Meta-Analysis

Somewhere Between Mega-Silliness and the Final Word, But Where?

Brian M. Ilfeld, MD, MS and Christopher L. Wu, MD†*

A meta-analysis aggregates quantitative data from multiple independent studies and subsequently applies statistics to produce an estimate of the net benefit of a common intervention. Since its inception, the validity of meta-analysis has been controversial, with some declaring it an "exercise in mega-silliness,"[1] while others vigorously defend its usefulness.[2] With such diverse views spread over multiple decades, we do not aim to resolve this debate in a relatively short editorial, but readers are left with the question of what to do with the results of a meta-analysis, such as the study published in this month's issue of *Regional Anesthesia and Pain Medicine*.[3] It is widely recognized that there is a hierarchy of the conclusiveness of results based on study design, listed here from lower to higher: case report, retrospective case series, prospective observational, and randomized controlled studies, with an infinite number of variations along this continuum. Where do meta-analyses fall upon this scale? Nearly all authorities consider large—often termed "mega"—randomized, double-masked, controlled trials as close to providing a definitive answer as is currently attainable within clinical medicine.[4] But, if there is no such megastudy involving an intervention, what are readers to do with the data of a meta-analysis compiling the findings of multiple smaller investigations? The purpose of this editorial is to help readers answer this question for themselves (hint: there is no widely accepted, definitive answer).

"Systematic reviews" provide an unbiased summary of the published data regarding a topic of interest and are now commonplace within anesthesia-related journals. The primary purpose of adding a meta-analysis is to calculate an effect size from the existing data to "increase the precision of the conclusions of a review."[5] But, do they? One way to answer this question is to compare the results from various meta-analyses and subsequent mega–randomized controlled trials (RCTs) on matching topics. The results of such comparisons are varied, with some excellent correlation—demonstrating the power of the meta-analysis to "predict" an accurate conclusion based on multiple small studies—and some abysmal results, in which an earlier meta-analysis produced evidence diametrically opposite subsequent findings.[6–10] Although somewhat controversial,[2,8,11–13] a review found that "the outcomes of the 12 large randomized controlled trials [RCT]… studied were not predicted accurately 35% of the time by the meta-analyses published previously on the same topics."[6] As noted by Dr Jadad,[5] "[readers] must be aware that an inappropriate meta-analysis may result in more harm than good. In these situations, they should understand that systematic qualitative review of the literature, in its own right, is more effective to summarize the evidence than a traditional unstructured (or narrative) review or an inappropriate or misleading meta-analysis." That being said, we should realize that "discrepancies between meta-analyses and large trials should be expected, given the variable characteristics and treatment responses in different persons, protocols, and populations."[8]

VALIDITY

Unfortunately, although there are guidelines to evaluate meta-analysis methodology[14–16] and techniques to help detect various sources of bias,[17] it is not currently possible to determine the accuracy of any 1 meta-analysis.[17] So, what are readers to "do" with results from these studies, such as the meta-analysis in this issue of the *Journal* by Bingham et al,[3] comparing single-injection and continuous peripheral nerve blocks? To help provide perspective, consider how much credence you would put in the results of the following hypothetical prospective, RCT, based on the meta-analysis of Bingham

From the *Department of Anesthesiology, University of California at San Diego, San Diego, CA; and †Johns Hopkins University, Baltimore, MD.
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Address correspondence to: Brian M. Ilfeld, MD, MS, Department of Anesthesiology, 200 W Arbor Dr, MC 8770, San Diego, CA 92103-8770 (e-mail: bilfeld@ucsd.edu).
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et al: no specific inclusion criteria shared by all subjects (other than age = adult),[2] no specific surgical procedure or anatomic location (not even exclusively orthopedic surgery), no shared intervention (eg, mepivacaine vs ropivacaine single injection; basal-only vs combined basal/bolus perineural infusion), variable blinding to treatment (eg, some subjects masked to their treatment with others unmasked),[18] no shared protocol (eg, 24 vs 96 hours of perineural infusion), no defined primary end point, no shared definitions for any secondary end point (eg, "worst pain" and "pain with movement" considered identical), and minimal correction for multiple comparisons among treatment groups (therefore, an unusually high risk of types 1 and 2 errors). Inclusion of any 1 of these characteristics would usually deem a manuscript unpublishable in any quality medical journal.

Meta-analyses should not automatically be considered "superior" to individual RCTs, as increasing the number of subjects does not automatically increase the precision or validity of the results. Nevertheless, these 2 study designs are not mutually exclusive, and meta-analysis can enable "the systematic exploration of bias and diversity in research rather than the distillation of a magic odds ratio."[19] As Dr Devereaux et al[20] recently opined, "the most informative meta-analyses include several large clinical studies and allow researchers to evaluate the impact across variations in patient populations."

HETEROGENEITY

For example, consider the following: your patients undergoing mastectomy are experiencing postoperative pain outlasting the single-injection paravertebral blocks you currently place. Should you add a postoperative perineural infusion to your single-injection block? The results of the meta-analysis of Bingham et al suggest that, indeed, you should: compared with single-injection blocks, continuous blocks were associated with decreased pain, overall opioid use, nausea, and patient dissatisfaction—with effect sizes provided for each.[3] However, the only randomized controlled clinical trial comparing single-injection and continuous paravertebral blocks following mastectomy—and included in the meta-analysis—identified no benefits whatsoever.[21] Should you, the clinician, conclude that by combining the results from this 1 negative study of paravertebral blocks/catheters with 20 other studies, including catheters in multiple other anatomic locations and surgical procedures, the meta-analysis provides more-reliable information for paravertebral blocks than the only available RCT specifically involving that catheter site? It may be difficult to apply the results of a meta-analysis to individual patients, and "an overall estimate from a meta-analysis can be misrepresentative if there is considerable heterogeneity among the included trials that has not been fully investigated."[11] A properly performed meta-analysis will evaluate heterogeneity and quantify the reasons for any discrepancies.[4] Unfortunately, the common test for homogeneity—based on the χ^2 distribution—frequently lacks power, leaving heterogeneity undetected.[22]

CONCLUSIONS

As noted previously, there is no general consensus. In our opinion, meta-analyses are often most useful in aggregating multiple studies—frequently published in a plethora of journals over multiple decades—into a single article for health care providers and consumers (ie, the "systematic review"). In this respect, the article of Bingham et al is outstanding: the information contained within its appendices—alone—is of enormous benefit worthy of publication, and we applaud our colleagues' tremendous efforts in this respect. However, great caution is required when interpreting effect sizes produced by meta-analysis, especially with increasing heterogeneity of the incorporated smaller studies,[23] as there may be "overstatements of the strength and precision of the results."[4] However, although potential biases exist in meta-analyses (as in clinical trials), properly performed meta-analyses attempt to highlight these biases and should explore the reasons for identified heterogeneity. As noted by Dr Ioannidis et al,[8] "meta-analysis is not statistical alchemy that makes life easier by distilling 1 magic number from confounded data; it is a scientific discipline that aims to quantify evidence and to explore bias and diversity in research systematically."

Thus, a report of a meta-analysis does not automatically confer scientific accuracy and finality, but a high-quality meta-analysis may be a valuable tool for summarizing data across multiple studies and generating hypotheses for future RCTs.

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Continuous Peripheral Nerve Block Compared With Single-Injection Peripheral Nerve Block

A Systematic Review and Meta-Analysis of Randomized Controlled Trials

Ann E. Bingham, MD, Rochelle Fu, PhD,† Jean-Louis Horn, MD,† and Matthew S. Abrahams, MD†*

Background and Objectives: Many practitioners consider continuous peripheral nerve blocks (cPNBs) to be superior to single-injection peripheral nerve blocks (siPNBs). Several randomized controlled trials have demonstrated improved pain control, patient satisfaction, and other outcomes for patients with cPNBs compared with patients with siPNBs, whereas other trials have not shown significant differences. We sought to clarify any potential advantages of cPNBs over siPNBs.

Methods: We conducted a systematic review and meta-analysis of all prospective, randomized trials comparing cPNBs with siPNBs. We used a validated systematic search strategy to identify potentially eligible studies. For studies meeting inclusion criteria, methodologic quality was scored independently by 2 reviewers. Data from the studies were abstracted and pooled for meta-analysis.

Results: Compared with siPNBs, cPNBs were associated with a decreased rating of worst pain on postoperative day 0 (effect size [ES], −1.29; 95% confidence interval [CI], −2.19 to −0.40; $P = 0.005$), postoperative day 1 (ES, −1.87; 95% CI, −2.44 to −1.31; $P < 0.001$), and postoperative day 2 (ES, −2.03; 95% CI, −2.78 to −1.290; $P < 0.001$); decreased overall opioid use (ES, −15.70; 95% CI, −21.84 to −9.55; $P < 0.001$); less nausea (ES, 0.633; 95% CI, 0.407–0.983; $P = 0.043$); and higher patient satisfaction scores (weighted mean difference, −2.04; 95% CI, 1.24–2.85; $P < 0.001$).

Conclusions: Compared with siPNBs, cPNBs were associated with improved pain control, decreased need for opioid analgesics, less nausea, and greater patient satisfaction. The effect of cPNBs on other clinically relevant outcomes, such as complications, long-term functional outcomes, or costs, remains unclear.

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Continuous peripheral nerve blocks (cPNBs) have many potential advantages over single-injection peripheral nerve blocks (siPNBs). By providing superior pain relief for several days after painful surgical procedures, cPNBs may facilitate early hospital discharge[1] and aggressive early rehabilitation[2,3] and may decrease adverse effects related to systemic analgesic medications.[4,5] In addition, by reducing complications and facilitating early discharge, cPNBs may reduce health care–associated costs. Whereas several randomized controlled trials (RCTs) have shown that, compared with siPNBs, cPNBs are associated with improved pain control, lower opioid requirements, and improved patient satisfaction,[6–10] several similar studies have not shown similar differences in pain control or other outcomes.[11–13]

Although cPNBs offer potential advantages over siPNBs, they also create potential problems. Prolonged peripheral nerve blocks could cause patients to injure the insensate limb[14] and fall due to a prolonged motor block (especially for lower-extremity blocks)[15] and could increase the potential for nerve injury.[16] Management of cPNBs requires coordination among care teams, especially if the patient is on anticoagulants.[17] In addition, catheter-related problems, such as dislodgment or malfunction of the catheter or infusion pump, can occur,[18–20] and catheters may be difficult to remove.[21]

To clarify the potential risks and benefits of cPNBs versus siPNBs, we performed a systematic review and meta-analysis of RCTs comparing the 2 techniques.

METHODS

Data Extraction and Quality Analysis

To find all relevant studies, we used a validated 2-step search methodology[22] to search the PubMed, Google Scholar, Scopus, and OVID databases. Inclusion criteria were RCTs, human subjects, and the comparison of single-injection nerve block versus continuous infusion nerve block. Studies were excluded if they compared different blocks (eg, axillary vs infraclavicular), were performed to evaluate different dosing regimens, or compared perineural techniques with different analgesic modalities, such as systemic opioids or neuraxial blocks. The initial search terms were as follows: *nerve block continuous*, *nerve block catheter*, and *peripheral nerve catheter*. Secondary search terms were *continuous* with *interscalene*, *supraclavicular*, *infraclavicular*, *axillary*, *paravertebral*, *intercostal*, *transversus abdominis plane*, *femoral, sciatic, lumbar plexus, and popliteal; and catheter with interscalene, supraclavicular, infraclavicular, axillary, intercostal, transversus abdominis plane, femoral, sciatic, lumbar plexus, and popliteal.*

Authors were contacted by e-mail for clarification of data, if needed. For the purposes of this review, the 4 relevant publications by Williams et al[23–26] are considered as 1 study (single data set). Data from each of the studies were extracted and compiled in a database with the following parameters: visual analog scale pain scores, opioid use, adverse effects such as nausea, and patient satisfaction. Where authors report pain scales of 0 to 10, we converted to a 0- to 100-point scale to allow pooling of data. Where authors reported opioid use, we converted to oral morphine equivalents to facilitate comparison.[27,28] The variables worst pain, pain with movement, and worst pain with movement

From the *Department of Anesthesiology, Columbia University, New York, NY; and †Department of Anesthesiology and Perioperative Medicine, Oregon Health Sciences University, Portland, OR.

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Address correspondence to: Matthew S. Abrahams, MD, Department of Anesthesiology and Perioperative Medicine, Oregon Health and Science University, 3181 SW Sam Jackson Park Rd, UHS-2, Portland, OR 97239 (e-mail: m.abrahams.md@gmail.com).

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were pooled for analysis as a single outcome measure, as we felt these were all indicative of the patients' maximum pain.

Methodologic quality of each study was scored independently by 2 of the authors (M.F.A. and A.E.B.) according to the following 9-item scoring system: (1) the method of randomization; (2) adequate measures taken to conceal allocation; (3) inclusion and exclusion criteria for patients entered into the study; (4) adequate description of treatment and control groups at the entry to the study; (5) the anesthetic care was identical between the groups other than the duration of nerve block; (6) block technique (true single-injection technique and true continuous block technique); (7) clear definition of the outcome measures in the text; (8) blinding of the patient, anesthesiologists, and assessors to the treatment group; and (9) statistical analysis on an intention-to-treat basis.

This scoring system was based on the system developed by Jadad et al[29] and was adapted from a scoring system used by the authors for a previous meta-analysis.[30] Each study could receive a maximum score of 13. The method of randomization and blinding techniques were considered the most important and could draw a maximum score of 3 points each. All other items could draw a score of 1 point. Studies with scores of 5 or less were considered poor quality and were excluded from further analysis. Those with scores of 6 to 10 were considered fair-quality studies, and those with scores of 11 or higher were considered good-quality studies.

Statistical Analysis

We conducted meta-analyses to obtain more precise estimates comparing single-injection to continuous nerve blocks. For binary outcomes such as complications, a pooled risk ratio (RR) was estimated using the fixed-effect Mantel-Haenszel method when the between-study heterogeneity was estimated to be 0. Otherwise, the DerSimonian-Laird[31] random-effects model[32] was used. For continuous outcomes, such as visual analog scale pain scores, opioid dose, adverse effects such as nausea, and patient satisfaction, the mean differences (standard errors) between the single-injection and continuous techniques were calculated from each study and combined using the DerSimonian-Laird[31] random-effects model to account for differences among studies. When median instead of mean values were reported, we used the difference in medians to approximate mean difference when the distribution of the data was quite symmetric, as in most cases. The SD, if not reported, was calculated based on the reported range.[33] When the reported data showed evidence of skewness, we calculated SD by assuming the log-transformed data had a normal distribution. Statistical heterogeneity was assessed by Cochran Q test and I^2 statistic.[34] Publication bias was tested using funnel plot and the linear regression method of Egger et al.[35,36] No publication bias was detected by these methods, although the interpretation of results may be limited because of the relatively small number of studies in each meta-analysis. All analyses were performed using Stata 10.0 (StataCorp, College Station, Texas [2007]).

RESULTS

Patients and Studies Included

Together, the primary and secondary search terms yielded 713 studies. The abstracts of these studies were reviewed, and 31 of these fit the inclusion criteria. "Related citations" were searched for each of these studies, yielding 1053 additional studies. However, only 1 of these met the inclusion criteria. The reference lists of eligible studies were also searched and yielded no additional articles. The 32 articles identified were reviewed in detail to determine ultimate eligibility for inclusion in our analysis. Non-English studies were not excluded, although 1 of these studies was excluded because of the unavailability of adequate Lithuanian translation.[37] Six studies were excluded for lack of a true siPNB group (comparison of overnight infusion with 4-day infusion).[1,38–41] One study was excluded because of comparison of siPNB with a cPNB group that did not receive an initial bolus of local anesthetic as part of the dosing regimen.[36–42] Four studies[23–26] were considered as 1 data set because data for all of these studies originated from a single prospective study (Table 1). Two studies were given methodologic quality scores of 5 or less and were therefore excluded from further analysis.[43,44] Ultimately, 21 studies involving a total of 702 patients met all inclusion criteria and were included for analysis. Thirteen studies were considered fair quality, and 8 were considered good quality. Reported data of included studies are summarized in Table 1 and are described in more detail in Appendix A (Supplemental Digital Content 1, http://links.lww.com/AAP/A53). Specifically excluded studies are summarized in Appendix B (Supplemental Digital Content 2, http://links.lww.com/AAP/A54).

Outcome Measures

Pain

Continuous PNBs resulted in decreased visual analog scale rating of worst pain compared with siPNBs on postoperative day (POD) 0 (effect size [ES], −1.29; 95% confidence interval [CI], −2.19 to −0.40; $P = 0.005$), POD 1 (ES, −1.87; 95% CI, −2.44 to −1.31; $P < 0.001$), and POD 2 (ES, −2.03; 95% CI, −2.78 to −1.290; $P < 0.001$). There was no significant difference in rating of worst pain on POD 3 (ES, −0.28; 95% CI, −0.90 to 0.34; $P = 0.375$) (Fig. 1A–D).

Continuous PNBs resulted in decreased visual analog scale rating of pain at rest compared with siPNBs on POD 0 (ES, −0.90; 95% CI, −1.61 to −0.20; $P = 0.012$), POD 1 (ES, −1.96; 95% CI, −2.39 to −1.53; $P < 0.001$), and POD 2 (ES, −1.32; 95% CI, −2.24 to −0.39; $P = 0.005$). There was no significant difference in rating of pain at rest on POD 3 (ES, −0.45; 95% CI, −1.07 to 0.16; $P = 0.150$) (Fig. 2A–D).

Satisfaction

Continuous PNBs were associated with higher patient satisfaction scores compared with siPNBs (weighted mean difference, 2.04; 95% CI, 1.24–2.85; $P < 0.001$) (Fig. 3).

Opioid Requirements

Compared with siPNBs, cPNBs were associated with decreased opioid consumption on POD 1 (ES, −29.14; 95% CI, −43.25 to −15.02; $P < 0.001$) and POD 2 (ES, −25.64; 95% CI, −37.01 to −14.27; $P < 0.001$) (Fig. 4A, B). There was no significant difference in opioid consumption on POD 3 (ES, −3.42; 95% CI, −9.41 to 2.57; $P = 0.263$). There was a statistically significant reduction in average daily opioid use over the entire study periods (ES, −15.70; 95% CI, −21.84 to 9.55; $P< 0.001$) (Fig. 4A–D).

Complications

Patients in the cPNB groups had significantly less nausea than did patients in the siPNB groups. For studies reporting results as number of patients per group experiencing adverse effects,[4,6,24,45–47] ES was calculated as the RR (overall RR, 0.35; 95% CI, 0.17–0.70; $P = 0.003$). For studies reporting the percentage of patients in each study group experiencing adverse effects,[11–13,48,49] ES was calculated as the incidence ratio (IR)

TABLE 1. Studies Included for Analysis

Author (Year Published)	N (Continuous/ Single-Injection)	Block Performed (Surgery)	VAS (Continuous/ Single-Injection)	Other Outcomes (cPNB/siPNB)	Quality Score
Buckenmaier et al[13] (2010)	(26/26/21) Adults undergoing unilateral surgery for localized breast cancer	Paravertebral (breast); initial block with 0.1% ropivacaine at T1 and T6 and 0.5% ropivacaine with catheter at T3; 0.2% ropivacaine/ 0.1% ropivacaine/normal saline (NS) infusion for 72 h	Worst postoperative VAS POD 1* 2.5/2.7/2.8† Worst postoperative VAS POD 3*: 2.2/2.4/1.8 Worst postoperative VAS POD 5*: 1.8/2.5/1.7 Worst postoperative VAS POD 7*: 1.2/2.7/1.9	Nausea, mood, level of symptom distress, time to return to normal activities not significantly different	11
Elliot et al[52] (2010)	(27/27) Adult patients, ASA status unspecified, undergoing ankle or hindfoot surgery	Popliteal (ankle and hindfoot); 20 mL of 0.5% bupivacaine initial bolus. 0.25% bupivacaine vs NS for 72 h	VAS POD 0‡: 1.2/1.0 VAS POD 1‡: 1.7/3.7† VAS POD 2‡: 1.3/2.8 †VAS POD 3‡: 1.1/2.6†	mg Morphine used POD 2‡:10/20† mg Morphine used POD 3‡: 7.5/10† Total mg morphine used POD 1–3‡: 30/52.5†	8
Fredrickson[8] (2010)	(31/30) Adult patients, ASA I–II, undergoing arthroscopic subacromial decompression, lateral clavicle excision, or stabilization	Interscalene (shoulder); initial bolus 30 mL ropivacaine 0.5%; infusion of 2 mL/h 0.2% ropivacaine with 5 mL/h demand dose for 48 h vs catheter removal in postanesthesia care unit (PACU)	Worst pain with movement POD 1‡: 2/4† Worst pain with movement POD 2†: 3/5	Satisfaction score†: 9/9 Tramadol tablets required POD 2†: 0/1† Tramadol tablets required POD 2†: 0/1†	10
Frassanito et al[11] (2009)	(22/22) Adult patients, ASA I–III, undergoing total knee arthroplasty under regional anesthesia (RA) with sedation	Lumbar plexus (knee); initial bolus 0.6% ropivacaine, 30-mL infusion of ropivacaine 0.2% at 10 mL/h for 48 h vs single injection. Also single-injection sciatic nerve block for all patients	Pain (VAS) at 6 h*: 0.4/0 Pain (VAS) at 12 h*: 1.7/1.6 Pain (VAS) at 24 h*: 3.7/5.1 Pain (VAS) at 36 h*: 4.8/3.1 Pain (VAS) at 48 h*: 3.2/1.7	Total mg tramadol consumption*: 185/236	9
Mariano[9] (2009)	(15/15) Adult subjects, ASA status unspecified, undergoing elective shoulder surgery	Interscalene (shoulder); initial bolus 40 mL ropivacaine 0.5%; infusion of 0.2% ropivacaine or 0.9% NS	Worst pain POD 0†: 0/0 Worst pain POD 1†: 4/7.5† Worst pain POD 2†: 2.8/8† Worst pain POD 3†: 5/6	Satisfaction with analgesia†: 10/7† mg Oxycodone consumed POD 1†: 0/20† mg Oxycodone consumed POD 2†: 0/30†	12
Williams et al[23–26] (2006, 2007, 2007 2009)	(76/79) Adult participants, ASA I–II, undergoing elective ACL reconstruction under spinal with sedation (block performed in PACU)	Femoral (knee); initial bolus 0.25% levobupivacaine 30 mL; infusion of 0.25% levobupivacaine or 0.9% NS at 5 mL/h until 270-mL reservoir depleted	NRS with movement POD 1†: 2/3† NRS with movement POD 2†: 2/4†	Mean mg oxycodone consumption POD 1–4: 88/94	12

(Continued on next page)

TABLE 1. *(Continued)*

Author (Year Published)	N (Continuous/ Single-Injection)	Block Performed (Surgery)	VAS (Continuous/ Single-Injection)	Other Outcomes (cPNB/siPNB)	Quality Score
Capdevila[7] (2006)	(23/30/30) Adult patients, ASA I–III, undergoing acromioplasty or hallux valgus surgery	Interscalene or popliteal (shoulder or foot); initial bolus 0.5% ropivacaine 30 mL followed by infusion of 0.2% ropivacaine 7 or 5 mL/h with ≤10 mL/h PCA bolus for 72 h; single-injection group had catheter removed in PACU	VAS with movement 10 min†: 0/0/0 VAS with movement 1 h†: 0/0/0 VAS with movement 4 h†: 0/0/1† VAS with movement 12 h†: 0/0/2.1† VAS with movement POD 1†: 1/0/2.1† VAS with movement POD 2†: 0/1/2.1† VAS with movement POD 3†: 0/0/1.2†	% Patients very satisfied: 63/57/22† % Patients satisfied: 17/23/24 % Patients mildly satisfied: 13/17/35† % Patients not satisfied: 7/3/9 mg Ketoprofen consumed in 72 h*: 100/200/500†	9
Kean et al[49] (2006)	(8/8) Adult patients, ASA I–III, undergoing open shoulder surgery	Interscalene (shoulder); initial block with 0.5% levobupivacaine 30 mL; continuous group: 0.25% levobupivacaine at 5 mL/h for 24 h. Single-injection group: sham catheter attached to skin	VAS in recovery room (scale 0–100)*: 5/10 VAS 6 h postoperatively (scale 0–100)*: 1.25/9 VAS 12 h postoperatively (scale 0–100)*: 0.13/26.88† VAS 24 h postoperatively (scale 0–100)*: 16.88/41.25	Mean satisfaction (scale 0–100): 87/78† mg IV Morphine consumed at 24 h*: 3.38/27.63†	8
Salinas et al[50] (2006)	(18/18) Adult patients, ASA I–III, scheduled for primary total knee arthroplasty under spinal anesthesia	Femoral (knee); initial block with 0.375% ropivacaine 30 mL; cPNB group 0.2% ropivacaine 10 mL/h for 36 h; single-injection group: initial block only	Peak VAS during PT POD 1*: 4.7/6.3† Peak VAS during PT POD 2*: 3.9/6.1†	Cumulative mg oxycodone consumed*: 45/109†	10
Cuignet et al[46] (2005)	(27/27) Adult burn patients undergoing unilateral skin graft of the thigh	Fascia iliaca (skin graft); initial bolus 0.2% ropivacaine 40 mL; 0.2% ropivacaine 10 mL/h vs 0.9% NS 10 mL/h; control group (0.9% NS 40-mL bolus followed by continuous infusion of NS) excluded from analysis	Mean dynamic VAS score 6 h†: ½ Mean dynamic VAS score 24 h†: 1/3 Mean dynamic VAS score 48 h†: 2/3 Mean dynamic VAS score 72 h†: 2/3 Mean dynamic VAS score with 1st dressing change†: 3/6†	mg IV Morphine consumption in 72 h*: 5/6 % Patients with satisfaction rated "very good": 33/48 % Patients with satisfaction rated "poor": 15/7 % Patients with satisfaction rated "very poor": 11/0	9
Watson et al[58] (2005)	(16/16) Adults with osteoarthritis, ASA I–III, undergoing total knee arthroplasty under spinal and sedation	Lumbar plexus (knee); initial bolus 0.5% levobupivacaine 25 mL, catheter in both groups; cPNB group 0.1% levobupivacaine at 10 mL/h; single-injection group NS 10 mL mL/h for 48 h; single-injection sciatic block performed for all patients	VAS with movement 4 h†: 0/0 VAS with movement 8 h†: 0/0 VAS with movement 12 h†: 2/1 VAS with movement 24 h†: 5.75/8 VAS with movement 36 h†: 4.5/5.5 VAS with movement 48 h†: 4.5/4.5 VAS with movement 72 h†: 3/4.4	Cumulative mg IV morphine†: 19/32†	12
Zaric[10] (2004)	(30/30) Adult patients, ASA I–II, undergoing elective hallux valgus surgery under spinal with sedation	Popliteal (hallux valgus); initial sciatic block with 0.5% ropivacaine 30 mL; infusion 5 mL/h of 0.2% ropivacaine vs NS; saphenous block with 0.75% ropivacaine 10 mL	Worst VAS POD 0*: 3.3/6.4† Worst VAS POD 1*: 4.9/7.6† Worst VAS POD 2*: 4.6/5.0	No; tablets ketomebidone consumed in 3 d†: 2/3 No; patients very satisfied: 18/13 No; patients satisfied: 11/14 No; patients neutral: 1/2	8

Ilfeld[61] (2003)	(10/10) Adult patients, ASA status unspecified, undergoing moderately painful ambulatory shoulder surgery	Interscalene (shoulder); catheter with initial 1.5% mepivacaine 40 mL block followed by continuous infusion of 0.2% ropivacaine or NS at 8 mL mL/h for 48 h	Worst VAS POD 0†: 1.5/8.0† Worst VAS POD 1†: 3.25/8.0† Worst VAS POD 2†: 3.5/7.0† Worst VAS POD 3†: 7.5/7.0	Tablets oxycodone used POD 0†: 0/4† Tablets oxycodone used POD 1‡: 0.5/8† Tablets oxycodone used POD 2‡: 0/6† Average patient satisfaction: 8.8/6.5†	12
White et al[6] (2003)	(10/10) Adult patients, ASA I-III, undergoing foot or ankle surgery	0.25% bupivacaine 30 mL injected through needle, catheter then thread; infusion of 0.25% bupivacaine vs NS at 5 mL/h for 48 h	Maximum VAS in hospital†: 4/8† Maximum VAS after discharge†: 2.5/7.5†	Cumulative mg morphine consumed*: 10.3/34.7† % Completely satisfied with pain control: 90/10†	11
Ilfeld et al[48] (2002)	(15/15) Adult patients, ASA I-II, undergoing elective upper extremity surgery under RA	Infraclavicular (upper extremity); initial block 1.5% mepivacaine 50 mL; 0.2% ropivacaine or NS at 8 mL/h for 48 h	Average pain with movement POD 0*: 0.6/4.7† Average pain with movement POD 1*: 2.5/6.1† Average pain with movement POD 2*: 1.5/5.1† Worst pain with movement POD 0*: 0.9/5.5† Worst pain with movement POD 1*: 4.5/7.9† Worst pain with movement POD 2*: 3.7/6.8†	Narcotic tabs used POD 0*: 0.3/2.5† Narcotic tabs used POD 1*: 1.7/5.5† Narcotic tabs used POD 2*: 1.4/5.3† Narcotic tabs used POD 3*: 2.8/4.6†	12
Ilfeld et al[48] (2002)	(15/15) Adult patients, ASA I-II, undergoing elective surgery distal to the knee	Popliteal (lower leg); initial block 1.5% mepivacaine 50 mL; 0.2% ropivacaine or NS at 8 mL/h for 48 h	Worst VAS POD 0†: 0/7† Worst VAS POD 1†: 0/7† Worst VAS POD 2†: 1/6† Worst VAS POD 3†: 4.5/4	Tablets oxycodone used POD 0‡: 0/3† Tablets oxycodone used POD 1‡: 0/8† Tablets oxycodone used POD 2‡: 0/5† Average satisfaction with analgesia: 9.7/5.5†	11
Borgeat et al[45] (2000)	(18/15) Adult patients, ASA I-II, undergoing elective shoulder surgery	Interscalene (shoulder); initial block 0.75% ropivacaine 30 mL; cPNB: 0.2% ropivacaine 5 mL/h plus up to 9–12 mL/h bolus (kg weight dependent) for 48 h; single-injection group: initial block only	VAS at rest 6 h†: 0/0 VAS at rest 12 h†: 6/30† VAS at rest 24 h†: 4.5/20† VAS at rest 36 h†: 0/14.5 VAS at rest 48 h block†: 0/0	Patient satisfaction*: 9.7/7.5†	9
Klein[62] (2000)	(22/18) Adult patients, ASA I-III, undergoing open rotator cuff repair under RA	Interscalene (shoulder); initial block 0.5% ropivacaine 30 mL; ropivacaine 0.2% or NS at 10 mL/h for 24 h; single-injection group: initial block only	VAS 12 h*: 1/3.4† VAS 14 h*: 1.2/3.2† VAS 16 h*: 0.55/3.15† VAS 18 h*: 0.85/2.75† VAS 20 h*: 1.3/2.5† VAS 22 h*: 0.8/3.2† VAS 24 h*: 1.6/2.85†	Total mg postoperative morphine used*: 18/36† Satisfaction with analgesia*: 10/9	8

(Continued on next page)

TABLE 1. *(Continued)*

Author (Year Published)	N (Continuous/ Single-Injection)	Block Performed (Surgery)	VAS (Continuous/ Single-Injection)	Other Outcomes (cPNB/siPNB)	Quality Score
Borgeat et al[4] (1998)	(30/30) Adult patients, ASA I–II, undergoing elective shoulder arthroplasty or rotator cuff repair under general anesthesia	Interscalene (shoulder); initial 0.75 % ropivacaine 30 mL; cPNB group: 0.2% ropivacaine at 5 mL/h for 48 h; single-injection group: initial block only	VAS 12 h*: 4/24† VAS 18 h*: 14/38† VAS 24 h*: 13/47† VAS 30 h*: 10/39† VAS 36 h*: 9/30† VAS 42 h*: 7/27 VAS 48 h*: 4/24†	Patient satisfaction*: 9.6/7.5†	9
Borgeat et al[47] (1997)	(20/20) Adult patients, ASA I–II, undergoing elective shoulder arthroplasty or rotator cuff repair	Interscalene (shoulder); initial block with 0.4% bupivacaine 30 mL; cPNB group: 0.15% bupivacaine 5 mL/h for 48 h; single-injection group: initial bolus only	VAS 12 h*: 2.5/24† VAS 18 h*: 12.5/31†	Patient satisfaction*: 9.8/7.6†	9
Hirst et al[12] (1996)	(11/11) Adult patients undergoing knee surgery under general anesthesia	Femoral 3-in-1 (knee); initial block with 0.5% bupivacaine 20 mL; cPNB group: 0.125% bupivacaine 6 mL/h for 48 h; single-injection group: initial bolus only	VAS with movement 0 h*: 52/48† VAS with movement 12 h*: 62/58 VAS with movement 24 h*: 60/68 VAS with movement 48 h*: 58/54 VAS with movement 72 h*: 42/45	mg morphine PCA 0–24 h*: 25/41 mg morphine PCA 24–48 h*: 18/24	7

*Mean.

†$P < 0.05$ favoring cPNB.

†Median.

ASA indicates American Society of Anesthesiologists ACL, anterior cruciate ligament.

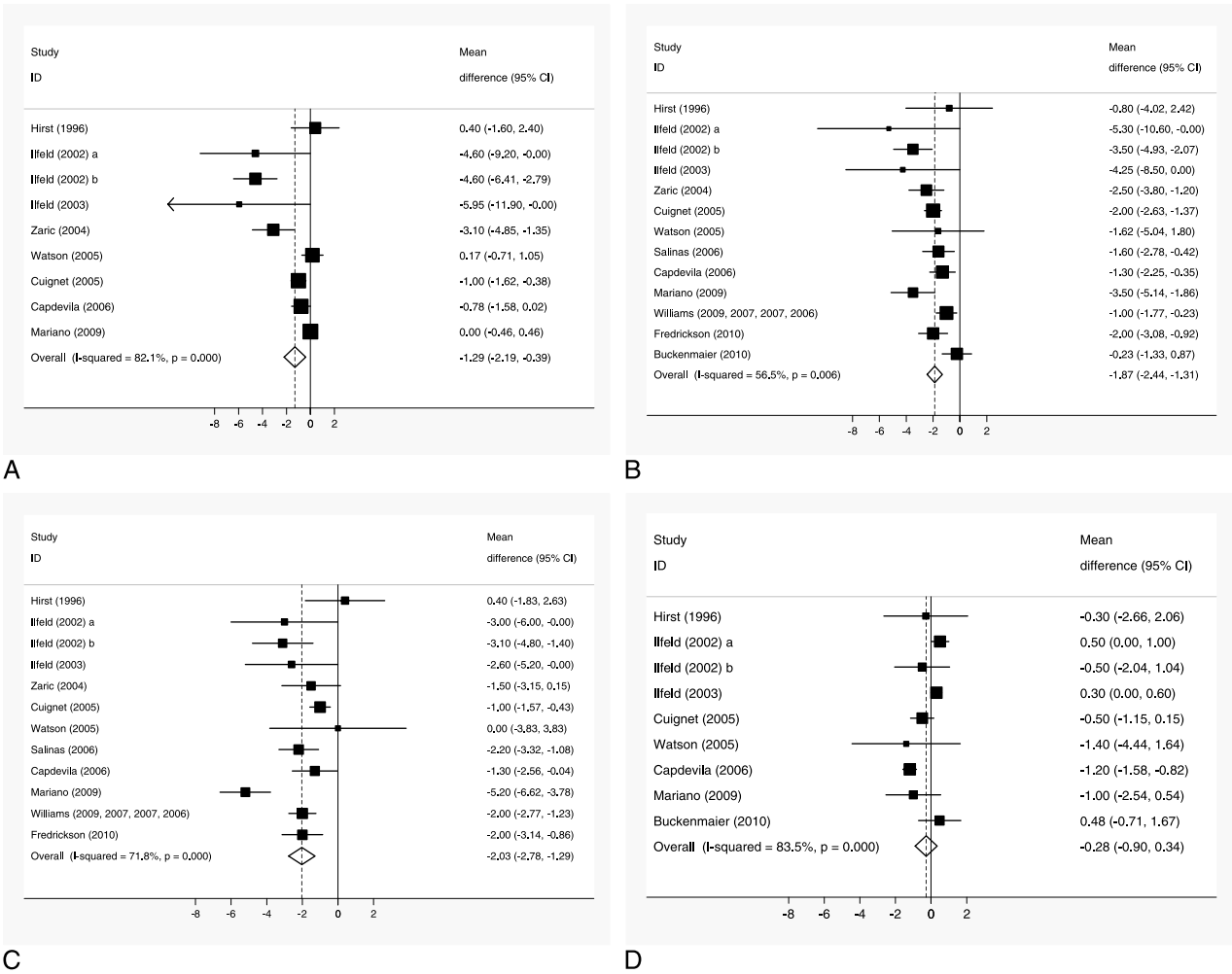

FIGURE 1. A, Worst pain (VAS) POD 0. Pooled VAS is lower in the cPNB groups (ES, −1.292; 95% CI, −2.190 to −0.395; $P = 0.000$). B, Worst pain (VAS) POD 1. Pooled VAS is lower in the cPNB groups (ES, −1.874; 95% CI, −2.442 to −1.306; $P = 0.000$). C, Worst pain (VAS) POD 2. Pooled VAS is lower in the cPNB groups (ES, −2.032; 95% CI, −2.775 to −1.289; $P = 0.000$). D, Worst pain VAS POD 3. There was no significant difference between patients in the cPNB and siPNB groups (ES, −0.279; 95% CI, −0.896 to 0.337; $P = 0.375$).

(overall IR, 0.77; 95% CI, 0.526–1.322; $P = 0.440$). By calculating ESs for the individual studies, we were able to pool results of all studies (ES, 0.633; 95% CI, 0.407–0.983; $P = 0.043$) (Fig. 5). Other types of complications were not reported by a sufficient number of studies to allow pooling of data for meta-analysis. However, the reported incidence of other complications was low, and there was no significant difference in type or frequency of complications between groups in any of the individual studies.

Functional Recovery

Although several studies have performed analyses of medium- to long-term functional outcomes,[13,26,50] the data reported were often incomplete for our purposes, were not sufficient, or were not in a format useful for meta-analysis. Therefore, our ability to compare long-term outcomes was limited.

DISCUSSION

This meta-analysis is, to our knowledge, the first comprehensive and systematic evaluation of studies comparing cPNBs versus siPNBs. Our results suggest that cPNBs do offer superior pain control, less nausea, and higher patient satisfaction, with decreased opioid consumption during the initial postoperative period. Although there were not enough similarly reported adverse effect data to pool for meta-analysis, there appeared to be a trend toward decreased opioid adverse effects in the cPNB groups. There were insufficient data in these studies to evaluate the effects of cPNBs on other clinically relevant outcomes, such as mortality, major morbidity, complications, long-term functional outcomes, or chronic pain. Data were also insufficient to determine any difference in economic outcomes in the short or long term.

Limitations of this analysis include those inherent in all meta-analyses, including the quality of individual studies and the possibility for publication bias and selective outcome reporting. The nature of the techniques being compared poses a challenge to the blinding of anesthesiologists, researchers doing data collection, and patients. A frequent cause of quality point subtraction was lack of blinding on the part of the anesthesiologist, patient, or data recorder. Some investigators have expressed concern about exposing the patient to the possible additional

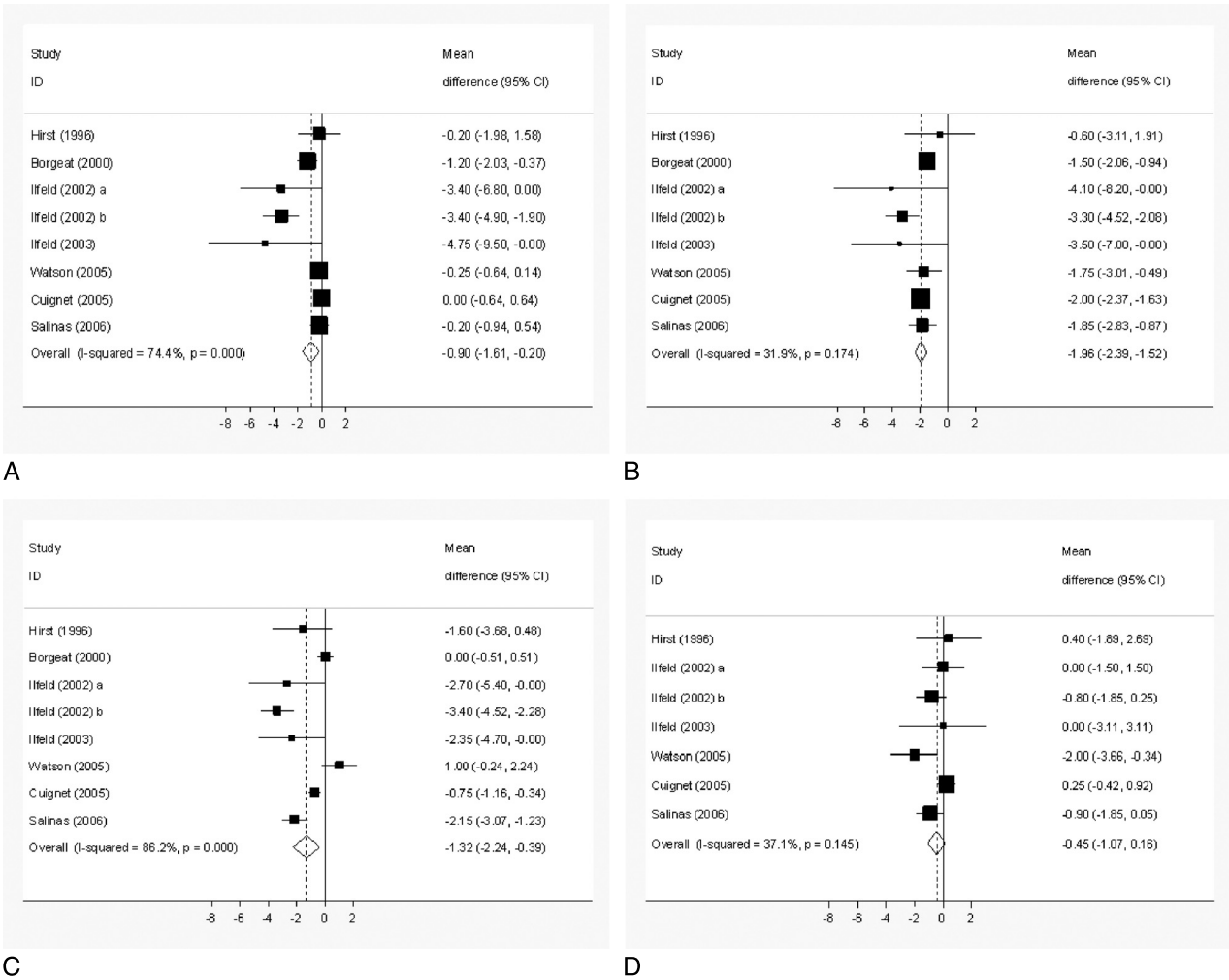

FIGURE 2. A, Pain at rest (VAS) POD 0. Pooled VAS is lower in the cPNB groups (ES, −0.903; 95% CI, −1.611 to −0.196; $P = 0.000$). B, Pain at rest (VAS) POD 1. Pooled VAS is lower in the cPNB groups (ES, −1.958; 95% CI, −2.390 to −1.525; $P = 0.000$). C, Pain at rest (VAS) POD 2. Pooled VAS is lower in the cPNB groups (ES, −1.317; 95% CI, −2.242 to −0.391; $P = 0.005$). D, Pain at rest (VAS) POD 3. There was no significant difference between patients in the cPNB and siPNB groups (ES, −0.451; 95% CI, −1.065 to 0.163; $P = 0.150$).

risk of performing an invasive placebo procedure, and at least 1 ethics committee refused to approve a study design involving an invasive placebo.[51]

Another potential limitation of several studies is the technique of giving the initial bolus of local anesthetic through an insulated needle, followed by placement of the catheter.[11,23,46,49,52] Although this is a commonly used technique, it may lead to a successful initial block but improper catheter position (secondary block failure). Although the incidence of secondary block failure was not reported in any of these studies, studies specifically comparing through-the-needle versus through-the-catheter methods suggest that the rate of secondary block failure may be as high as 60% to 80% for through-the-needle dosing.[53,54] This may have led to a significant underestimation of the potential benefits of the cPNBs in these studies. Perhaps use of ultrasound confirmation of catheter location or stimulating catheter designs could decrease secondary block failure rates[54] and further increase the efficacy of cPNBs.

Although high in both groups, patient satisfaction was higher with the cPNB, as measured by a 10- or 100-point scale. In the absence of a validated measure of satisfaction, the number

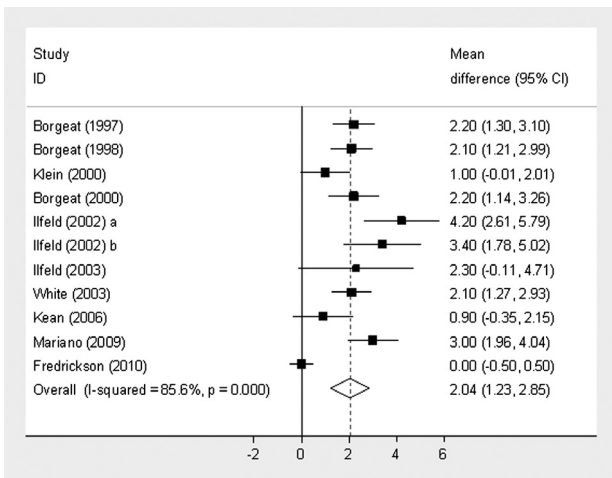

FIGURE 3. Patient satisfaction. Overall patient satisfaction was higher for patients in the cPNB groups (ES, 2.043; 95% CI, 1.235 to 2.851; $P = 0.000$).

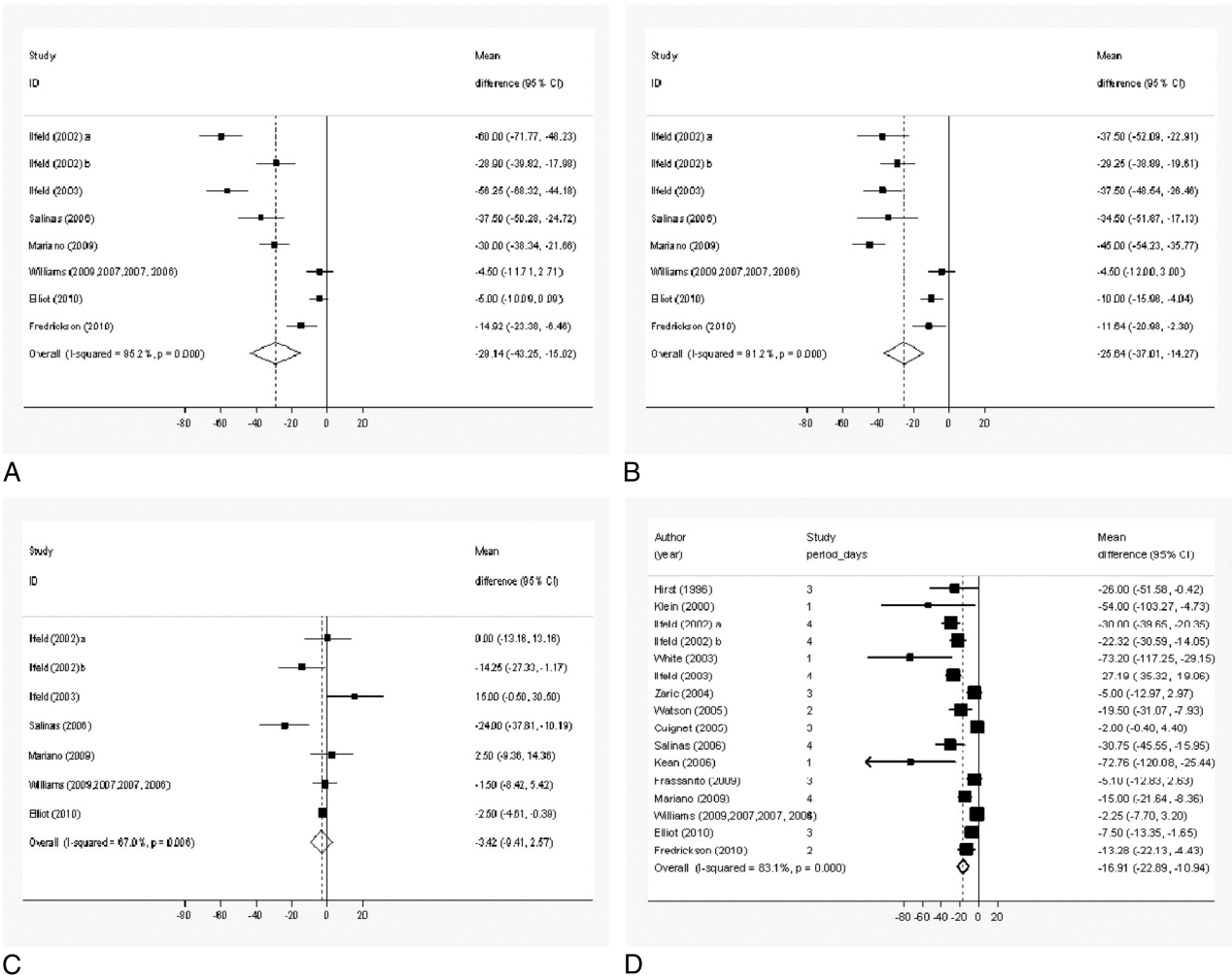

FIGURE 4. A, Opioid use (type/route of medication converted to oral morphine equivalents to facilitate pooling of data) POD 1. Patients in the cPNB groups had lower opioid requirements (ES, −29.137; 95% CI, −43.249 to −15.024; $P = 0.000$). B, Opioid use POD 2. Patients in the cPNB groups had lower opioid requirements (ES, −25.638; 95% CI, −37.007 to −14.270; $P = 0.000$). C, Opioid use POD 3. There was no significant difference in opioid requirements between groups (ES, −3.419; 95% CI, −9.408 to 2.569; $P = 0.263$). D, Opioid use over the entire study period. Patients in the cPNB groups had lower opioid requirements (ES, −16.911; 95% CI, −22.885 to −10.938; $P = 0.000$).

at which an improved patient satisfaction score becomes clinically relevant is unknown. To what extent patient satisfaction drives or will affect decision making by payers or other entities involved in the allocation of resources in the health care industry is questionable. Although patient satisfaction may be important for providers to maintain or increase market share, it may not be viewed to be as compelling as other factors, such as mortality/major morbidity and long-term function or cost.

Because of the relatively small number of patients and the (fortunately) small number of serious complications in each study, we were unable to evaluate the effect of cPNBs on mortality or major morbidity relative to siPNBs, even using pooled data. A retrospective database review comparing cPNBs[55] (as the cornerstone of a multimodal analgesic pathway) to systemic analgesics did show fewer complications in patients who were treated according to the pathway. However, that study did not include patients with siPNBs. Several studies have shown neuraxial techniques to be associated with decreased mortality and fewer complications.[56,57] Additional studies are needed to determine whether PNBs are associated with similar protective effects and whether cPNBs or siPNBs provide greater benefit.

Although we were not able to pool data for analysis of short- or long-term functional outcomes, several studies deserve mention. Whereas Watson et al[58] demonstrated an earlier time to mobilization with a lumbar plexus block for total knee arthroplasty, and Ilfeld et al[1] have shown that patients receiving cPNBs meet discharge criteria sooner than do patients receiving only an initial bolus of local anesthetic via the perineural catheter, Salinas et al[50] did not find a difference between the continuous and single-injection groups in degrees of knee flexion at 6 or 12 weeks. Likewise, Buckenmaier et al[13] found no statistical difference in the time to return to employment or time to return to activities of daily life in patients receiving single-injection versus those receiving continuous paravertebral blocks for breast surgery. It may be that the improved pain control associated with cPNBs can improve early mobilization but that this

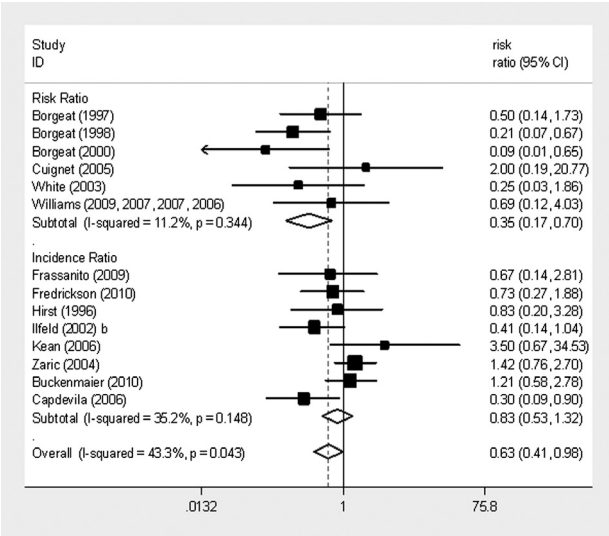

FIGURE 5. Nausea reported by patients during the entire study period. For studies reporting data as number of patients experiencing nausea, ES was calculated as the RR. For studies reporting data as the percentage of patients experiencing nausea, ES was calculated as the IR. Both types of data were pooled, and overall, patients in the cPNB groups experienced less nausea (ES, 0.633; 95% CI, 0.407 to 0.983; $P = 0.043$).

does not lead to long-term improvements in functional outcomes. Ilfeld et al[38,40] found that patients who received an extended infusion of local anesthetic did not have improved long-term functional outcomes, despite improved pain control and early function relative to patients receiving an infusion of shorter duration.

From the available data, we cannot determine the effect of cPNBs on direct or indirect costs to patients, payers, or health care facilities. Elliot et al[52] and White et al[6] reported decreased hospital length of stay for patients in the cPNB groups. Although Salinas et al[50] did not find a difference in time to discharge, the surgical and physical therapy protocol involved keeping patients in-house, even though discharge criteria may have been met earlier. Indeed, Ilfeld et al[1] have shown a decrease in time to discharge readiness for patients receiving cPNBs following total knee or total hip arthroplasty[59] compared with patients who received only an initial injection of local anesthetic via a perineural catheter. Although cPNBs may reduce costs by facilitating early hospital discharge or by decreasing early or late complications[60] (ie, respiratory depression or ileus from opioid analgesics, myocardial infarction from hemodynamic changes because of poor pain control, or complications such as surgical site infection, deep vein thrombosis/pulmonary embolism, or chronic pain), cPNBs could potentially increase cost directly (equipment, anesthesia charges, operating room time, pharmacy charges) or indirectly by causing other complications (catheter-related complications or falls).[14,15] A secondary analysis of the same retrospective database mentioned above, focusing on cost, demonstrated lower costs for patients in the cPNB pathway group, especially for sicker patients (American Society of Anesthesiologists physical status III and IV).[60] These cost savings were attributed to fewer complications requiring intervention. Again, because of the lack of a siPNB group, we can only speculate whether siPNBs could have had a similar effect on cost.

Our data clearly show that cPNBs provide superior pain control, fewer adverse effects, and greater patient satisfaction than siPNBs. We believe that this is additional evidence in favor of performing a continuous technique when a PNB is indicated for postoperative pain control. However, at this point, we cannot endorse the universal use of cPNBs, as many questions remain unanswered. Further study is needed to determine which technique can produce optimal outcomes for various patient populations, surgical procedures, and settings. To clarify the potential benefits of cPNBs, future studies comparing cPNBs and siPNBs should be designed to focus on their effect on complications (both as a result of the blocks and as a result of poorly controlled pain or alternative analgesic modalities), long-term functional outcomes, and cost.

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