 $\mu$g had significantly longer associated block durations (N = 126, 35.5 [IQR 27–46] hours) than did patients receiving $<$200 $\mu$g buprenorphine (N = 55, 29 [IQR 24–41] hours, $P = 0.01$). No specific factors were associated with differences in rebound pain, although these data are likely underpowered.

## Discussion

### *Overall Summary of Observational Data (Table 1) and Applicability to Future Hypotheses*

#### For Total Knee and Hip Replacement

In the described MMPNA program that included routine use of single-injection MMPNA (comprised of BPV–CBD) for L2–L4 and L4–S3 nerves/plexi, combined with spinal anesthesia and the avoidance of GETA, the median observed time from block injections to the recorded peak rebound pain score after TKA/THA was 37 hours. This analgesic *duration* was not specifically associated with specific drug dose thresholds in the MMPNA injections. However, *rebound pain* was influenced (association, not causation) by preoperative baseline pain score with movement/ambulation (on a 0–10 numeric rating scale). This is consistent with the well-described phenomenon (unrelated specifically to nerve blocks) where higher preoperative pain scores with movement predict higher postoperative pain scores [9–11]. To a lesser degree, rebound pain after the described blocks was associated with total perineural dexamethasone and buprenorphine dosing in the described nerve/plexus blocks. Total perineural dexamethasone dosing of "other than 2 mg" (i.e., no dexamethasone or 4 mg total perineural dexamethasone) was associated with less favorable rebound pain than was 2 mg total perineural dexamethasone, whereas total perineural buprenorphine exceeding 300 $\mu$g (most commonly 600 $\mu$g total) was associated with more favorable rebound pain profiles than was total perineural buprenorphine $\leq$300 $\mu$g. For future MMPNA research regarding joint replacement surgery that includes spinal anesthesia as the definitive intraoperative anesthetic, we do not recommend dose–response studies involving dexamethasone; these plexus injections should be restricted to 1 mg per plexus, under the guiding principle that "less may be better" [12], given the theoretical risks of wound or prosthesis infections with higher perineural dexamethasone doses. Alterations of local anesthetic drugs and concentrations (e.g., varying concentrations of bupivacaine or ropivacaine) would be useful research ideas to determine the duration of motor block that is sufficient to preclude *vs* allow for postoperative physical therapy. Similarly, alterations of buprenorphine dosing with special attention to patient baseline opioid consumption will be valuable research *en route* to substituting oral or parenteral opioids with perineural buprenorphine and minimizing systemic opioid side effects.

For TKA-specific analyses, although the associated block duration (as defined) was approximately 4 hours less for Lum-Sci patients (when compared with Spi-Fem-Sci patients), this statistically significant difference is likely not clinically significant. The overall duration does not lead to timing that would be expected to be associated with a middle-of-the-night awakening on the night after surgery: both 35 and 39 hours durations extend well into the first postoperative day. It should be noted, however, that patients receiving Spi-Fem-Sci may have middle-of-the-night pain awakening as their spinal anesthetic (which included intrathecal clonidine 10–25 $\mu$g for our patients) effects abruptly dissipate, even though the ongoing femoral and sciatic analgesic blocks are continuing to offset or delay the peak pain occurrence. There may be a positive effect to the abrupt dissipation of the spinal; namely, these patients may be more ready for postoperative physical therapy efforts on the morning after surgery than Lum-Sci patients may be, as the Lum-Sci blocks are designed to be not motor-sparing (as a surgical anesthetic block). Prospective comparison of Lum-Sci against Spi-Fem-Sci (with all blocks featuring MMPNA and single injections) certainly warrants head-to-head evaluation with respect to physical therapy outcomes, but the pragmatism of a 3-injection 3-position block (Spi-Fem-Sci) seems lacking if

the 2-injection 1-position (Lum-Sci) block is reasonably efficacious and avoids the risks of neuraxial trespass. Likewise, although the alternative strategy of a spinal anesthetic with a femoral perineural catheter (which may represent an RA-based standard of care) involves only two injections and two patient positions, it seems logical that catheter placement would still create sizable workload disadvantages when compared with a single-position, double-injection Lum-Sci technique. The Lum-Sci MMPNA block may prove to eliminate 1) the need for postoperative catheter/infusion follow-up in the hospital, and 2) catheter-associated overhead [2] and equipment-supplies [2,3] costs.

### Diabetes Effects

We noted a difference in block duration based on diabetes status for both TKA and for upper extremity surgery, which we previously forecasted [13]. This longer block duration was despite a bupivacaine concentration reduction for diabetic patients by about 20%. Diabetic status effects on block duration should continue to be actively evaluated in future research, and we continue to recommend local anesthetic concentration reduction [8,13] for diabetic patients for both anesthetic blocks and analgesic blocks.

### Additional Considerations Regarding Upper Extremity Blocks

Buprenorphine dose threshold ($\geq$200 $\mu$g) was associated with longer block duration after upper extremity surgery. Our data did not indicate buprenorphine dosing being associated with block duration in lower extremity joint replacement surgery, but our data may be underpowered. Future hypotheses should consider preoperative baseline opioid consumption, severity of preoperative pain at rest and with movement, and diabetes status, as factors influencing duration and/or rebound, let alone potential opioid-induced side effects. If coadministered buprenorphine (and other perineural adjuvants) with a low concentration of local anesthetics to diabetic patients can yield successful surgical anesthesia, then this may be an important public health advance for diabetics and for neuropathic patients without the diagnosis of diabetes. The extent to which buprenorphine doses can be escalated without encountering opioid-related sequelae should be an active research focus.

## Conclusions

Our overall objective of presenting data preparatory to research is to narrow down the scope of future research hypotheses. Block duration and rebound pain comparisons of plain bupivacaine vs the MMPNA with BPV–CBD would seem to be a logical starting point for either a prospective randomized trial or for comparative effectiveness analysis. As a clinical activity preparatory to research, there are obvious restrictions in data collection and interpretation that would preclude the identification of individual patients, preoperative/postoperative opioid requirements, and other factors related to general health status. Thus, none of our observations should be interpreted as suggestive or definitive for future (and off-label) clinical practice. However, due diligence in preclinical research has been done, with respect to known neuronal safety (*in vitro* [5]) in the described CBD adjuvants, and more recently with respect to drug compatibility and *in vivo* safety in laboratory animals [4]. In the absence of an industry sponsor, such research (or hypothesis generation for such research) would either occur slowly or not at all.

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