Ultrasound Guidance Reduces the Risk of Local Anesthetic Systemic Toxicity Following Peripheral Nerve Blockade

Michael J. Barrington, PhD, MBBS, FANZCA and Roman Kluger, MBBS, FANZCA, PGDipBiostat

Background and Objectives: Local anesthetic systemic toxicity (LAST) is a potentially life-threatening complication of local anesthetic administration. In this article, the results of the Australian and New Zealand Registry of Regional Anaesthesia were analyzed to determine if ultrasound-guided peripheral nerve blockade (PNB) was associated with a reduced risk of LAST compared with techniques not utilizing ultrasound technology.

Methods: The period of study for this multicenter study involving 20 hospitals was from January 2007 through May 2012. The primary outcome was LAST comprising minor, major, and cardiac arrest (due to toxicity) events determined using standardized definitions. Multivariable logistic regression models and propensity score analyses were used to determine significant event predictors.

Results: The study population comprised 20,021 patients who received 25,336 PNBs. There were 22 episodes of LAST, resulting in an incidence of LAST of 0.87 per 1000 PNBs (95% confidence interval, 0.54–1.3 per 1000). Ultrasound guidance was associated with a reduced incidence of local anesthetic toxicity. Site of injection, local anesthetic type, dose per weight, dose, and patient weight were all predictors of LAST.

Conclusions: This study provides the strongest evidence, to date, that ultrasound guidance may improve safety because it is associated with a reduced risk of LAST following PNB.

(*Reg Anesth Pain Med* 2013;38: 289–299)

Local anesthetic systemic toxicity (LAST) is a well-known and potentially life-threatening complication of regional anesthesia. Peripheral nerve blockade (PNB) commonly utilizes large doses of local anesthetic, and therefore, techniques that reduce the risk and severity of LAST are important.[1] During obstetric epidural anesthesia, preventive strategies such as test doses, incremental injections, dose limitation, aspiration, and intravascular markers are thought to be responsible for improvement in outcomes.[2] In contrast, the American Society of Anesthesiologists Closed Claims database indicates that LAST is a significant source of morbidity and mortality following PNB, being associated with 7 of 19 claims involving death or brain damage.[3] Case reports or series are another important source of information on LAST, but potentially these are subject to publication bias leading to the reporting of favorable outcomes only.[4]

From Department of Anaesthesia, St Vincent's Hospital, Melbourne, Fitzroy, Victoria, Australia.
Accepted for publication March 10, 2013.
Address correspondence to: Michael J. Barrington, PhD, MBBS, FANZCA, Department of Anaesthesia, St Vincent's Hospital, Melbourne, PO Box 2900, Fitzroy, Victoria 3065, Australia (e-mail: michael.barrington@svhm.org.au).
This work was supported by a scholarship grant (10/023) from the Australian and New Zealand College of Anaesthetists, 2010–2012.
These results were presented during the Best of Abstracts, Clinical Science session at the 2012 American Society of Anesthesiologists Annual Meeting, Washington, District of Columbia.
The authors declare no conflict of interest.

ISSN: 1098-7339
DOI: 10.1097/AAP.0b013e318292669b

Ultrasound-guided PNB is associated with a reduced incidence of inadvertent vascular puncture[5,6] and reduced local anesthetic requirements compared with nonultrasound techniques.[7] Therefore, there exist plausible mechanisms for ultrasound-guided PNB reducing the incidence of LAST from either inadvertent intravenous injection or delayed absorption of a tissue depot of local anesthetic. However, factors unrelated to ultrasound imaging such as the site of injection, patient comorbidities, and other practice patterns may contribute to LAST.

In this article, we analyze results of the Australian and New Zealand Registry of Regional Anaesthesia (AURORA). This project was formerly known as the Australasian Regional Anaesthesia Collaboration[5] and is a prospective multicenter clinical registry that monitors and reports on the quality and safety of contemporary PNB. AURORA utilizes a Web-based interface to a remote database, allowing collection of clinical information on many PNBs. The primary objective of this analysis was to ascertain if ultrasound-guided PNB was associated with a reduced incidence of LAST compared with PNB techniques that do not use ultrasound.

METHODS

The institutional review board of all hospitals contributing to AURORA approved this project as a quality-assurance activity or low-risk research, or waived the requirement for approval. The study period for this analysis is from January 2007 through May 2012. Data from January 2007 to May 2008 have previously been reported[5] and included data merged from different databases (online and off-line). This created a data set that was suitable for descriptive analysis but not suitable for multivariable logistic regression analysis. From June 2008 on, AURORA has only collected information directly to an online interface. To facilitate formation of a data set suitable for multivariable analysis (eg, covariates known for patients who did and did not have the event), only data entered directly to the Web-based interface (before June 2008) and all data from June 2008 onward are included for analysis. Study methodology has been previously documented,[5] and a key requirement is that all patients who received PNB from all recruiting hospitals are included. During 2007 to 2008, 9 hospitals contributed, and during 2008 to 2012, 18 hospitals contributed (7 of these 18 also contributed during 2007–2008) to this project. Patients younger than 13 years were excluded from this analysis. Demographics (age, weight, sex), PNB type, technology used to locate nerve/plexus, local anesthetic type and dosage used to perform PNB, and immediate complications (LAST, inadvertent vascular puncture) were extracted from the database using structured query language commands. Site of PNB was categorized as upper limb, paravertebral (thoracic paravertebral, posterior approach to the lumbar plexus), lower limb (femoral, saphenous, lateral femoral cutaneous, obturator, sciatic nerve blocks), and trunk (transversus abdominis plane, ilioinguinal/iliohypogastric, rectus sheath blocks). Technology was categorized as using or not using ultrasound guidance. Ultrasound guidance included ultrasound alone and ultrasound

and nerve stimulation combined. If more than 1 PNB was performed per episode of care, technology and anesthetic type and dose for each PNB were recorded. The primary outcome was LAST, defined as minor LAST (eg, central nervous system features such as agitation), major LAST (eg, seizures), and cardiac arrest due to toxicity.[8] The definitions for LAST events have been utilized previously[5] and incorporate the range of clinical presentations of LAST that are observed clinically,[1] reported in both case series [4] and anesthesiology textbooks. In addition, the free comment section was searched for text that potentially indicated LAST. All events were confirmed with the practitioners, and spurious entries were excluded.

Statistical Analysis

All statistical analyses were performed using Stata 12.1 (StataCorp, College Station, Texas). Continuous variables are reported as median (10th–90th percentiles), and categorical variables as frequency (percentages). The incidence of LAST is summarized with point estimates (n/1000) and exact 95% binomial confidence intervals (CIs). To evaluate the potential effect of time on LAST, tertiles were calculated by dividing the number of PNBs into 3 equal groups, and this variable was treated as categorical. Categorical variables (technology, PNB category, local anesthetic type, sex, tertile) and continuous variables (local anesthetic dosage/weight, local anesthetic dosage, weight, age) were evaluated as potential risk factors for LAST using simple (univariate) logistic regression. Comparative analyses utilized Fisher exact, χ^2, Mann–Whitney, or Kruskal-Wallis test as appropriate. Parameters with $P \leq 0.2$ in univariate analysis were then entered as covariates in multivariable logistic regression models. The logistic regression models were then used to determine significant predictors of LAST. Two main analyses were performed: a per-PNB analysis and a per-patient analysis. Only observations with a complete set of covariates were

TABLE 1. Univariate Analysis of Potential Risk Factors for Local Anesthetic Systemic Toxicity

Categorical Variables		**n (%)***	**No. LAST Events**	**OR†**	**95% CI**	***P***
Ultrasound	Yes	20,401 (81)	12	0.28	0.12–0.65	0.003
	No	4745 (19)	10	1.0		
	Total	25,146				
PNB category	Upper	7434 (29)	13	7.19	2.05–25.2	0.002
	Paravertebral	1657 (7)	6	14.9	3.73–59.7	<0.0005
	Lower limb	12,316 (49)	3	1.0		
	Trunk	3914 (15)	0			
	Total	25,321				
LA type	Ropivacaine	21,918 (87)	16	1.0		
	Lidocaine	1799 (7)	6	4.58	1.79–11.7	0.001
	Bupivacaine	982 (4)	0			
	L-Bupivacaine	453 (2)	0			
	Other	4 (0)	0			
	Total	25,156				
Sex	Male	12,682 (51)	14	1.71	0.72–4.08	0.23
	Female	12,395 (49)	8	1.0		
	Total	25,077				
Tertile	First	8446	12	1.0		
	Second	8445	5	0.42	0.15–1.18	0.10
	Third	8445	5	0.42	0.15–1.18	0.10
Continuous Variables		**n**	**Median (10th–90th Centile)**	**OR†**	**95% CI**	***P***
LA dosage/weight, mg/kg	Ropivacaine	20,225	1.5 (0.7–2.7)	2.21	1.73–2.84	<0.0005
	Lidocaine	1559	4.4 (1.4–7.5)	1.54	1.16–2.06	0.003
LA dosage,‡ mg	Ropivacaine	21,550	112.5 (70–200)	2.20	1.66–2.90	<0.0005
	Lidocaine	1695	375 (100–600)	1.23	0.84–1.78	0.285
Weight,§ kg		23,541	80 (58–105)	0.74	0.57–0.96	0.025
Age,‖ y		24,958	62 (28–81)	0.84	0.68–1.04	0.11

Results from univariate analysis on a per-block basis using all local anesthetic (LA) types. LA type tabulated for first LA type only. Numbers of PNB per categorical variable are expressed as n (%) and total for each variable. Tertiles were calculated by dividing the number of blocks into 3 groups. The dates for the tertiles were as follows: first (01-10-2007 to 08-11-2009), second (08-11-2009 to 01-24-2011), and third (01-24-2011 to 05-31-2012). For continuous variables, n is the total number of observations.

*Total number of observations varies and does not equal 25,336 because of missing data. Data could be submitted, even though some fields were missing. This is because some fields were nonmandatory.

†OR for LAST.

†ORs are per 80-mg (median patient weight) change in LA dosage.

§ORs are per 10-kg change in weight.

‖ORs are per 10-year change in age

LAST indicates local anesthetic systemic toxicity; OR, odds ratio for LAST; CI, confidence interval; PNB, peripheral nerve block.

included in the multivariable analyses. Additional analyses were performed to evaluate associations given the different practice patterns that included multiple PNBs on the same patient utilizing different local anesthetics and technologies. To further evaluate the effects of technology, multivariable logistic regression analysis of patients who received only 1 PNB was performed. To further evaluate the effect of local anesthetic dosage (in milligrams per kilogram), multivariable logistic regression analysis on a per-patient basis was repeated for patients who received only ropivacaine. The influence of local anesthetic dose and weight as independent factors was assessed by entering dose and weight as separate covariates in 1 model. The different potencies of local anesthetics were accounted for based on the observed practice pattern. Exact percentile bootstrap 95% CIs (using 1000 replications) were also estimated for the impact of ultrasound use on LAST in each of the multivariable analyses. To evaluate the possibility that technology or local anesthetic type may have differing effects on LAST for individual PNB categories, multivariable logistic regressions were also performed for each PNB category.

Propensity score analysis was performed to include interactions and hospital as a predictor. Propensity scores were calculated for the use of ultrasound. These scores included interactions between local anesthetic type and block category and implicitly took into account any interactions between use of ultrasound and block category. The calculated propensity scores were used as a covariate (together with use of technology) in a regression model for LAST (ie, covariate adjustment).

Finally, to evaluate the possibility that technology would have differing effects on severity of LAST, multivariable logistic regressions on a per-PNB and a per-patient basis were also performed separately for (1) minor LAST events and (2) major LAST and (3) cardiac arrest (due to toxicity) events. For all analyses, $P < 0.05$ was used to determine statistical significance.

RESULTS

The study population comprised 20,021 patients who received 25,336 PNBs. Fourteen thousand eight hundred sixty patients received 1 block, 5033 received 2 blocks, 102 received 3 blocks, and 26 received 4 blocks. Univariate analysis of potential risk factors for LAST is presented in Table 1 on a per-block basis using all local anesthetic types. There were 22 episodes of LAST (13 minor, 8 major, and 1 cardiac arrest). There were 12 episodes of LAST (8, minor; 4, major) with PNB performed with ultrasound (n = 20,401) and 10 episodes of LAST (5, minor; 4, major; 1, cardiac arrest) with PNB not performed with ultrasound (n = 4745). These cases are summarized in Table 2. The patient who suffered cardiac arrest was having a paravertebral block inserted. The clinical features were consistent with direct intravascular injection of local anesthetic rather than neuraxial spread. The patient was successfully resuscitated with airway management, advanced cardiac life support, and lipid emulsion therapy. Twenty patients with LAST episodes received 1 block, and 2 patients received 2 blocks.

TABLE 2. Local Anesthetic Systemic Toxicity (LAST)—Summary of Events

Case	Ultrasound Use	PNB	Local Anesthetic	Dose, mg/kg	Severity	Comments
1	No	PVB	Ropivacaine	1.4	Cardiac arrest	Preceded by bloody tap
2	Yes	PVB	Ropivacaine	3.75	Major	Unconscious
3	No	FNB	Ropivacaine	2.1	Major	Tonic-clonic seizure, procedure abandoned, associated with ST depression
4	No	FI	Ropivacaine	3.6	Major	Tonic-clonic seizure, overestimated weight
5	Yes	AXB	Ropivacaine	1.8	Major	Unconsciousness, tachycardia
6	No	PVB	Ropivacaine	4.0	Major	Seizure
7	Yes	ISB	Ropivacaine	5.0	Major	Seizure
8	No	PVB	Ropivacaine	1.8	Major	Seizure, case cancelled
9	Yes	Upper	Ropivacaine	2.9	Major	Unconscious then seizure
10	No	AXB	Ropivacaine	1.2	Minor	Immediate central nervous system excitation, auditory symptoms, disinhibition, agitation
11	Yes	AXB	Ropivacaine	5.5	Minor	Agitation
12	No	ISB	Ropivacaine	2.7	Minor	Tinnitus, twitching, drowsy
13	Yes	AXB	Lidocaine	7.5	Minor	Tinnitus, twitching, tingling in ear
14	Yes	AXB	Ropivacaine	4.5	Minor	Agitation for 4–5 h
15	No	AXB	Lidocaine	4.6	Minor	Procedure abandoned because of intravenous injection*
16	Yes	PVB	Ropivacaine	3.1	Minor	Agitation, disinhibition
17	No	AXB	Ropivacaine	2.3	Minor	Agitation, procedure ceased for 5 min until symptoms settled
18	Yes	AXB	Lidocaine	6.7	Minor	Prodromal features, circumoral paresthesia
19	Yes	AXB	Lidocaine	6.7	Minor	Procedure halted because of feeling unwell
20	Yes	AXB	Lidocaine	9.8	Minor	Prodromal features, intravenous injection suspected
21	Yes	Lower	Lidocaine	12.8	Minor	Severe agitation*†
22	No	PVB	Ropivacaine	2.2	Minor	Agitation settled with intralipid

*Two PNBs performed.

†Two PNBs performed with different technologies; for purpose of analysis, technology entered as ultrasound.

PVB indicates paravertebral block; FNB, femoral nerve block; FI, fascia iliaca block; AXB, axillary brachial plexus block; ISB, interscalene block; Upper, nerve block distal to axilla; Lower, nerve block other than FNB or sciatic block.

TABLE 3. Local Anesthetic Systemic Toxicity (LAST) Events, LA Dosage, and Inadvertent Vascular Puncture Per Ultrasound Use and Use of Ultrasound Per-PNB Category

	No Ultrasound, n = 4745 (19%)	Ultrasound, n = 20,401 (81%)
No. LAST events*	10	12
	2.1 (1.0–3.9)	0.59 (0.30–1.03)
Inadvertent vascular puncture†	21	83
	4.4 (2.7–6.8)	4.1 (3.2–5.0)
Ropivacaine,‡ mg/kg	1.63 (0.74–2.88)	1.48 (0.73–2.71)
Lidocaine,‡ mg/kg	3.38 (1.10–6.67)	4.55 (1.54–7.5)
Upper§	705 (9.6)	6639 (90.4)
Paravertebral‖	811 (49.3)	833 (50.7)
Trunk	128 (3.3)	3785 (96.7)
Lower	3092 (25.3)	9140 (74.7)

*$P = 0.004$, Fisher exact test; no ultrasound compared with ultrasound; results are expressed as n (n/1000) (95% CI) for number of events.

†$P = 0.73$; no ultrasound compared with ultrasound; results are expressed as n (n/1000) (95% CI) for number of events.

‡$P < 0.0005$, Mann–Whitney test; median (10–90% percentile) for dosage and n (%) for block category.

§Significantly different spectrum of PNB categories between ultrasound and no ultrasound groups ($P < 0.0005$, χ^2 test). Missing data n (%): ultrasound, 190 (0.7); block category, 13 (0.05).

‖Comprises thoracic paravertebral and posterior approach to the lumbar plexus.

LA indicates local anesthetic; LAST, local anesthetic systemic toxicity; and PNB, peripheral nerve block.

Overall, the incidence of LAST was 0.87 per 1000 PNBs (95% CI, 0.54–1.3 per 1000). Table 3 details LAST events, inadvertent vascular puncture, and local anesthetic dosage per technology. Table 3 also details the use of technology per PNB category. The incidences of LAST per 1000 PNBs, at different sites of PNB, were upper limb (1.75 [95% CI, 0.93–2.99]), paravertebral (3.62 [95% CI, 1.33–7.86]), lower limb (0.24 [95% CI, 0.05–0.71]), and trunk (0.00 [95% CI, 0–0.94]). Local anesthetic dosages (in milligrams per kilogram) per PNB category for ropivacaine were upper limb, 1.79 (0.75–3.13); paravertebral, 1.85 (0.86–3.61); lower limb, 1.49 (0.71–2.5); and trunk, 1.25 (0.75–2.14); $P = 0.0001$, Kruskal-Wallis test. Table 4 details the dosages of ropivacaine and lidocaine and utilization of ultrasound per tertile of procedure.

Table 5 details the results of the multivariable logistic regression analysis of risk factors for LAST presented on a per-PNB basis with all local anesthetic types included. Table 6 details the results of the multivariable logistic regression analysis of risk factors for LAST presented on a per-patient basis for all local anesthetic types. The PNB practice patterns were relatively complex. For example, of 5033 patients who had 2 PNBs per episode of care, 1019 had different technologies used to perform the 2 PNBs. The results of multivariable logistic regression analysis of patients who received 1 PNB only are listed in Appendix 1. A single local anesthetic was used following 21,671 PNBs, whereas 2399 used 2 local anesthetics, of which 2289 (95%) were ropivacaine/lidocaine. The results of multivariable logistic regression analysis on a per-patient basis for patients who received only ropivacaine are listed in Appendix 2. The results of multivariable logistic regression analysis with local anesthetic dose and weight entered as independent covariates are listed in Appendix 3, with increasing weight being protective against LAST. The range of point estimates for the odds ratio (OR) of LAST with the use of ultrasound technology was 0.19 to 0.25.

Separate multivariable logistic regressions were also performed for each PNB category, and the results were as follows: upper limb OR, 0.18 ($P = 0.006$); paravertebral OR, 0.35 ($P = 0.26$); and lower limb OR, 0.20 ($P = 0.20$).

TABLE 4. Local Anesthetic Dosage and Use of Ultrasound Per Tertile

Tertile	Ropivacaine Dosage,* mg/kg	Lidocaine Dosage,* mg/kg	Ultrasound Use,† %
1	1.76 (0.87–3.08)	5.00 (1.71–7.92)	75.3
2	1.44 (0.73–2.54)	4.00 (1.28–7.32)	82.8
3	1.33 (0.65–2.47)	4.00 (1.18–6.91)	85.2

Peripheral nerve block numbers divided into tertiles (n = 8446, 8445, 8445). Tertiles were calculated by dividing the number of blocks into 3 groups. The dates for the tertiles were as follows: first (01-10-2007 to 08-11-2009), second (08-11-2009 to 01-24-2011), and third (01-24-2011 to 05-31-2012). Local anesthetic dosage presented as median (10th-90th percentile).

*$P = 0.0001$, Kruskal-Wallis test.

†$P < 0.0005$ Fisher exact test.

TABLE 5. Multivariable Logistic Regression Analysis of Risk Factors for LAST on a Per-PNB Basis With All LA Types Included

Model 1* Covariate (n = 18,219)	OR	95% CI	*P*
Ultrasound use	0.23	0.088–0.59†	0.002
LA dosage/weight,‡ mg/kg	2.13	1.61–2.82	<0.0005
LA type			
Ropivacaine	1.0		
Lidocaine	5.64	2.02–15.7	0.001
PNB category			
Paravertebral	9.20	2.24–37.8	0.002
Upper limb	4.80	1.23–18.7	0.024
Lower limb	1.0		
Tertiles			
First	1.0		
Second	0.84	0.28–2.51	0.76
Third	0.90	0.30–2.75	0.85
Age,§ y	0.85	0.68–1.07	0.18
Model 2‖ Covariate (n = 18,296)	**OR**	**95% CI**	***P***
Ultrasound use	0.22	0.086–0.54	0.001
LA dosage/weight, mg/kg	2.19	1.67–2.86	<0.0005
LA type			
Ropivacaine	1.0		
Lidocaine	5.47	1.97–15.2	0.001
PNB category			
Paravertebral	8.32	2.05–33.8	0.003
Upper limb	6.16	1.66–22.9	0.007
Lower limb	1.0		

PNB category "Trunk" and LA other than lidocaine and ropivacaine cannot be included in the above analysis as they had no local anesthetic systemic toxicity events. Tertiles were calculated by dividing the number of blocks into 3 groups. The dates for the tertiles were as follows: first (01-10-2007 to 08-11-2009), second (08-11-2009 to 01-24-2011), and third (01-24-2011 to 05-31-2012).

*Includes all covariates with $P \leq 0.20$ from univariate analysis.

†Exact percentile bootstrap 95% CI was 0.084 to 0.56.

‡Lidocaine dosage/kg adjusted to be equivalent to ropivacaine based on practice patterns, that is, divided by the ratio of medians of the lidocaine and ropivacaine doses/kg, that is, 4.4/1.5 or 2.93.

§ORs are per 10-year change in age.

‖Includes only covariates that were statistically significant from model 1.

LA indicates local anesthetic; LAST, local anesthetic systemic toxicity; OR, odds ratio for LAST; CI, confidence interval; and PNB, peripheral nerve block.

Propensity score analysis on a per-PNB basis (as in Table 5) including sex, all local anesthetic types, and all interactions with block category produced an OR of LAST with the use of ultrasound technology of 0.28 (95% CI, 0.11–0.71; $P = 0.007$). When hospital was included in this propensity score analysis, the OR of LAST with the use of ultrasound technology was 0.36 (95% CI, 0.14–0.97; $P = 0.043$). Propensity score analysis on a per-patient basis (as in Table 6) including sex, all local anesthetic types, and all interactions with block category produced an OR of LAST with the use of ultrasound technology of 0.27 (CI, 0.11–0.69; $P = 0.006$). When hospital was included in this propensity score analysis, the OR of LAST with the use of ultrasound technology was 0.35 (95% CI, 0.13–0.97; $P = 0.044$).

Finally, separate multivariable logistic regressions for minor and major LAST identified similar predictors and estimated similar ORs for the impact of ultrasound. On a per-PNB basis, the OR (for the impact of use of ultrasound) on major LAST was (OR, 0.22 [95% CI, 0.054–0.92]; $P = 0.038$) and on minor LAST was (OR, 0.21 [95% CI, 0.06–0.69]; $P = 0.01$). On a per-patient basis, these results for major LAST were (OR, .22 [95% CI, 0.054–0.90]; $P = 0.035$) and for minor LAST were (OR, 0.20 [95% CI, 0.06–0.68]; $P = 0.010$).

DISCUSSION

This study indicates that ultrasound guidance is associated with a reduced incidence of LAST following PNB. All univariate, multiple multivariable, and propensity analyses resulted in almost identical conclusions. The point estimate for the OR for LAST

TABLE 6. Multivariable Logistic Regression Analysis of Risk Factors for LAST, on a Per-Patient Basis, With All LA Types Included

Model 1* Covariate (n = 14,884)	OR	95% CI	*P*
Ultrasound use	0.21	0.083–0.55†	0.001
LA dosage/weight,‡ mg/kg	2.10	1.57–2.79	<0.0005
LA type			
Ropivacaine	1.0		
Lidocaine	5.69	2.06–15.8	0.001
PNB category			
Paravertebral	7.64	1.86–31.4	0.005
Upper limb	4.17	1.09–16.0	0.037
Lower limb	1.0		
Tertiles			
First	1.0		
Second	0.90	0.30–2.71	0.85
Third	1.16	0.40–3.38	0.79
Age,§ y	0.86	0.68–1.07	0.18
Model 2‖ Covariate (n = 14,952)	**OR**	**95% CI**	***P***
Ultrasound use	0.21	0.085–0.53	0.001
LA dosage/weight, mg/kg	2.11	1.60–2.79	<0.0005
LA type			
Ropivacaine	1.0		
Lidocaine	5.43	1.97–15.0	0.001
PNB category			
Paravertebral	7.00	1.72–28.4	0.006
Upper limb	5.11	1.39–18.8	0.014
Lower limb	1.0		

PNB category "Trunk" and LA other than lidocaine and ropivacaine cannot be included in the above analysis as they had no local anesthetic systemic toxicity events. Tertiles were calculated by dividing the number of blocks into 3 groups. The dates for the tertiles were as follows: first (01-10-2007 to 08-11-2009), second (08-11-2009 to 01-24-2011), and third (01-24-2011 to 05-31-2012).

*Includes all covariates with $P \leq 0.20$ from univariate analysis.

†Exact percentile bootstrap 95% CI was 0.088 to 0.59.

‡Lidocaine dosage/kg adjusted to be equivalent to ropivacaine dosage/kg based on practice patterns, that is, divided by the ratio of medians of the lidocaine and ropivacaine doses/kg, that is, 4.4/1.5 or 2.93.

§Odds ratios are per 10-year change in age.

‖Includes only statistically significant covariates from model 1.

LA indicates local anesthetic; LAST, local anesthetic systemic toxicity; OR, odds ratio for LAST; CI, confidence interval; and PNB, peripheral nerve block.

with ultrasound guidance, compared with no ultrasound use, ranged from 0.19 to 0.28, and the *P* values from 0.001 to 0.007, depending on the model used. When hospital was added to the propensity analysis, there remained a significantly reduced risk of LAST when ultrasound was used (OR, 0.35–0.36; $P = 0.043$–0.044). That is, the results of this analysis indicate that the risk of LAST was reduced by greater than 65% with ultrasound guidance. These results are consistent with a single hospital study where the incidence of LAST was higher with landmark-nerve stimulator technique compared with ultrasound-guided PNB (6/5436 vs 0/9069; $P = 0.0061$).[9]

Ultrasound Imaging

There are valid reasons why ultrasound imaging may reduce the risk of LAST. These include real-time guidance of the needle trajectory to avoid vascular trauma and, hence, intravascular injection of local anesthetic. Even if inadvertent vascular puncture occurs, ultrasound imaging may detect entry of local anesthetic into a blood vessel or lack of injectate spread around the neural target, alerting the physician to cease the injection, thereby minimizing the dose of local anesthetic entering the circulation. Previous studies have demonstrated that ultrasound guidance reduces the risk of inadvertent vascular puncture during PNB.[5,6] However, this analysis indicates that inadvertent vascular puncture was not reduced with ultrasound guidance (3.9 per 1000 PNBs) compared with nonultrasound techniques (4.4 per 1000 PNBs). It is possible that inadvertent vascular puncture was unnoticed and underreported; however, the reported incidence in this study exceeds that reported (0.6 and 1.2 per 1000 PNBs for inadvertent venous and arterial puncture, respectively) in a recent single-center registry.[10]

However, there are other mechanisms whereby ultrasound guidance may reduce the risk of LAST because LAST may occur secondary to delayed absorption of local anesthetic. Ultrasound-guided PNB may be executed successfully with reduced local anesthetic doses.[11–14] These findings are consistent with our results, as ultrasound guidance was associated with a reduced dosage of ropivacaine, and ropivacaine dosages were reduced over time. Furthermore, ultrasound-guided PNB often includes assessment and reassessment of the spread of local anesthetic injectate, and therefore the technique of ultrasound-guided PNB is incremental. This will reduce the maximum local anesthetic blood level following the PNB and potentially the risk of LAST.[15]

There may be other unknown mechanisms by which ultrasound guidance reduces the risk of vascular puncture and direct intravascular injection. For example, potentially the ultrasound transducer may compress veins during injection of local anesthetic. Furthermore, ultrasound guidance is associated with needle trajectories that are different than traditional methods of nerve localization. This may also reduce the risk of injection into key structures including the vertebral artery during interscalene block.[16]

Site of Injection, Dose, and Weight

This study indicates that paravertebral and upper limb blocks were associated with an increased risk of LAST compared with lower limb and trunk blocks. The site of injection is known to correlate with local anesthetic blood levels following PNB. Tucker et al[17] measured highest levels following bilateral intercostal blocks and, in descending order, reduced levels with lumbar epidural, brachial plexus, and combined sciatic/femoral block following a fixed dose of mepivacaine. More recently, Auroy et al[18] demonstrated that lumbar plexus block was associated with a higher risk of LAST compared with upper- and lower-limb PNB.

Previous studies investigating LAST following epidural anesthesia and PNB showed no correlation between blood levels of bupivacaine and dosage, sex, age, height, and physical status,[19,20] and for mepivacaine, weight and dosage.[17] Furthermore, in a study of 9287 regional anesthesia procedures, there was no correlation between LAST and the local anesthetic dosage or physical status.[21] This current study provides clinical evidence from real-world practice, beyond pharmacokinetic studies, that site of injection, local anesthetic dose per weight, local anesthetic dose, and patient weight are important predictors of LAST. It is relevant to note that the importance of both the site of injection and local anesthetic dose have been thought to be relevant risk factors for LAST for almost 100 years.[22] The results of this current study support using a minimum effective dose achieving either adequate anesthesia or postoperative analgesia, taking into account the site of injection and patient weight.

Local Anesthetic Type

We can draw no conclusions about the relative risk of bupivacaine use because no LAST events occurred using this local anesthetic, and less than 4% of PNBs were performed using bupivacaine. However, this analysis indicates that lidocaine was associated with a higher risk of LAST than ropivacaine. This was a surprising result because lidocaine is thought to be associated with an increased margin of safety. Perhaps this perception influenced the way in which lidocaine was utilized, resulting in reduced vigilance regarding incremental injection and frequent aspirations of local anesthetic. The perceived safety margin may have contributed to the use of relatively excessive doses of lidocaine, particularly when ultrasound guidance was used (Table 3). This is in contrast to the reduced dosage of ropivacaine that was associated with ultrasound guidance. Potentially, lidocaine was associated with a higher risk because relatively inexperienced practitioners were more likely to use lidocaine with the aim of hastening onset and improving block success. Of course, the possibility exists that the intrinsic safety of lidocaine has been overstated, and hence the recommended dosages may be too high.

Age and Sex

Age was not a significant predictor of LAST in this analysis. Age may have been expected to be a significant predictor, as patients with comorbidities feature more prominently in case reports of LAST, especially those involving lipid emulsion therapy.[4] However, this may be the result of publication bias, where anesthesiologists consider it more important to report (and journals publish) the successful use of lipid emulsion therapy in a vulnerable population. Sex was not a significant predictor in this analysis, and with the exception of LAST occurring in association with obstetric anesthesia, there is no plausible reason why males or females would be more susceptible to LAST.

Limitations

This study has important limitations, particularly the small number of outcome events (22) to model and the ratio of the number of outcome events to the number of covariates.[23] However, our finding of the reduced risk of LAST with use of ultrasound was consistent across univariate, multiple multivariable models (including bootstrap 95% CIs), and propensity analyses. In this analysis, we made assumptions regarding clinical techniques. For example, we assumed that ultrasound guidance was utilized in a consistent manner for different PNBs. However, PNB includes a wide spectrum of techniques, and ultrasound guidance is arguably more challenging and still evolving for techniques such as posterior lumbar plexus and paravertebral blocks. For this reason, we

performed additional per-block category logistic regression analyses, and those results indicated that the use of ultrasound guidance was likely to be protective for all PNB categories. Our main analyses combined major and minor LAST events; however, ultrasound similarly reduced the incidence of both minor and major LAST events, and this is consistent with LAST events having similar etiologies existing along a continuum of severity. A further limitation relates to the registry study design, with uncontrolled observational measurements, which holds a higher risk for unrecognized bias and incorrect conclusions about cause and effect than more rigorous designs. This stems from the influence that unmeasured or unknown confounders may have on the results. Examples of potentially important unmeasured confounders are American Society of Anesthesiologists physical status and patient comorbidities. However, currently there is no definitive evidence that specific comorbidities increase the risk of LAST. Epinephrine was not included as a covariate because this was not consistently measured over the entire study period. However, we estimate (based on a reduced cohort) that in this study less than 3% of PNBs utilizing ropivacaine (used in 87% of our cases) received epinephrine, and a minimum of 57% of PNBs utilizing lidocaine blocks received epinephrine. This practice is consistent with the awareness that ropivacaine has intrinsic vasoconstrictor activity (although this does not influence its own absorption).[24] One recommendation for preventing LAST is the use of an intravascular marker such as epinephrine.[25] In this study, had all PNBs been performed with epinephrine, potentially the results may have been different. Our results demonstrate an association between clinical covariates and LAST but are not definitive in the same way that the results of a randomized controlled trial would be. However, a randomized controlled trial with LAST as the outcome would be impractical because of the rarity of the event and the associated ethical and logistic issues. Ideally, the multivariable models we created for this analysis will be tested again with a different and larger data set in the future, when ultrasound-guided PNB has evolved further. However, this study indicates that ultrasound guidance is so frequently (and with increasing frequency) used in routine practice that obtaining robust comparative data (of non–ultrasound-guided PNBs) in the future may not be possible. The exception to this is paravertebral block where ultrasound was utilized in only 51% of PNBs. The hospitals contributing to this project mostly used ropivacaine (87%), and in the future collecting data from practices that routinely use bupivacaine would be valuable to further explore local anesthetic type as a potential risk factor for LAST.

Twenty hospitals contributed to this study, and therefore it was not appropriate to enter study site as a covariate in the logistic regression models. To address this potential source of residual confounding, propensity score analysis (including hospital as a covariate) was performed, and the results still indicated that ultrasound guidance was protective. A further potential limitation is selective reporting of events, perhaps even favoring ultrasound-guided PNB. Although this possibility cannot be absolutely excluded, the authors consider selective reporting unlikely for the following reasons: (1) the background culture of reporting adverse events and incidents that existed in Australia and New Zealand before the commencement of this project and (2) the development of the registry with its governance and strategies for data quality control.

CONCLUSIONS

This study has demonstrated that LAST occurs rarely in our contemporary practice of PNB. Important risk factors for LAST were site of injection, local anesthetic type, dosage, weight, and the technology used to perform the PNB. Importantly, this study comprising 25,336 PNBs provides the strongest evidence, to date, that ultrasound guidance may improve safety because it is associated with a reduced risk of LAST following PNB.

ACKNOWLEDGMENTS

The authors acknowledge the following individuals: Dr Elizabeth Williamson, PhD, biostatistician at the Department of Epidemiology & Preventive Medicine, Monash University, Australia; Dr Steve Watts, MBChB, FANZCA, and Ms Gemma Ayre, RN, Department of Anaesthesia, Sir Charles Gairdner Hospital, Perth, Western Australia, Australia; Ms Colleen Ward, RN, and Dr Myles Conroy, MBBS, FANZCA, Department of Anaesthesia, Geelong Hospital, Geelong, Victoria, Australia; Dr Bronwen Evans, MBBS, FANZCA, and Dr Gabrielle Van Essen, MBBS, FANZCA, Department of Anaesthesia, Western Hospital, Footscray, Melbourne, Victoria, Australia; Dr Steven Fowler, MBBS, FANZCA, Department of Anaesthesia, The Alfred, Prahran, Melbourne, Victoria, Australia; Dr Elizabeth Bashford, MBBS, FANZCA, Dr John Oswald, MBBS, FANZCA, and Dr Fred Rosewarne, MBBS, FANZCA, Department of Anaesthesia, Ballarat Base Hospital, Ballarat, Victoria, Australia; Dr David Scott MBBS, FANZCA, Dr Dougall Miller, MBBS, FANZCA, and Dr Andrew Peart, MBBS, FANZCA, Department of Anaesthesia, Lismore Base Hospital, Northern Rivers Anaesthesia Services, Lismore, New South Wales, Australia; Dr Alan Mahoney, MBBS, FANZCA, Department of Anaesthesia, Bendigo Base Hospital, Bendigo, Victoria, Australia; Dr Barbara Robertson, MBBS, FANZCA, Department of Anaesthesia, Shepparton Hospital, Shepparton, Victoria, Australia; Prof Ramani Vijayan and Dr Hou Yee Lai, MBBS, FANZCA, University of Malaya Medical Centre, Kuala Lumpar, Federal Territory of Kuala Lumpur, Malaysia; Dr Danny McGlone and Ms Sue Kube, RN, Department of Anaesthesia, Royal Hobart Hospital, Hobart, Tasmania, Australia; Dr David Pirotta, Department of Anaesthesia, Wellington Hospital, Wellington, New Zealand; Dr Rod Van Twest, Dr Simon Pattullo, and Dr Halia O'Shea, MBBS, FANZCA, Department of Anaesthesia, Gold Coast Hospital, Queensland, Australia; Dr Nicolas Mostert, Department of Anaesthesia, Waikato Hospital, Hamilton, Waikato, New Zealand; Dr Philip Cornish, MBChB, FANZCA, Department of Anaesthesia, Nelson Hospital, Nelson, Tasmania, New Zealand; Dr Adam Rehak, MBBS, FANZCA, Department of Anaesthesia, Royal North Shore Hospital, Sydney, New South Wales, Australia; Dr David Belavy, MBBS, FANZCA, and Dr Adrian Chin, MBBS, FANZCA, Department of Anaesthesia, Royal Brisbane and Women's Hospital, Brisbane, Queensland, Australia; Dr Andrew Fenton, MBChB, FANZCA, Department of Anaesthesia, Royal Darwin Hospital, Northern Territory, Australia; Dr Rowan Thomas, MBBS, FANZCA, Department of Anaesthesia, St Vincent's Hospital, Melbourne, Australia; Dr Phillip Cowlishaw, MBBS, FANZCA, and Leanne Gleeson, RN, Department of Anaesthesia, Mater Adult Hospital, Brisbane, Queensland, Australia; Dr Jarrod Ngan, MBBS, FANZCA, Catherine Jowett, RN, Department of Anaesthesia, Princess Alexandra Hospital, Brisbane, Queensland, Australia; and Dr Geoffrey Crawford, MBBS, FANZCA, Department of Anaesthesia, Logan Hospital, Brisbane, Queensland, Australia.

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APPENDIX 1. Multivariable Logistic Regression Analysis of Risk Factors for LAST for Patients Who Received 1 PNB Only

Model 1* Covariate (n = 11,624)	**OR**	**95% CI**	***P***
Ultrasound use	0.25	0.092–0.68[†]	0.007
LA dosage/weight,[‡] mg/kg	2.00	1.47–2.72	<0.0005
LA type			
Ropivacaine	1.0		
Lidocaine	3.63	1.13–11.6	0.03
PNB category			
Paravertebral	10.2	2.00–51.7	0.005
Upper limb	4.87	1.00–23.7	0.050
Lower limb	1.0		
Tertiles			
First	1.0		
Second	0.84	0.28–2.55	0.76
Third	0.74	0.22–2.48	0.63
Age,[§] y	0.84	0.66–1.06	0.145
Model 2[‖] Covariate (n = 11,683)	**OR**	**95% CI**	***P***
Ultrasound use	0.23	0.087–0.62	0.003
LA dosage/weight, mg/kg	2.07	1.54–2.78	<0.0005
LA type			
Ropivacaine	1.0		
Lidocaine	3.54	1.11–11.3	0.033
PNB category			
Paravertebral	8.93	1.78–44.7	0.008
Upper limb	6.39	1.35–30.2	0.019
Lower limb	1.0		

Tertiles were calculated by dividing the number of blocks into 3 groups. The dates for the tertiles were as follows: first (01-10-2007 to 08-11-2009), second (08-11-2009 to 01-24-2011), and third (01-24-2011 to 05-31-2012).

*Includes all covariates with $P \leq 0.20$ in univariate analysis.

[†]Exact percentile bootstrap 95% CI was 0.089 to 0.61.

[‡]Lidocaine dosage/kg adjusted to be equivalent to ropivacaine based on practice patterns, that is, divided by the ratio of medians of the lidocaine and ropivacaine doses/kg, that is, 4.4/1.5 or 2.93.

[§]ORs are per 10-year change in age.

[‖]Includes only statistically significant covariates from model 1.

LA indicates local anesthetic; LAST, local anesthetic systemic toxicity; OR, odds ratio for LAST; CI, confidence interval; and PNB, peripheral nerve block.