

# Are Caudal Blocks for Pain Control Safe in Children? An Analysis of 18,650 Caudal Blocks from the Pediatric Regional Anesthesia Network (PRAN) Database

Santhanam Suresh, MD,\* Justin Long, MD,\* Patrick K. Birmingham, MD,\* and Gildasio S. De Oliveira, Jr, MD, MSCI†

**BACKGROUND:** The caudal block is the most commonly performed regional anesthesia technique in pediatric patients undergoing surgical procedures, but safety concerns raised by previous reports remain to be addressed. Our main objective in current investigation was to estimate the overall and specific incidence of complications associated with the performance of caudal block in children.

**METHODS:** This was an observational study using the Pediatric Regional Anesthesia Network database. A complication after a caudal block was defined by the presence of at least 1 of the following: block failure, vascular puncture, intravascular test dose, dural puncture, seizure, cardiac arrest, sacral pain, or neurologic symptoms. In addition, if a complication was also coded, the presence of temporary or permanent sequelae was evaluated. Additional exploratory analyses were performed to identify patterns of local anesthetic dosage.

**RESULTS:** Eighteen thousand six hundred-fifty children who received a caudal block were included in the study. The overall estimated incidence (95% confidence interval [CI]) of complications after caudal blocks was 1.9% (1.7%–2.1%). Patients who developed complications were younger, median (interquartile range) of 11 (5–24) months, compared to those who did not develop any complications, 14 (7–29) months,  $P = 0.001$ . The most common complications were block failure, blood aspiration, and intravascular injection. No cases of temporary or permanent sequelae were identified leading to an estimated incidence (95% CI) of 0.005% (– % to 0.03%). Four thousand four hundred-six of 17,867 (24.6%; 95% CI, 24%–25.2%) subjects received doses (>2 mg of bupivacaine equivalents/kg) that could be potentially unsafe.

**CONCLUSIONS:** Safety concerns should not be a barrier to the use of caudal blocks in children assuming an appropriate selection of local anesthetic dosage. (*Anesth Analg* 2015;120:151–6)

Regional anesthesia techniques are widely used to improve postoperative analgesia in the adult population. However, in children, there are not enough data in terms of regional techniques benefits and safety.<sup>1–4</sup> Safety concerns are a major impediment to the performance of clinical trials in children.<sup>5</sup> Neuraxial techniques are most often performed in awake adults, but neuraxial techniques are most frequently performed in pediatric patients under general anesthesia.<sup>6</sup> This difference in adult and pediatric practice has been considered a potential risk factor for the development of neurological complications in children.<sup>7–10</sup>

The caudal block was first described for anesthetic use in children by Campbell in 1933, and it is likely the most common regional anesthesia technique performed in children undergoing surgery.<sup>11</sup> However, recent systematic reviews have failed to address safety concerns associated with the performance of caudal blocks in pediatric patients.<sup>12,13</sup> A previous multicenter study in Europe evaluated the safety of 8493 caudal blocks performed in children,<sup>14</sup> but current safety data of the caudal block in the United States are limited to single institution studies with small numbers of patients, which impaired the generalizability of results to common practice patterns.<sup>15</sup> A large safety analysis can provide practitioners and parents crucial risk information when deciding whether to perform caudal blocks in children.

The main objective of the current investigation was to evaluate the incidence of overall and individual complications associated with the performance of a caudal block in children across multiple pediatric hospitals. In addition, we also sought to evaluate patterns of local anesthetic dosing selection for caudal block in that same patient population.

## METHODS

The study was performed using data obtained from the Pediatric Regional Anesthesia Network (PRAN) database. Study approval was obtained from the Ann & Robert H.

From the \*Department of Anesthesiology, Ann & Robert H. Lurie Children's Hospital of Chicago, Northwestern University, Chicago, Illinois; and †Department of Anesthesiology, Northwestern University, Chicago, Illinois.

Accepted for publication July 24, 2014.

Funding: Ann & Robert H. Lurie Children's Hospital of Chicago.

The authors declare no conflicts of interest.

Reprints will not be available from the authors.

Address correspondence to Gildasio S. De Oliveira, Jr, MD, MSCI, Department of Anesthesiology, Northwestern University, 241 E. Huron St., F5-704, Chicago, IL 60611. Address e-mail to g-jr@northwestern.edu.

Copyright © 2014 International Anesthesia Research Society  
DOI: 10.1213/ANE.0000000000000446

Lurie Children's Hospital of Chicago IRB (IRB number is 2013-12926). Specific IRB approval for the analysis of the current data was waived by the Ann & Robert H. Lurie Children's Hospital of Chicago IRB. Individual sites participating in the PRAN consortium obtained approval for data collection. Approval for the study protocol was obtained from the PRAN publication committee. All centers were granted waivers of informed consent by their IRBs because the data had no protected health information and there were no changes in patient care due to database entry. Eligible subjects were pediatric patients (younger than 18 years) undergoing surgery who received a caudal block for intraoperative or postoperative analgesia/anesthesia.

All audited data available from the PRAN database at the time of the analysis were examined. The data collection form for the current study followed the same variables established by the PRAN that has been described in detail.<sup>16</sup> Data were collected from 2007 through 2012. A list of clinical sites that contributed data to the current study is provided in Appendix 1.

Demographic characteristics included the subject's age, weight, ASA physical status, and gender. Data regarding block performance included patient consciousness status during block performance (awake, sedated, or anesthetized), and the technique used to perform the block (landmark or ultrasound-guided). In addition, the local anesthetic type, dose, and volume were also recorded.

A complication from caudal block was defined by the presence of at least 1 of the following intraoperative and/or postoperative factors: block failure (unable to place, difficult to inject, subcutaneous injection), vascular puncture (defined by the presence of blood with aspiration), positive intravascular test dose (defined by the reporting institution), dural puncture (defined by the presence of cerebrospinal fluid with aspiration), seizure, cardiac arrest, sacral pain, or other neurologic symptoms. In addition, if a complication was recorded in the database, the presence of temporary or permanent sequelae was further evaluated. If a complication or adverse event was detected, it was followed until resolved, usually by the clinicians on the pain service. The file remained open until follow-up data were completed and entered in the database. Audits, completed monthly, cannot be performed while a record remains open. All data included in the current study were audited.

The Shapiro-Wilk test was used to test the hypothesis of normal distribution. Normally distributed interval data are reported as mean (SD). Non-normally distributed interval and ordinal data are reported as median (interquartile range [IQR]), and they were evaluated using Mann-Whitney *U* test.<sup>17,18</sup> Categorical variables are presented as counts and were evaluated using Fisher exact test. The 95% binomial confidence interval (CI) for the incidence of caudal block complications was calculated using the Jeffreys method. The coverage properties of that method are similar to others, but they have the advantage of being equal-tailed (e.g., for a 95% CI, the probabilities of the interval lying above or below the true value are both close to 2.5%).<sup>19</sup> The Clopper-Pearson exact method was used in binomial interval estimations when zero successes were observed. Since not enough information was available regarding dosage of local anesthetics used in caudal block for children, an exploratory

**Table 1. Demographic and Block Characteristics**

	Subjects (n = 18,650)
Age (mo)	14 (7-29)
Gender	
Male	16,236
Female	2414
Weight (kg)	10.3 (8-14)
ASA class	
I	11,198
II	5744
III	1596
IV	111
V	1
Calendar year of block performance	
2007	1398
2008	1737
2009	2181
2010	2949
2011	4645
2012	5740
Anesthetic technique used with the block	
None (awake)	92
Sedation	108
General anesthesia without muscle paralysis	15,430
General anesthesia with muscle paralysis	3020
Ultrasound	
Yes	443
No	16,342
Not determined	1865
Local anesthetic type	
Bupivacaine	12,075
Ropivacaine	6358
Unknown/other	217

analysis was also performed to identify patterns of local anesthetic dose and patient demographic characteristics. Simple linear regression was performed using a natural logarithmic transformation of total local anesthetic dose as a dependent variable and a natural logarithm transformation of patient characteristics (age and weight) as independent variables for caudal blocks. A logistic regression analysis was performed to examine the association between type of anesthesia (general versus awake) on the development of complications while controlling for subjects' ages. When the block was performed using ropivacaine, doses of ropivacaine were converted to equipotent doses of bupivacaine (1 mg ropivacaine = 0.7 mg bupivacaine).<sup>20,21</sup> Two-tailed *P* values <0.05 were used in order to reject null hypotheses.

## RESULTS

Eighteen thousand six hundred-fifty children who received a caudal block were included in the analysis. Demographic and block characteristics of subjects are presented in Table 1. Before the year 2010, 263 of 7740 (3.3%) blocks were performed with ultrasound compared to 180 of 9046 (1.9%) in the subsequent years, *P* < 0.001. Subjects who had their caudal block performed while awake and/or sedated were younger than subjects who had the caudal block performed under general anesthesia, median (IQR) of 5 (2-18) months and 14 (7-29) months, respectively, *P* < 0.001.

The overall estimated incidence (95% CI) of complications after caudal blocks was 1.9% (1.7%-2.1%). Patients who developed complications were younger, median (IQR) of 11 (5-24) months compared to those who did not develop any

complications, 14 (7–29) months,  $P = 0.001$ , but there was no significant difference in the incidence of complication between male and female patients ( $P = 0.08$ ). The rate of complications did not differ regarding the blocks performed using ultrasound, 6 of 450 (1.3%), when compared to the blocks performed without ultrasound, 307 of 16,343 (1.8%),  $P = 0.32$ . The rate of complications in subjects having the block awake was 8 of 200 (4%) compared to 354 of 18,450 (1.9%) in patients under general anesthesia ( $P = 0.06$ ). After adjusting for age, blocks performed under general anesthesia were not associated with a more frequent incidence of complications compared to blocks performed in awake patients, OR (95% CI) of 0.49 (0.24–1.01),  $P = 0.06$ . By univariate analysis (i.e., without controlling for the factors influencing the clinical decision), the observed complication rate was less for blocks that used a test dose, 208 of 12,612 (1.6%), compared to the blocks that did not use a test dose, 102 out of 4583 (2.2%).

The most common complications were block failure, blood aspiration, and intravascular injection (as detected by positive test dose). The incidence of specific complications is presented in Table 2. None of the reported complications resulted in long-term sequelae for children resulting in an estimated incidence (95% CI) of complications with sequelae of 0.005% (– to 0.03%). Detailed patient and block information on serious but infrequent complications is presented in Table 3.

The median (95% range) for the local anesthetic dose per weight for caudal blocks was 1.4 mg (0.78–2.51 mg) of bupivacaine equivalents/kg representing a large variation in clinical practice. There was a direct linear relationship between the total local anesthetic dose and patients' weights; however, subjects' weight was not sufficient to explain much of the variability in dose (Fig. 1). Variation in the local anesthetic dose was not better explained by variations in age of subjects (slope of regression line  $0.32 \pm 0.00$ ; goodness of fit  $r^2 = 0.41$  and slope significantly different from 0,  $P < 0.0001$ . Examination of a residual plot demonstrated a fairly random pattern).

**Table 2. Incidence of Specific Complications in Caudal Block**

	Incidence (95% confidence interval)
Block failure	1% (0.8 to 1.1)
Blood aspiration	0.6% (0.5 to 0.8)
Positive test dose	0.1% (0.1 to 0.2)
Dural puncture	0.08% (0.005 to 0.01)
Cardiac arrest	0.005% (– to 0.002)
Seizure	0.005% (– to 0.002)
Sacral pain	0.005% (– to 0.002)
Muscle spasm	0.005% (– to 0.002)

**Table 3. Detailed Patient Information on Serious but Infrequent Complications**

	Age (mo)	Gender	Weight (kg)	Local anesthetic drug	Dose (mg/kg)	Patient state	Test dose	Comments
Cardiac arrest	36	Male	17.3	Ropivacaine	1.08	General anesthesia	No	Delayed hospital discharge 1–2 d
Seizure	1	Male	4	Lidocaine	1.5	General anesthesia	Unknown	Seizure occurred in postanesthesia care unit
Sacral pain	24	Female	11.5	Ropivacaine	2.2	General anesthesia	Yes	Sacral pain lasting 1 wk
Muscle spasms	2	Male	4.3	Ropivacaine	1.5	Awake	No	Spasms in bilateral lower extremities lasting for 1 wk

The median (IQR) local anesthetic dose per weight was larger when epinephrine was used as a block adjunct compared to when no epinephrine was used, 1.4 mg (1.2–1.6 mg) and 1.3 mg (1.2–1.6 mg) of bupivacaine equivalents/kg, respectively ( $P < 0.001$ ). After adjusting for different local anesthetic potencies, subjects who had a caudal block with ropivacaine received a greater dose of local anesthetics than those who had a caudal block with bupivacaine, median (IQR) of 1.66 mg (1.25–2.31 mg) and 1.34 mg (1.13–1.4 mg) of bupivacaine/kg equivalents, respectively,  $P < 0.001$ .

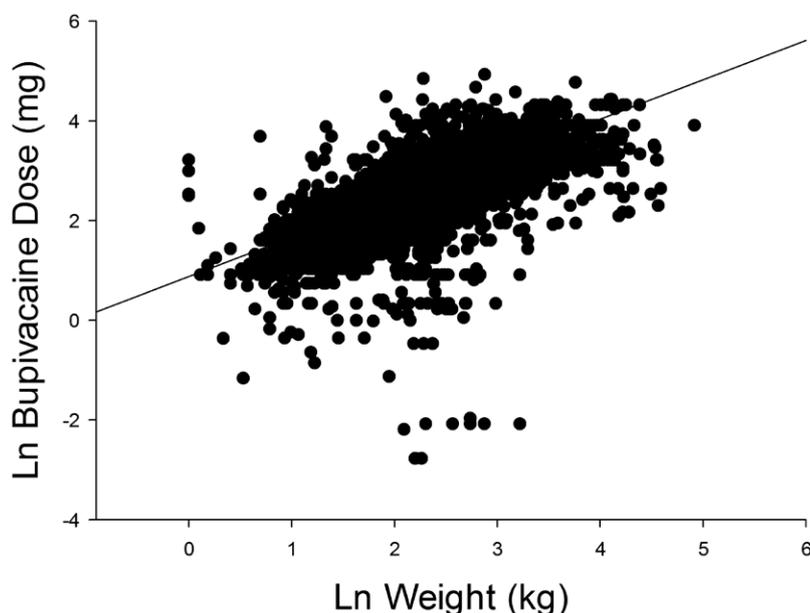
Four thousand four hundred-six of 17,867 (24.6%; 95% CI, 24%–25.2%) subjects received larger doses than 2 mg of bupivacaine equivalents/kg that potentially could have been unsafe. When a less conservative limit of 2.5 mg/kg dose of bupivacaine was evaluated, 968 of 17,867 (5.4%; 95% CI, 5.0%–5.4%) subjects received potentially toxic doses. Subjects who received doses larger than the maximal safe local anesthetic doses were younger than subjects who did not receive potentially unsafe doses, 11 (6–20) months and 15 (7–36) months, respectively ( $P < 0.001$ ).

## DISCUSSION

The most important finding of the current investigation was the low rate of complications when the caudal block was performed in pediatric patients undergoing surgical procedures. The upper incidence limit of severe complications such as cardiac arrest and seizure was 0.02%. More importantly, no cases of long-term sequelae were detected in any of the 18,650 patients in this cohort. Taken together, our results suggest that caudal block is a safe regional anesthesia technique when performed in children undergoing surgery.

Our results are clinically important since reports of complications associated with the performance of caudal block in the literature have questioned its safety in children.<sup>22–24</sup> In addition, prior safety studies that specifically examined caudal block were limited by a small number of patients and the evaluation of only a single center.<sup>25,26</sup> In Europe, a large study on the safety of several regional anesthesia techniques in children demonstrated a low incidence of complications for 8493 caudal blocks.<sup>14</sup> Our study establishes the safety of caudal block in children across multiple pediatric hospitals in the United States. The current study is, to the best of our knowledge, the largest study to demonstrate safety of a single regional anesthesia technique in children.

Another important finding of the current investigation was the detection of a large variation in local anesthetic dose used in caudal blocks (IQR, 1.23 mg of bupivacaine/kg to 1.98 mg of bupivacaine/kg). In addition, the dose variation was not largely explained by changes in weight of the subjects  $R^2$  (95% CI) = 0.5 (0.48 to 0.52). Current data suggest that approximately 25% of patients undergoing a caudal



**Figure 1.** Scatter plot and regression analysis demonstrating a direct relationship between natural logarithm (Ln) distribution of local anesthetic dose (mg of bupivacaine equivalents) and natural logarithm (Ln) distribution of weight in pediatric patients receiving a caudal block. Slope of regression line  $0.79 \pm 0.00$ . Goodness of fit  $r^2 = 0.50$  and slope significantly different from 0,  $P < 0.0001$ . Examination of a residual plot demonstrated a fairly random pattern.

block receive a local anesthetic dose that has the potential to cause local anesthetic toxicity.<sup>27–31</sup> Younger children seem to be at greatest risk for receiving a toxic dose. Quality improvement projects should be implemented across different institutions to detect and avoid unsafe local anesthetic doses when caudal block is performed in pediatric patients.

We did not detect a beneficial role in the use of ultrasound to minimize complications of caudal block in children. It was also interesting that the use of ultrasound decreased across the years. The use of ultrasound assistance has been shown to minimize complications and/or improve efficacy of peripheral regional anesthesia techniques in adults when compared to nerve stimulation.<sup>32–35</sup> Although the current data do not suggest that ultrasound improves safety of caudal block, future studies examining the role of ultrasound guidance on the efficacy of caudal blocks are still needed.

The efficacy of caudal block to minimize postoperative pain in specific surgical procedures has yet to be established.<sup>2</sup> In addition, optimal dose regimens also need to be determined to help reduce the large variation in clinical practice we observed. Given the safety of caudal blocks in children demonstrated by the current analysis, the performance of randomized controlled trials is justified not only to establish procedure-specific efficacy but also to detect optimal local anesthetic dose regimens.

Our study should only be interpreted within the context of its limitations. We evaluated the safety of caudal block but did not examine its efficacy. Since the PRAN database does not capture type of surgical procedure, we were not able to investigate if specific types of surgical procedures carry a greater risk for patients to receive potentially toxic doses of local anesthetics or to have postoperative complications. Similar to other national quality improvement programs, site-specific contributions were not available and could not be incorporated into the analysis.<sup>36–39</sup>

In summary, we established a safety profile for caudal block in children using data from >20 pediatric hospitals in the United States in 18,650 pediatric patients. However, we detected a large variation in clinical practice regarding

#### Appendix 1

1	American Family Children's Hospital—U of Wisc.
2	University of Minnesota Children's Hospital
3	Boston Children's Hospital
4	Children's Hospital Colorado
5	Children's Medical Center Dallas
6	Children's Memorial Hermann Hospital/UT Houston
7	Children's Hospital at Dartmouth
8	Hospital Municipal Jesus—Rio de Janeiro
9	Lucile Packard Children's Hospital Stanford
10	Ann & Robert H. Lurie Children's Hospital of Chicago
11	Nationwide Children's Hospital
12	Oregon Health Sciences University
13	Seattle Children's
14	Texas Children's
15	The Cleveland Clinic
16	University of New Mexico
17	Columbia University <sup>a</sup>
18	University Hospital Rijeka <sup>a</sup>

<sup>a</sup>Represent sites that contributed to the current study but are no longer part of the Pediatric Regional Anesthesia Network.

dose of local anesthetics for caudal block that may lead to local anesthetic toxicity. Safety concerns should not be a barrier to the development of randomized trials in order to test the efficacy of caudal block on analgesic outcomes in children pending the appropriate selection of local anesthetic doses. ■■

#### DISCLOSURES

**Name:** Santhanam Suresh, MD.

**Contribution:** This author contributed to study design, conduct of the study, and manuscript preparation.

**Attestation:** Santhanam Suresh approved the final manuscript. Santhanam Suresh attests to the integrity of the original data and the analysis reported in this manuscript.

**Name:** Justin Long, MD.

**Contribution:** This author contributed to conduct of the study and manuscript preparation.

**Attestation:** Justin Long approved the final manuscript. Justin Long attests to the integrity of the original data and the analysis reported in this manuscript.

**Name:** Patrick K. Birmingham, MD.

**Contribution:** This author contributed to manuscript preparation.

**Attestation:** Patrick K. Birmingham approved the final manuscript.

**Name:** Gildasio S. De Oliveira, Jr, MD, MSCI.

**Contribution:** This author contributed to study design, statistical analysis, and manuscript preparation.

**Attestation:** Gildasio S. De Oliveira, Jr, approved the final manuscript. Gildasio S. De Oliveira, Jr, attests to the integrity of the original data and the analysis reported in this manuscript.

**This manuscript was handled by:** James A. DiNardo, MD.

## ACKNOWLEDGMENTS

We would like to acknowledge the PRAN steering committee members: Drs. Martin, Polaner, Krane, Bosenberg, Walker, and Taenzer for their dedication in conceptually forming the PRAN database, all sites that have contributed data to the consortium, and Christie Wolf from Axio Research whose contributions to the database are invaluable.

## REFERENCES

1. Shah RD, Suresh S. Applications of regional anaesthesia in paediatrics. *Br J Anaesth* 2013;111 Suppl 1:i114–24
2. Suresh S, Schaldenbrand K, Wallis B, De Oliveira GS. Regional anaesthesia to improve pain outcomes in pediatric surgical patients: a qualitative systematic review of randomized controlled trials. *Br J Anaesth* 2014;113:375–90
3. Krane EJ, Polaner D. The safety and effectiveness of continuous peripheral nerve blockade in children. *Anesth Analg* 2014;118:499–500
4. Varughese AM, Rampasad SE, Whitney GM, Flick RP, Anton B, Heitmiller ES. Quality and safety in pediatric anesthesia. *Anesth Analg* 2013;117:1408–18
5. Kahn MG, Bailey LC, Forrest CB, Padula MA, Hirschfeld S. Building a common pediatric research terminology for accelerating child health research. *Pediatrics* 2014;133:516–25
6. Kim EM, Lee JR, Koo BN, Im YJ, Oh HJ, Lee JH. Analgesic efficacy of caudal dexamethasone combined with ropivacaine in children undergoing orchiopexy. *Br J Anaesth* 2014;112:885–91
7. Gurnaney H, Kraemer FW, Maxwell L, Muhly WT, Schleelein L, Ganesh A. Ambulatory continuous peripheral nerve blocks in children and adolescents: a longitudinal 8-year single center study. *Anesth Analg* 2014;118:621–7
8. Naja ZM, Ziade FM, Kamel R, El-Kayali S, Daoud N, El-Rajab MA. The effectiveness of pudendal nerve block versus caudal block anesthesia for hypospadias in children. *Anesth Analg* 2013;117:1401–7
9. Muhly W, Gurnaney H, Hosalkar H, Kraemer F, Davidson R, Ganesh A. Continuous perineural infusion after lower extremity osteotomies in children: a feasibility and safety analysis. *Br J Anaesth* 2013;110:851–2
10. Hall Burton DM, Boretsky KR. A comparison of paravertebral nerve block catheters and thoracic epidural catheters for postoperative analgesia following the Nuss procedure for pectus excavatum repair. *Paediatr Anaesth* 2014;24:516–20
11. Campbell MF. Caudal anesthesia in children. *Am J Urol* 1933;30:245–9
12. Schnabel A, Poepping DM, Kranke P, Zahn PK, Pogatzki-Zahn EM. Efficacy and adverse effects of ketamine as an additive for paediatric caudal anaesthesia: a quantitative systematic review of randomized controlled trials. *Br J Anaesth* 2011;107:601–11
13. Jöhr M, Berger TM. Caudal blocks. *Paediatr Anaesth* 2012;22:44–50
14. Ecoffey C, Lacroix F, Giaufre E, Orliaguet G, Courrèges P; Association des Anesthésistes Réanimateurs Pédiatriques d'Expression Française (ADARPEF). Epidemiology and morbidity of regional anesthesia in children: a follow-up one-year prospective survey of the French-Language Society of Paediatric Anaesthesiologists (ADARPEF). *Paediatr Anaesth* 2010;20:1061–9
15. Jagannathan N, Sohn L, Sawardekar A, Ambrosy A, Hagerty J, Chin A, Barsness K, Suresh S. Unilateral groin surgery in children: will the addition of an ultrasound-guided ilioinguinal nerve block enhance the duration of analgesia of a single-shot caudal block? *Paediatr Anaesth* 2009;19:892–8
16. Polaner DM, Taenzer AH, Walker BJ, Bosenberg A, Krane EJ, Suresh S, Wolf C, Martin LD. Pediatric Regional Anesthesia Network (PRAN): a multi-institutional study of the use and incidence of complications of pediatric regional anesthesia. *Anesth Analg* 2012;115:1353–64
17. Divine G, Norton HJ, Hunt R, Dienemann J. Statistical grand rounds: a review of analysis and sample size calculation considerations for Wilcoxon tests. *Anesth Analg* 2013;117:699–710
18. Dexter F. Wilcoxon-Mann-Whitney test used for data that are not normally distributed. *Anesth Analg* 2013;117:537–8
19. Dann RS, Koch GG. Review and evaluation of methods for computing confidence intervals for the ratio of two proportions and considerations for non-inferiority clinical trials. *J Biopharm Stat* 2005;15:85–107
20. Lee YY, Ngan Kee WD, Fong SY, Liu JT, Gin T. The median effective dose of bupivacaine, levobupivacaine, and ropivacaine after intrathecal injection in lower limb surgery. *Anesth Analg* 2009;109:1331–4
21. Cox B, Durieux ME, Marcus MA. Toxicity of local anaesthetics. *Best Pract Res Clin Anaesthesiol* 2003;17:111–36
22. Na EH, Han SJ, Kim MH. Delayed occurrence of spinal arachnoiditis following a caudal block. *J Spinal Cord Med* 2011;34:616–9
23. Lin EP, Aronson LA. Successful resuscitation of bupivacaine-induced cardiotoxicity in a neonate. *Paediatr Anaesth* 2010;20:955–7
24. Symons JA, Palmer GM. Neuropathic pain and foot drop related to nerve injury after short duration surgery and caudal analgesia. *Clin J Pain* 2008;24:647–9
25. Beyaz SG, Tokgöz O, Tüfek A. Caudal epidural block in children and infants: retrospective analysis of 2088 cases. *Ann Saudi Med* 2011;31:494–7
26. Aprodu GS, Munteanu V, Filciu G, Goția DG. [Caudal anesthesia in pediatric surgery]. *Rev Med Chir Soc Med Nat Iasi* 2008;112:142–7
27. Hessian EC, Evans BE, Woods JA, Taylor DJ, Kinkel E, Bjorksten AR. Plasma ropivacaine concentrations during bilateral transverse abdominis plane infusions. *Br J Anaesth* 2013;111:488–95
28. Griffiths JD, Le NV, Grant S, Bjorksten A, Hebbard P, Royse C. Symptomatic local anaesthetic toxicity and plasma ropivacaine concentrations after transverse abdominis plane block for Caesarean section. *Br J Anaesth* 2013;110:996–1000
29. Barreveld A, Witte J, Chahal H, Durieux ME, Strichartz G. Preventive analgesia by local anesthetics: the reduction of postoperative pain by peripheral nerve blocks and intravenous drugs. *Anesth Analg* 2013;116:1141–61
30. McAlvin JB, Reznor G, Shankarappa SA, Stefanescu CF, Kohane DS. Local toxicity from local anesthetic polymeric microparticles. *Anesth Analg* 2013;116:794–803
31. Li B, Yan J, Shen Y, Li B, Hu Z, Ma Z. Association of sustained cardiovascular recovery with epinephrine in the delayed lipid-based resuscitation from cardiac arrest induced by bupivacaine overdose in rats. *Br J Anaesth* 2012;108:857–63
32. Schnabel A, Meyer-Frießem CH, Zahn PK, Pogatzki-Zahn EM. Ultrasound compared with nerve stimulation guidance for peripheral nerve catheter placement: a meta-analysis of randomized controlled trials. *Br J Anaesth* 2013;111:564–72
33. Kent ML, Hackworth RJ, Riffenburgh RH, Kaesberg JL, Asseff DC, Lujan E, Corey JM. A comparison of ultrasound-guided and landmark-based approaches to saphenous nerve blockade: a prospective, controlled, blinded, crossover trial. *Anesth Analg* 2013;117:265–70
34. Bhatia A, Brull R. Review article: is ultrasound guidance advantageous for interventional pain management? A systematic review of chronic pain outcomes. *Anesth Analg* 2013;117:236–51

35. Taha AM, Abd-Elmaksoud AM. Lidocaine use in ultrasound-guided femoral nerve block: what is the minimum effective anaesthetic concentration (MEAC90)? *Br J Anaesth* 2013;110:1040–4
36. Mascha EJ, Dalton JE, Kurz A, Saager L. Statistical grand rounds: understanding the mechanism: mediation analysis in randomized and nonrandomized studies. *Anesth Analg* 2013;117:980–94
37. Maile MD, Engoren MC, Tremper KK, Jewell E, Kheterpal S. Worsening preoperative heart failure is associated with mortality and noncardiac complications, but not myocardial infarction after noncardiac surgery: a retrospective cohort study. *Anesth Analg* 2014;119:522–3
38. Sharifpour M, Moore LE, Shanks AM, Didier TJ, Kheterpal S, Mashour GA. Incidence, predictors, and outcomes of perioperative stroke in noncarotid major vascular surgery. *Anesth Analg* 2013;116:424–34
39. Long JB, Birmingham PK, De Oliveira GS Jr, Schaldenbrand KM, Suresh S. Transversus abdominis plane block in children: a multicenter safety analysis of 1994 cases from the PRAN (Pediatric Regional Anesthesia Network) database. *Anesth Analg* 2014;119:395–9