Critical Review Form
Therapy

Morrison RS, Dickman E, Hwang U, et al. Regional Nerve Blocks Improve Pain and Functional Outcomes in Hip Fracture: A Randomized Controlled Trial. J Am Geriatr Soc. 2016 Dec;64(12):2433-2439.

Objective: **To compare "a pain management program consisting of a single-injection femoral nerve block (FNB) administered by an emergency physician followed by placement of a continuous fascia iliaca block (cFIB) by an anesthesiologist 24 hours later with conventional analgesic treatment (opioids and acetaminophen administered at treat physician discretion) at three New York hospitals." (p 2434)**

Methods: **This was a randomized controlled trial at three New York emergency departments (ED) – Mount Sinai and Beth Israel in Manhattan and Maimonides in Brooklyn between April 2009 and March 2013. In July of each year, incoming emergency medicine residents received FNB training to administer 20 mL of 0.5% bupivacaine under ultrasound guidance. Within 24 hours after FNB anesthesiologists inserted cFIB under ultrasound guidance with bolus of 15 mL 0.2% ropivacaine followed by continuous infusion of 0.2% ropivacaine at 5 mL/h. Catheters were removed on post-op day 3.**

Eligibility included patients over age 60 years with an acute hip fracture and arrival at one of these three ED's between 8A and 8P. Exclusion criteria (Figure 1, p 2435) included multiple trauma, cancer-related fractures, bilateral hip fractures, previous fracture or surgery at the current fracture site, transfer from another hospital, presentation >48 hours after fracture, affirmative response to either of first two items on Drug Abuse Screening Test or documentation of substance abuse in the medical chart, inability to speak either English or Spanish or Russian, history of adverse reaction to bupivacainie or ropivacaine, allergy to opioids, bleeding diatheses, inability to self-report pain, or moderate cognitive impairment defined by score of 3 or less on Six Item Screener.

Eligible subjects were randomized to FNB or standard care (control). The control patients received conventional standing and as-needed parenteral or oral analgesics (opioids and acetaminophen) as determined by the treating physician. Trained research interviewees identified potential subjects for enrollment and interviewed them daily about pain and opioid-related side effects and physical performance testing after post-op day 3. Walking ability at 6-weeks was ascertained by telephone. Pain was assessed using 0-10 numeric rating scale. Ambulation was evaluated by ability to walk past a bedside chair. To identify delirium the Confusion Assessment Method was checked for daily in chart reviews. Other factors evaluated included Charlson Comorbidity Index, Functional Independence Measure, Geriatric Depression Scale, and overall health-related quality of life.

The primary outcome is unclear, but "main outcomes" included pain at 1- and 2-hours after ED admission, as well as with transfers and walking on post-op day 3. With a total sample size of 396 patients the study had 80% power to detect a 0.5-point difference in ED and post-

operative pain with a two-sided alpha of 0.05. To reduce the risk of alpha inflation secondary to multiple comparisons the Benjamini-Hochberg False Discovery Rate adjustment (reported below as "q") was used for quantifying statistical significance. Although a multivariable analysis was performed, it is not reported in this manuscript.

Name:	PGY:	Date:

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Guide	Comments
Are the results valid?	
Did experimental and control groups being the study with a similar prognosis?	
Were patients randomized?	Yes. "Subjects were randomized to FNB or standard care (control) using a computer-generated, stratified, blocked randomization list, with stratification according to site. The block size for the randomization was randomly chosen for each block as two, four, or six participants." (p 2434)
Was allocation concealed? Was it possible to subvert the randomization to ensure a patient would be "randomized" to a particular group?	Yes. "After conducting the initial interview, interviewers informed the treating physician that the individual was enrolled in the trial, left the ED, and contacted the project manager to inform her of a study enrollee in the ED and the identity of the treating physician. The project manager determined randomization status by opening a sealed envelope and, remaining blinded to the individual's identity, contacted the treating EP to let them know whether the enrolled participant was to receive a FNB or standard analgesic care." (p 2434)
Were patients analyzed in the groups to which they were randomized?	Yes. "All analyses were intention to treat." (p 2436)
Were patients in the treatment and control groups similar with respect to known prognostic factors?	Yes. "There were no significant differences in baseline participant characteristics between the two groups and between participants who completed the study and those lost to follow-up." (p 2436)
Did experimental and control groups retain a similar prognosis after the study started?	
Were patients aware of group allocation?	Yes. "Sham saline injections and catheter infusions were considered, but rejected as pilot data demonstrated that neither EP's nor anesthesiologists would perform sham injections because they believed them to be unethical. Sham catheters taped to the skin were initially employed as a blinding technique for the cFIB but were subsequently discarded early in the course of the study because clinical nursing staff were routinely able to detect the difference between sham and actual catheters." (p 2435)
Were clinicians aware of group allocation?	Yes – see above.
Were outcome assessors aware of group allocation?	No. "Interviewers remained blinded to participants' randomization status throughout the trial, as did the investigators." (p 2434)
Was follow-up complete?	No. 2% of controls and 9% of intervention patients were lost before hospital discharge. In addition, 30% of controls and 29% of intervention participants were lost at 6-week follow-up. (p 2436)
What are the results?	
How large was the treatment effect?	Sufficiently complete data obtained to analyze for 81 controls and 72 intervention patients at the time of hospital discharge. The mean age was 82 and 72% were female with over 90% living at home and over 90% were non-Hispanic Caucasian ethnicity. The majority of fractures were intertrochanteric and operative repair occurred at 1.5 days on average. Over 75% were discharged to a rehabilitation facility with the average hospital length-of-stay just over 6 days. No significant differences in baseline pain, but significant reduction in pain favoring nerve block at day 1 (mean pain score 3.7 in nerve block versus 5.3 in control) and day 2 (3.5 vs. 5.3, p <0.001). Nerve block patients had significantly less pain at rest, with transfers, and with walking. (p 2436) Nerve block patients were able to ambulate farther on Day 3 (171 feet [95% CI 109-232] vs. 100 feet [95% CI 65-135], p = 0.048) and significantly more likely to report ability to walk beyond bedside chair (82% vs. 64%, OR 2.49 [95% CI 1.17-5.29), p= 0.02, q = 0.039). **Nerve block patients were significantly less likely to have PT session missed or shortened (12.5% vs. 27.2%, OR 0.38 [95% CI 0.16-0.89], p = 0.03, q = 0.048).** At 6-weeks nerve block patients

	reported better ambulation and stair-climbing ability on the FIM locomotion score. Nerve block patients required 33% less morphine equivalents (0.8 mg/hour, 95% CI 0.64-1.05 mg/hour vs. 1.2 mg/hour, 95% CI 0.94-1.40 mg/hour, p = 0.03, q = 0.048). The number of reported severe opioid-related side effects (>1 day of severe nausea, sedation, or unclear thinking) was lower in the nerve block group (3% vs. 12%, OR 0.20 [95% CI 0.04-0.96], p = 0.04, q = 0.048). There were no episodes of bleeding, falls, or catheter-related infections in the intervention group and delirium rates were similar in both groups (17% control vs. 16% intervention, p = 0.83). (p 2437) Seven intervention patients did have cFIB catheter removed by nursing before post-op day 3 "because nursing staff insisted they be removed because participants developed delirium that staff attributed to catheters". (p 2436)
How precise was the estimate of the treatment effect? (i.e. what 95% CIs were associated with the results?)	See 95% CI above.
How can I apply the results to patient care?	
Were the study patients similar to my patient?	In some regards yes, older hip fracture patients in an urban ED. However, predominantly English-speaking Caucasians living in Manhattan so likely different socio-economic strata then many in urban St. Louis.
Were all clinically important outcomes considered?	Very nearly yes. Follow-up at 6-weeks and analysis of positive impact on ability to participate in rehabilitation are essential. Since cognitively frail may be more likely to benefit from nerve blocks to prevent (or ameliorate) delirium, would have preferred these patients not be excluded but understand research challenges (with IRB and with confidence in pain reporting) to inclusion of these patients.
Are the likely treatment benefits worth the potential harm and costs?	Based upon this research in urban academic centers that are predominantly Caucasian and with Anesthesia partnering to provide catheter-based follow-up field blocks, the benefits of trained ED physicians to administer bupivacaine nerve blocks for hip fracture patients using ultrasound guidance appears safe and effective.

Limitations:

1) **Failure to explicitly state adherence to CONSORT reporting standards. EQUATOR Network reporting guidelines like CONSORT are designed to standardize manuscript reporting across medical fields and reduce the Tower of Babel that can ensue when different journals and specialties use different reporting strategies.**

2) **Failure to report the multivariable analysis controlling for age, prefracture functional status, prefracture pain level, type of fracture and repair, and pre-existing comorbidity.**
3) **Failure to report per-protocol analysis with intention to treat analysis. This is particularly important since 11% of the FNB patients went to operating room before nerve block could be performed so the positive effect size might be under-estimated.**

4) **Significant 6-month lost to follow-up without sensitivity analysis. Based on 40% lost to 6-month follow-up, these longitudinal outcomes should be interpreted very cautiously.**

5) **Lack of details about experience of individual residents with FNB as a predictor variable for outcomes assessed.**

6) **No clear single primary outcome. As with the movie Highlander, there can be only one.**

7) **Grossly underpowered with a priori sample size 396 compared with 153 ultimately enrolled with sufficient data to analyze. Although probably unlikely that a clinically relevant effect size was found by chance alone (Type I error), that is a possibility.**

8) **The mean difference in numeric pain rating observed has not been defined. For a visual analogue scale by Gallagher identified 13 mm threshold as clinically relevant on. However, regardless of whether the observed improvement in pain relief is clinically significant or not in research, this observation must be mitigated by multiple other improved patient-centric outcomes without observable harms.**

9) **Uncertain external validity in settings with different patient populations (non-Caucasian, non-Manhattan wealth) or with single nerve block in ED without subsequent Anesthesia catheter.**

10) **Exclusion of cognitively impaired patients. Ethical approaches to recruit cognitively impaired patients into research has now been developed because excluding these patients is also unethical. Methods to accurately identify dementia and delirium now exist, as well as transdisciplinary approaches to research in undifferentiated cognitive impairment.**

Bottom Line:

In largely Caucasian population, emergency medicine residents with structured point-of-care ultrasound training to administer femoral nerve block with bupivacaine followed by pre-operative Anesthesia continuous fascia iliaca block with ropivacaine, reduces pain immediately and in the first days of post-operative recovery at rest or with movement. In addition, functional recovery improves with less missed physical therapy time, lower morphine equivalents required, and less opioid side effects.

No nerve block procedural complications are reported, but the July 2019 issue of EM:RAP reviewed concerns about bupivacaine toxicity with the following recommendations. 1) Withdraw to ensure not in vascular structure before injecting and repeat withdraw after every 5-10 mL to ensure you haven't drifted into a vessel; 2) hydrolocate with POCUS before you inject; 3) be aware that the 20-30 mL of 0.25% to 0.5% bupivacaine required for hip fracture nerve blocks can induce cardiotoxicity including hypotension and seizures – since lidocaine does not have this cardiotoxicity or neurotoxicity consider using lidocaine rather than bupivacaine; and 4) don't use bupivacaine without intralipid nearby (in the ED).