Title

In Response

Journal

Anesthesia & Analgesia, 125(2)

ISSN

0003-2999

Authors

Ilfeld, Brian M

Khatibi, Bahareh

Publication Date

2017-08-01

DOI

10.1213/ane.0000000000002268

Peer reviewed

Second, volunteers lack the actual sensation of pain and therefore lack the ischemic-like conditions including decrease in pH, oxygen tension, and an increase in lactate concentration, which correlate well with pain behaviors like guarding after incision in postoperative period. An increase in neutrophils in the wound tissue occurs shortly after surgery, peaks around 24 hours, and is associated with the release of proinflammatory mediators and endogenous opioids peptides. The proinflammatory mediators contribute to hypersensitization after incision. These mechanisms are not activated in volunteers.[3]

Third, earlier evidence of advantage of intermittent boluses over continuous infusion was provided by Hogan[4] in cadavers using cryomicrotome imaging. They demonstrated a uniform spread of an ink in epidural space of cadavers after bolus dosing but nonuniform spread in rivulets for infusions. A larger volume and a higher infusion pressure produced a more uniform spread. This observation was supported in popliteal nerve block[5] and femoral nerve block[6] studies in which intermittent bolus technique was found to be superior to continuous infusion in surgical patients. Additional validation was provided in surgical patients receiving adductor canal block for postoperative pain relief by Thapa et al.[7] Though the present study[1] demonstrated the extent of spread, it did not comment upon uniformity of spread, an important factor in quality of analgesia in postoperative period. The role of continuous abdominal muscle movements during respiration in spread of drugs is also not known in TAP block.

Fourth, clinically intercepting and breaking the pain cycle in the initial postoperative period is important and may reduce the incidence of hyperalgesia and persistent postoperative pain. This cannot be assessed in a volunteer study.

In summary, we need to know whether bolus dosing or continuous basal infusion is best in immediate postoperative period where and when it is most important. The results of the study by Khatibi et al[1] suggest a relook.

Deepak Thapa, DNB, PDCC
Vanita Ahuja, MD
Department of Anaesthesia and Intensive Care
Government Medical College and Hospital
Chandigarh, India
vanitaanupam@yahoo.co.in

REFERENCES

1. Khatibi B, Said ET, Sztain JF, et al. Continuous transversus abdominis plane nerve blocks: does varying local anesthetic delivery method-automatic repeated bolus versus continuous basal infusion-influence the extent of sensation to cold?: a randomized, triple-masked, crossover study in volunteers. *Anesth Analg*. 2017;124:1298–1303.
2. White P, Lewith G, Prescott P. Should we recruit patients or healthy volunteers for acupuncture studies of chronic pain? *Clin J Pain*. 2007;23:714–719.
3. Kido K, Gautam M, Benson CJ, Gu H, Brennan TJ. Effect of deep tissue incision on pH responses of afferent fibers and dorsal root ganglia innervating muscle. *Anesthesiology*. 2013;119:1186–1197.
4. Hogan Q. Distribution of solution in the epidural space: examination by cryomicrotome section. *Reg Anesth Pain Med*. 2002;27:150–156.
5. Taboada M, Rodríguez J, Bermudez M, et al. A "new" automated bolus technique for continuous popliteal block: a prospective, randomized comparison with a continuous infusion technique. *Anesth Analg*. 2008;107:1433–1437.
6. Hillegass MG, Field LC, Stewart SR, et al. The efficacy of automated intermittent boluses for continuous femoral nerve block: a prospective, randomized comparison to continuous infusions. *J Clin Anesth*. 2013;25:281–288.
7. Thapa D, Ahuja V, Verma P, Gombar S, Gupta R, Dhiman D. Post-operative analgesia using intermittent vs. continuous adductor canal block technique: a randomized controlled trial. *Acta Anaesthesiol Scand*. 2016;60:1379–1385.

DOI: 10.1213/ANE.0000000000002267

In Response

We would like to thank our colleagues for their thoughtful and informative letter[1] addressing our recent article.[2] The letter notes that "there are a few pertinent points *in study design* which need to be looked into before the results are extrapolated to postoperative surgical patients [emphasis added]."[1] However, of the 4 points delineated, none directly address our study's design. Rather, 3 of the 4 points (the first, second, and fourth) question the ability to extrapolate results involving healthy volunteers to postsurgical patients due to multiple reasons that the authors describe. We concur with our colleagues on these 3 points. As we emphasized in our article: "Whether cutaneous sensation correlates well with postoperative pain following various abdominal procedures remains unknown, making extrapolation to clinical practice more difficult." Our concluding sentence specifically cautions that "further research is warranted … in a post-surgical patient population."[2]

We would like to address further our colleagues' third point, which, although not clearly specified, appears to question the validity of our negative results given the "positive" results of 3 previously published clinical studies. It appears inconsistent that our colleagues question the validity of extrapolating from the transversus abdominis plane (TAP) in volunteers to the TAP in surgical patients (for which we agree), yet voice no issue extrapolating data from studies involving perineural popliteal,[3] femoral,[4] adductor canal,[5] and even the epidural space of cadavers[6] to the perineural TAP.[2] On this point, we differ with our colleagues, considering that multiple previous investigations demonstrate that the optimal method of local anesthetic administration often varies with anatomic location.[7] For example, when using femoral catheters, a basal infusion (exclusively or added to bolus doses) does not necessarily add infusion benefits.[8] However, for popliteal sciatic catheters, only a basal infusion is required to maximize infusion benefits,[9] while infraclavicular catheters require both a basal infusion and bolus doses to optimize analgesia.[10] Additional studies provide contrasting results as well, emphasizing the complexity of these issues.[7] Clearly, data from one anatomic catheter location may not automatically be applied to another.

However, even if the various catheter locations were analogous, the preponderance of published data fails to demonstrate much benefit, if any, of administering repeated bolus doses compared with a basal infusion via perineural catheters.[7] Our colleagues referenced 3 positive clinical studies. One involved adductor canal catheters, which found that intermittent 15 mL of 0.5% ropivacaine boluses every 6 hours reduced morphine consumption in the 24

hours following knee surgery compared with a continuous 2.5 mL/h basal infusion with an equivalent ropivacaine dose.[5] Critical to evaluating these results is the fact that continuous adductor canal blocks appear to require a higher basal infusion rate of local anesthetic than their femoral counterparts. Recent studies demonstrate that even with a relatively high rate of 8 mL/h, analgesia for total knee arthroplasty remains suboptimal compared to a higher rate,[11] and contrast injected at pressures comparable to 8 mL/h resulted in somewhat limited spread in the adductor canal.[12] Therefore, it is highly questionable whether the study cited by our colleagues was positive due to the inherent superiority of repeated bolus doses as they opine, or rather inadequacy of the extraordinarily low basal infusion rate of 2.5 mL/h, when even 8 mL/h has been found to be suboptimal.[5] Confidence in these findings is further decreased with the publication of contrary evidence from a much larger clinical trial published subsequently that utilized a 9 mL/h basal infusion in postoperative patients with adductor canal catheters. A 27-mL ropivacaine bolus every 3 hours resulted in no statistically—or clinically—significant difference compared with the basal infusion.[13]

Similarly, there are issues limiting confidence in the results of the article our colleagues cited involving femoral catheters.[4] The investigators of that study "hypothesized that the intermittent bolus technique would provide enhanced *analgesia* [emphasis added] compared with a continuous infusion rate for continuous femoral nerve block in patients receiving TKA." No time point was specified as the primary end point nor was the study registered, so it is impossible to interpret the results in which pain scores at 6 different time points were compared, and only 1 difference—the morning of postoperative day 1—was statistically significant in favor of the bolus group. At 4 other time points, the basal group had a lower average pain score, although these comparisons did not reach statistical significance. Furthermore, the authors did not adjust for multiple comparisons among these variables nor among the approximately 30 other comparisons that were made. Therefore, the risk of a type 1 error is so high that little or no confidence may be placed in the single positive finding. The only other detected difference between treatments was a 5.1 mg lower consumption of morphine in the bolus group. However, as this was a cumulative total over 36 hours, the result is a savings of 0.1 mg of morphine each hour. Even if this finding is not a type 1 error due to the multiplicity of comparisons without statistical correction, it is clinically irrelevant. Furthermore, this opioid difference failed to result in a statistically significant difference in opioid-related side effects. Given these issues, this study can hardly be considered a conclusive "positive" investigation demonstrating the superiority of repeated bolus doses.

The popliteal catheter study noted by our colleagues does not share the weaknesses of the other 2 investigations.[3] Its positive findings in favor of repeated bolus doses were supported by a similar subsequent investigation that reported decreased opioid requirements with repeated boluses, although no decrease in pain itself.[14] However, this evidence from older studies utilizing electrical stimulation to guide needle insertion followed by blind nonstimulating catheter advancement must be weighed against the 5 negative studies utilizing ultrasound-guided catheter insertion including both volunteers (adductor canal,[15] femoral,[16] and TAP[2]) and postsurgical patients (adductor canal[13] and interscalene[17]).

It remains unknown whether the results from other anatomic catheter locations may be extrapolated to TAP catheters. Regardless, we disagree with our colleagues in their assessment of the published literature's support for the clinical superiority of repeated bolus doses over a continuous basal infusion. In contrast, we agree with our colleagues that our study involving volunteer subjects should not be viewed as the final word on this topic. We stand by the ultimate conclusion statement within our article that "further research is warranted investigating larger volumes of local anesthetic bolus doses in a postsurgical patient population."[2] We appreciate our colleagues advancing the discussion of this topic with their letter.

Brian M. Ilfeld, MD, MS
Bahareh Khatibi, MD
Department of Anesthesiology
University California San Diego
San Diego, California
bilfeld@ucsd.edu

REFERENCES

1. Thapa D, Ahuja V. Continuous versus bolus local anesthetic administration in peripheral nerve blocks: time to relook. *Anesth Analg*. 2017;125:710–711.
2. Khatibi B, Said ET, Sztain JF, et al. Continuous transversus abdominis plane nerve blocks: does varying local anesthetic delivery method—automatic repeated bolus versus continuous basal infusion—influence the extent of sensation to cold?: a randomized, triple-masked, crossover study in volunteers. *Anesth Analg*. 2017;124:1298–1303.
3. Taboada M, Rodríguez J, Bermudez M, et al. A "new" automated bolus technique for continuous popliteal block: a prospective, randomized comparison with a continuous infusion technique. *Anesth Analg*. 2008;107:1433–1437.
4. Hillegass MG, Field LC, Stewart SR, et al. The efficacy of automated intermittent boluses for continuous femoral nerve block: a prospective, randomized comparison to continuous infusions. *J Clin Anesth*. 2013;25:281–288.
5. Thapa D, Ahuja V, Verma P, Gombar S, Gupta R, Dhiman D. Post-operative analgesia using intermittent vs. continuous adductor canal block technique: a randomized controlled trial. *Acta Anaesthesiol Scand*. 2016;60:1379–1385.
6. Hogan Q. Distribution of solution in the epidural space: examination by cryomicrotome section. *Reg Anesth Pain Med*. 2002;27:150–156.
7. Ilfeld BM. Continuous peripheral nerve blocks: an update of the published evidence and comparison with novel, alternative analgesic modalities. *Anesth Analg*. 2017;124:308–335.
8. Singelyn FJ, Gouverneur JM. Extended "three-in-one" block after total knee arthroplasty: continuous versus patient-controlled techniques. *Anesth Analg*. 2000;91:176–180.
9. Ilfeld BM, Thannikary LJ, Morey TE, Vander Griend RA, Enneking FK. Popliteal sciatic perineural local anesthetic infusion: a comparison of three dosing regimens for postoperative analgesia. *Anesthesiology*. 2004;101:970–977.
10. Ilfeld BM, Morey TE, Enneking FK. Infraclavicular perineural local anesthetic infusion: a comparison of three dosing regimens for postoperative analgesia. *Anesthesiology*. 2004;100:395–402.
11. Machi AT, Sztain JF, Kormylo NJ, et al. Discharge readiness after tricompartment knee arthroplasty: adductor canal versus femoral continuous nerve blocks—a dual-center, randomized trial. *Anesthesiology*. 2015;123:444–456.
12. Yuan SC, Hanson NA, Auyong DB, Choi DS, Coy D, Strodtbeck WM. Fluoroscopic evaluation of contrast distribution within the adductor canal. *Reg Anesth Pain Med*. 2015;40:154–157.

13. Jaeger P, Baggesgaard J, Sorensen JK, et al. Adductor canal block with continuous infusion versus intermittent boluses and morphine consumption: a randomized, triple-masked, controlled clinical trial [abstract]. *Reg Anesth Pain Med*. 2017:3841.
14. Taboada M, Rodríguez J, Bermudez M, et al. Comparison of continuous infusion versus automated bolus for postoperative patient-controlled analgesia with popliteal sciatic nerve catheters. *Anesthesiology*. 2009;110:150–154.
15. Monahan AM, Sztain JF, Khatibi B, et al. Continuous adductor canal blocks: does varying local anesthetic delivery method (automatic repeated bolus doses versus continuous basal infusion) influence cutaneous analgesia and quadriceps femoris strength? A randomized, double-masked, controlled, split-body volunteer study. *Anesth Analg*. 2016;122:1681–1688.
16. Charous MT, Madison SJ, Suresh PJ, et al. Continuous femoral nerve blocks: varying local anesthetic delivery method (bolus versus basal) to minimize quadriceps motor block while maintaining sensory block. *Anesthesiology*. 2011;115:774–781.
17. Hamdani M, Chassot O, Fournier R. Ultrasound-guided continuous interscalene block: the influence of local anesthetic background delivery method on postoperative analgesia after shoulder surgery: a randomized trial. *Reg Anesth Pain Med*. 2014;39:387–393.

DOI: 10.1213/ANE.0000000000002268

Is Etomidate Sedation Associated With Excess Mortality in Intensive Care Unit Patients? What Is the Evidence?

To the Editor

The review article on the hypothalamic–pituitary–adrenal axis by Besnier et al[1] discusses the effects of etomidate at some length. The authors cite the letter by Ledingham and Watt[2] from 1983 as evidence that "etomidate has been associated with high mortality in sedated intensive care unit patients as a result of adrenal failure." Many other authors have cited this letter as well.

However, close inspection of the Ledingham and Watt citation does not strongly support the conclusion that etomidate caused "high mortality." Ledingham and Watt published a letter to the editor in *Lancet*, which briefly reported a retrospective observation comparing trauma patients from 1979 to 1980 sedated with opioids and benzodiazepines to trauma patients from 1981 to 1982 sedated with opioids and etomidate. The case mortality rate was 12 of 47 (25%) for the earlier (benzodiazepine) group and 18 of 26 (69%) for the later (etomidate) group. Ledingham and Watt did not actually draw a conclusion from these data.

Subsequent to their letter, these authors published a more detailed article in *Anaesthesia*.[3] Consistent with their letter in *Lancet*, Watt and Ledingham reported that there was an increased mortality in ventilated trauma patients sedated with etomidate and morphine compared to patients sedated with benzodiazepines and morphine. They attributed this to low cortisol levels resulting from inhibition of cortisol biosynthesis by etomidate, although they did not actually measure cortisol in patients sedated with morphine and benzodiazepines. The comparison of mortality rate was made from 50 patients treated with morphine and benzodiazepines in 1979–1980 (28% mortality) to 27 patients treated with morphine and etomidate in 1981–1982 (77% mortality; $P < .0005$).

The mean dose of morphine per 24 hours was 117 mg in the benzodiazepine-treated group and 120 mg in the etomidate-treated group. As described by the authors, patients from the earlier group who did not receive etomidate were treated primarily with morphine, "while benzodiazepines were rarely used for >2 or 3 days and then in less than half the patients," whereas patients treated in the later group received etomidate "in a dose sufficient to maintain sleep, more or less uninterruptedly." Thus, it appears that patients treated with etomidate were likely more "deeply" sedated than those in the group who did not receive etomidate. Cortisol concentrations were measured in 17 of 27 patients who received etomidate and none of the patients who did not receive etomidate. The cortisol data are not actually reported in the article, although the cortisol concentrations were described as being "<260 nmol/L on at least 1 occasion"; 260 nmol/L is given by the authors as the lower limit of "normal" cortisol levels.

This study is difficult to interpret for numerous reasons. It was retrospective, and the 2 patient groups were not contemporaneous. It is impossible to know whether patients receiving etomidate were at a greater risk of mortality than the preceding group of patients. Patients receiving etomidate appear to have been sedated to a substantially greater "depth" than earlier patients, based on the description given by the authors. The number of patients studied is small. The cortisol data are incomplete.

I submit that neither the letter of Ledingham and Watt nor the subsequent paper by them convincingly show that etomidate is "associated with high mortality as a result of adrenal failure" in sedated intensive care unit patients.

T. Andrew Bowdle, MD, PhD, FASE
Departments of Anesthesiology and Pharmaceutics
University of Washington
Seattle, Washington
bowdle@u.washington.edu

REFERENCES

1. Besnier E, Clavier T, Compere V. The hypothalamic-pituitary-adrenal axis and anesthetics: a review. *Anesth Analg*. 2017;124:1181–1189.
2. Ledingham IM, Watt I. Influence of sedation on mortality in critically ill multiple trauma patients. *Lancet*. 1983;1:1270.
3. Watt I, Ledingham IM. Mortality amongst multiple trauma patients admitted to an intensive therapy unit. *Anaesthesia*. 1984;39:973–981.

DOI: 10.1213/ANE.0000000000002266