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Original Article

Local Anesthetic Delivery and Resuscitation for Systemic Toxicity in China: A Survey of 250 Hospitals

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ABSTRACT

Background: The optimized procedures for local anesthetic (LA) delivery and resuscitation for LA systemic toxicity (LAST) have improved the safety of regional anesthesia. Lipid emulsion (LE) has been the valid treatment for LAST. However, adoption of these revised procedures in developing countries remains unknown.

Methods: We conducted a 17-question survey to access the basic knowledge of LA delivery, the practice procedures for LAST resuscitation and an overall understanding of LE usage in both academic and non-academic hospitals of the Chinese Society of Anesthesiology.

Results: A total of 250 hospitals completed the survey. Ropivacaine was the most preferred long-acting LA for regional anesthesia. Among the responders, 10 hospitals did not apply test-dosing before epidural anesthesia, including more non-academic than academic hospitals (7.1% versus 1.4%, P=0.0223). 77.5% (107/138) of academic hospitals and 69.6% (78/112) of non-academic hospitals had a protocol for LAST resuscitation. Only 28.2% of academic and 18.8% of non-academic hospitals stated LE preference for LAST. Furthermore, 17% (22/132) academic hospitals and 13% (12/89) non-academic hospitals chose the recommended epinephrine dosage based on the guideline of ARSA for LA-induced cardiac arrest. Significantly higher proportion (1.6 times more, 95% CI 1.082-3.991) of academic hospitals considered LE as the resuscitation method for LA-induced seizure than non-academic hospitals (44.9% versus 28.2%, P=0.0269). Finally, LE was available in only half of the hospitals which adopted its feasibility for LAST resuscitation.

Conclusions: The survey revealed the poor practice procedures for regional anesthesia and non-standard use of LE for LAST resuscitation in China, especially among non-academic hospitals. (Funded by the National Natural Science Foundation of China.)

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Evidence Based Communications

Improved techniques for regional anesthesia appear to be associated with the increasing usage of local anesthetic (LA). The adoption of electrical stimulation and ultrasound guidance for nerve localization has reduced vascular puncture and improved the precision of site injections. However, several factors contribute to LA induced systemic toxicity (LAST), including the patient characteristics, the operator dependence, LA dosage, and LA pharmacokinetics (1). Through new LA, advanced nerve localization techniques, test-dosing requirements and most importantly, awareness for LAST resuscitation have, together, significantly improved the safety of regional anesthesia (2, 3). Although rare, LAST may be life-threatening. LA providers should be familiar with the standard delivery protocols, as well as procedures for LAST resuscitation (4, 5). The efficacy of lipid emulsion (LE) for resuscitation has been tested through case reports and series (6), and has been recommended as the valid resuscitation method ever since 2010 by the American Society of Regional Anesthesia and Pain Medicine (ASRA) (7). The avoidance of LAST related death depends on standard practice procedures for LA delivery and LAST resuscitation, in addition to the precise method of LE use (8). Therefore, we surveyed the clinical management of LAST prevention and resuscitation in anesthesiology departments across China. We hypothesized that there is a difference in the procedures for LA delivery and LAST resuscitation between the academic hospital and non-academic hospital, and the overall understanding of LE for resuscitation is limited. To test this, we conducted a 17-question survey, relating to LA usage for regional anesthesia, the incidence rate of LAST, resuscitation procedures, especially with LE, and LE handling procedures.

MATERIALS AND METHODS

The survey was conducted under the approval of the Human Research Ethics Committee in Zhujiang Hospital of Southern Medical University (Aprroval no.20150112) and was conducted between January and June in 2015. In this cross-sectional survey, we focused on the basic knowledge of LA delivery during regional anesthesia, and the treatments for LAST, especially the LE usage for resuscitation. There were 4,327 hospitals on the list of the Chinese Society of Anesthesiology in 2015. Forty-five percents of them are academic while 55% of them are non-academic. Based on the former study LE usage of incidence of 60% versus 40% between the two groups, 194 of total hospitals should be picked (97 of each) when we set $\alpha=0.05$, $\beta=0.2$ for sample calculation. In order to avoid the lost of follow-up, we used the computer to help us randomly pick 200 hospitals for each group. By telephone interviewing with the Chairman of the picked department, we got 375 voluntary hospitals and sent them the questionnaires for the further procedures (10 in academic hospitals and 15 in non-academic hospitals are not willing to conduct the survey). The percentage of voluntary hospitals is 93.75%. The 17-question surveys (Appendices) with return envelopes were mailed to the chiefs or the vice chiefs who are responsible for the regional anesthesia. Regional anesthesia includes epidural anesthesia, spinal anesthesia, combined spinal and epidural anesthesia, brachial or cervical plexus block, sciatic nerve block, and other types of peripheral nerve block. When responses were not received after two months, the survey recipients were called to maximize response rate. Received information and results were sorted blindly to the categories of the hospitals. Institutions were categorized as the academic and non-academic hospitals for further analysis after sorting. According to the protocol for survey analysis, odds ratios with 95% confidence intervals (95% CI) were used to index the effect size of the differences (9). Chi-square test was performed using GraphPad Prism (version 5.0 for Windows, GraphPad Software, La Jolla, California, USA), Fisher's test was used to calculate an exact P value when $n<40$. The α-value was set at 0.05. The criteria of the responders is the completion of the survey. Partially completed questionnaires were considered non-responders and data were excluded accordingly.

RESULTS

Survey Responders and Non-responders

We received 317 feedback questionnaires, which represents 84.5% of the delivered surveys. Out of the returned surveys, 250 (rate of 78.9%) fit the criteria of responders that are suitable for

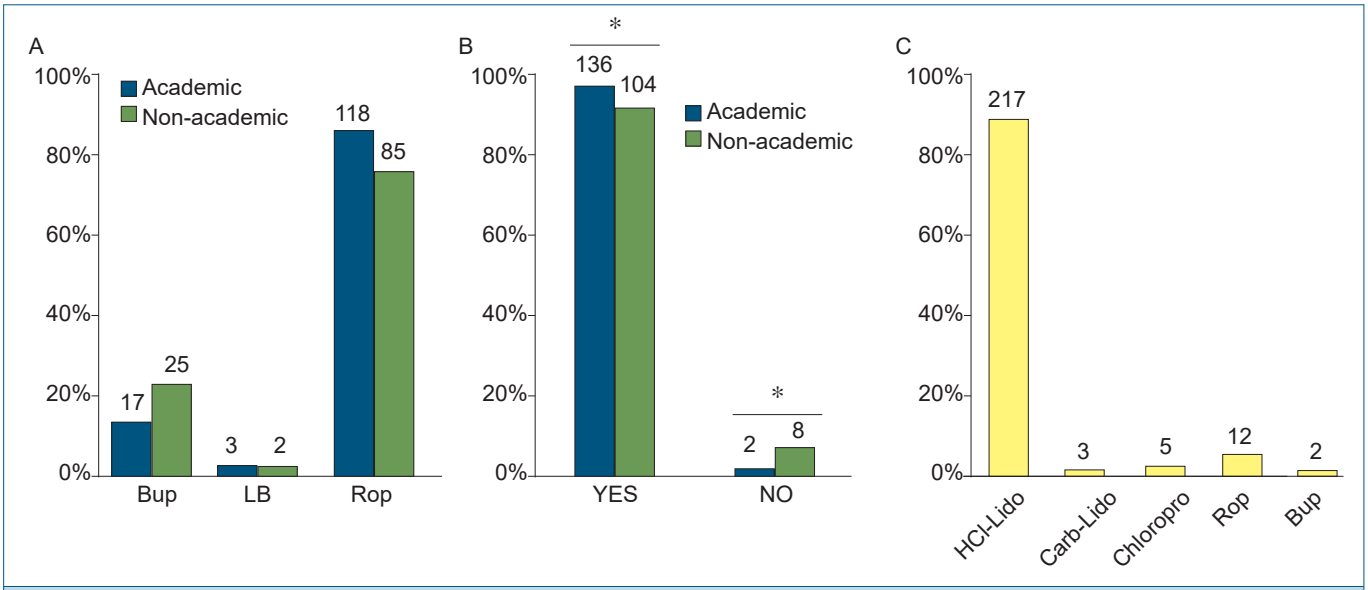

Figure 1. Local Anesthetic (LA) Delivery in Academic and Non-academic Hospitals.
A. Percentage of the most often used LA in academic and non-academic hospitals. Ropivacaine was the most preferred LA in both academic and non-academic hospitals, followed by Bup and LB; B. Percentages of hospitals in which test-dosing was administrated or not before epidural anesthesia among all surveyed hospitals; C. Drugs adopted for test-dosing. Numbers on top of the bar chart shows the exact amount of hospitals. Percentage is calculated from the categorical types of hospitals with academic and non-academic hospital. *Represents significant difference (P<0.05) between academic and non-academic hospitals. Bup: bupivacaine; LB: levobupivacaine: Rop: ropivacaine; HCl-Lido: HCl-lidocaine; Carb-Lido: lidocaine carbonate; Chloropro: chloroprocaine.

further analysis. Among the responders, 55% (138) were from academic hospitals while 45% (112) were from non-academic hospitals.

Long-acting LA Preference and Dosage

Ropivacaine was the most preferred long-acting LA used in both academic (85.5%, 118 out of 138) and non-academic (75.9%, 85 out of 112) hospitals for regional anesthesia. Other preferred LAs, ordered in decreasing preference, were bupivacaine and levobupivacaine (Figure 1A).

Test-dosing for Epidural Anesthesia

Among the responders, 240/250 (96%) used test-dosing before epidural anesthesia while 10/250 (4%) did not. Of note, there is a significant difference between academic hospitals (98.6%, 136/138) and non-academic hospitals (92.9%, 104/112) for the use of test-dosing (x^2=5.2, P=0.0223) (Figure 1B). 3-5ml HCl-lidocaine (either 1% in 47 hospitals or 2% in 170 hospitals) was the favourite LA for test-dosing, followed by lidocaine carbonate, chloroprocaine, ropivacaine and bupivacaine (Figure 1C).

LAST Induced Cardiac Arrest (CA) and Epinephrine Usage

There is a significant difference between academic and non-academic hospitals in their preference for epinephrine to treat LAST induced CA (Figure 2A). While only 79.5% (89/112) of non-academic hospital stated that they would choose epinephrine for resuscitation, 95.7% (132/138) of academic hospitals stated so (x^2=15.80, P<0.0001). Among those hospitals, the most preferred initial dose of epinephrine for CA resuscitation in a 70 kg patient (Figure 2B) was 1mg, representing 68% (90/132) academic hospitals and 65% (58/89) non-academic hospitals; followed by 0.06-0.1 mg, 17% (22/132) academic hospitals and 13% (12/89) non-academic hospitals; 0.5 mg in 14% (18/132) academic hospitals and 20% (18/89) non-academic hospitals; and other doses (2/132 academic hospitals and 1/89 non-academic hospitals).

LE Resuscitation

Details for LE resuscitation procedures are shown in Table. LE delivery during LAST was

adopted at the rate of 28.2% (39 /138) and 18.8% (21/112) in academic and non-academic hospitals. Furthermore, 77.5% (107/138) of academic hospital and 69.6% (78/112) of non-academic hospitals had a protocol for LAST resuscitation. Among those hospitals with protocol, there is a significant difference between academic (66.4%, 71/107) and non-academic (50%, 39/78) hospitals in their recommendation for LE as the preferred choice for resuscitation (x^2= 5.006, P=0.0253). Among the hospitals where LE was recommended for LAST resuscitation, 76.1% (54/71) of academic and 71.8% (28/39) of non-academic hospitals specifies the precise methods for LE delivery. On the other hand, among the hospitals lack of LAST resuscitation protocol or where LE was not included in the protocol, 46.5% (40/86) of academic hospitals and 48.8% (41/84) of non-academic hospitals were not aware of LE as a LAST resuscitation treatment. Among those hospitals being aware of LE for LAST resuscitation or adopt LE for resuscitation, 27.6% (27/98) of academic and 32.4% (23/71) of non-academic hospitals presumed the feasibility of propofol for CA resuscitation because it also contains lipid component, while 22.4% (22/98) of academic hospitals and 18.3% (13/71) of non-academic hospitals refrained from judgments.

Table. LE for LAST resuscitation.

	Academic n (%)	Non-academic n (%)	P-value
LE during LAST			
Yes	39 (28.3%)	21 (18.8%)	
No	99 (71.7%)	91 (81.2%)	0.0799
LAST protocol			
Yes	107 (77.5%)	78 (69.6%)	
No	31 (22.5%)	34 (30.4%)	0.1571
LE included			
Yes	71 (66.4%)	39 (50.0%)	
No	36 (33.6%)	39 (50.0%)	0.0253*
Precise method			
Yes	54 (76.1%)	28 (71.8%)	
No	17 (23.9%)	11 (28.2%)	0.6235
LE for LAST			
Known	46 (53.5%)	43 (51.2%)	
Unknown	40 (46.5%)	41 (48.8%)	0.7642
Propofol instead of LE			
Yes	27 (27.6%)	23 (32.4%)	
No	49 (50.0%)	35 (49.3%)	
Uncertain	22 (22.4%)	13 (18.3%)	0.7149

Numbers and percentages of hospitals display details of LAST resuscitation protocol and LE knowledge. Note that percentage is calculated from the categorical types of hospitals with academic and non-academic hospital. *Represents significant difference (P < 0.05) between academic and non-academic hospitals. LE: lipid emulsion; LAST: local anaesthetic induced systemic toxicity.

LE for Seizure Resuscitation

Among the hospitals who adopted LE as the resuscitation treatment for LAST, significantly higher proportion (1.6 times more, 95% CI 1.082-3.991) of academic (44/98) hospitals considered LE as the resuscitation method for LA-induced seizure than non-academic (20/71) hospitals (44.9% versus 28.2%, P=0.0269) (Figure 3).

LE Storage and Availability

Among the academic and non-academic hospitals, which know the LE can be used for LAST resuscitation, there is no significant difference in their LE storage places (53.1%, 52/98 versus 45.1%, 32/71) (Figure 4A). In those hospitals, the LE was stocked in the specified storage room in the operation area, the hospital pharmacy, the code cart, the operation rooms, and other unspecified places (Figure 4B). LE is accessible within 10 minutes in 84.6% (44/52) of academic hospitals and 84.4% (27/32) of non-academic hospitals, 10-30 minutes in 11.5% (6/52) of academic hospitals and 9.4% (3/32) of non-academic hospitals, and >30 minutes in 3.8% (2/52) of academic hospitals and 3.1% (1/32) of non-academic hospitals, respectively (Figure 4C). The medium-long-chain LE (MLLE) is the most common type of storage, followed by the long-chain LE (LLE) in both academic and non-academic hospitals (Figure 4D). Among the hospitals that did not stock LE, several reasons were cited. First, these hospitals considered LAST as a rare event. Second, these hospitals did not know that LE can be used for LAST resuscitation. Third, the hospitals administrators did not authorize LE stocks for LAST resuscitation (Figure 4E).

DISCUSSION

The survey of 250 Anesthesiology departments that we have presented here indicates that a pro-

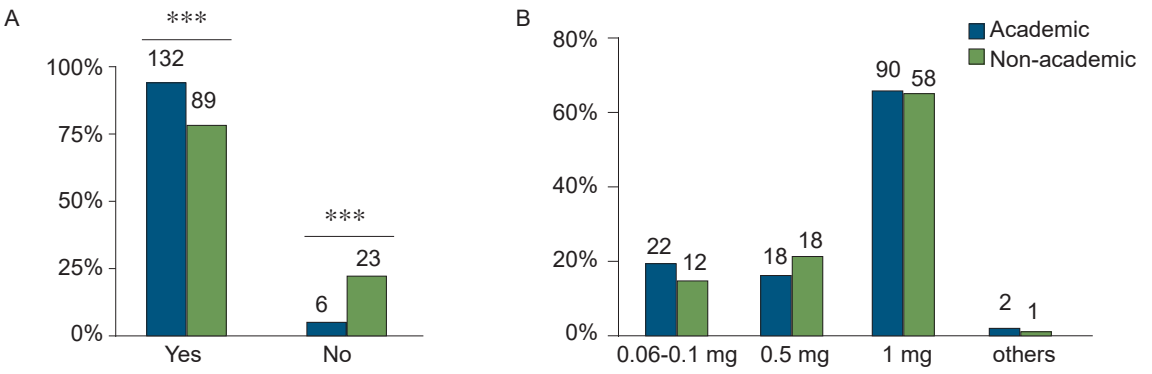

Figure 2. Epinephrine Usage for Local Anesthetic (LA) Induced Cardiac Arrest.
A. Choice of epinephrine for LA induced CA between academic and non-academic hospitals; B. Dosage distribution among hospitals in which epinephrine is chosen for CA resuscitation. Numbers on top of the bar chart shows the exact amount of the hospitals. Percentage is calculated from the categorical types of hospitals with academic and non-academic hospital. ***Represents significant difference (P<0.001) between academic and non-academic hospitals.

found portion of anesthesia providers in China have limited knowledge about the usage LE for LAST resuscitation, as well as the poor managements during LAST, especially in non-academic hospitals. Better understanding of the LAST resuscitation and the usage of LE should be improved in countries such as China, where the LA usage is increasing.

LA Usage and Preference

As nerve stimulator and ultrasound guided techniques have become available in China, the use of regional anesthesia has become increasingly popular especially for the growing aging population. Hence, the usage of LA is growing. Moreover, the development of safer drugs and increased awareness of LAST have greatly improved the safety of LA administration. Because of its lower cardiac toxicity, longer effective duration and effective sensory-motor segregation during labor, ropivacaine is the most preferred long-acting LA for regional anesthesia according to our survey, which is consistent as in other countries (10). In addition to restricted maximum dose (11), LA test-dosing is an extremely important part of safe anesthesia delivery and aim to alert the provider to accidental insertion of the epidural catheter into subarachnoid space or blood vessels (12, 13). However, 10 out of 250 hospitals do not practice test-dosing in the

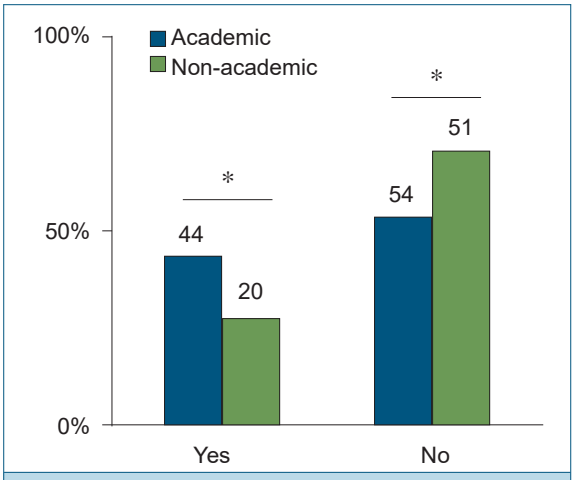

Figure 3. LE Delivery for the Resuscitation during LA-induced Seizure in Academic and Non-academic Hospitals.
Numbers on top of the bar chart shows the exact amount of the hospitals. Percentage is calculated from the categorical types of hospitals with academic and non-academic hospital. *Represents significant difference between academic and non-academic hospitals (P<0.05).

surveyed hospitals. This poor practice is more epidemic in non-academic hospitals than academic hospitals. Unlike the western countries, some hospitals in China used bupivacaine for test-dosing, which needs to be approved as safe for testing. All these factors underscore the need to standardize LA usage across all hospitals in China, as well as in other countries.

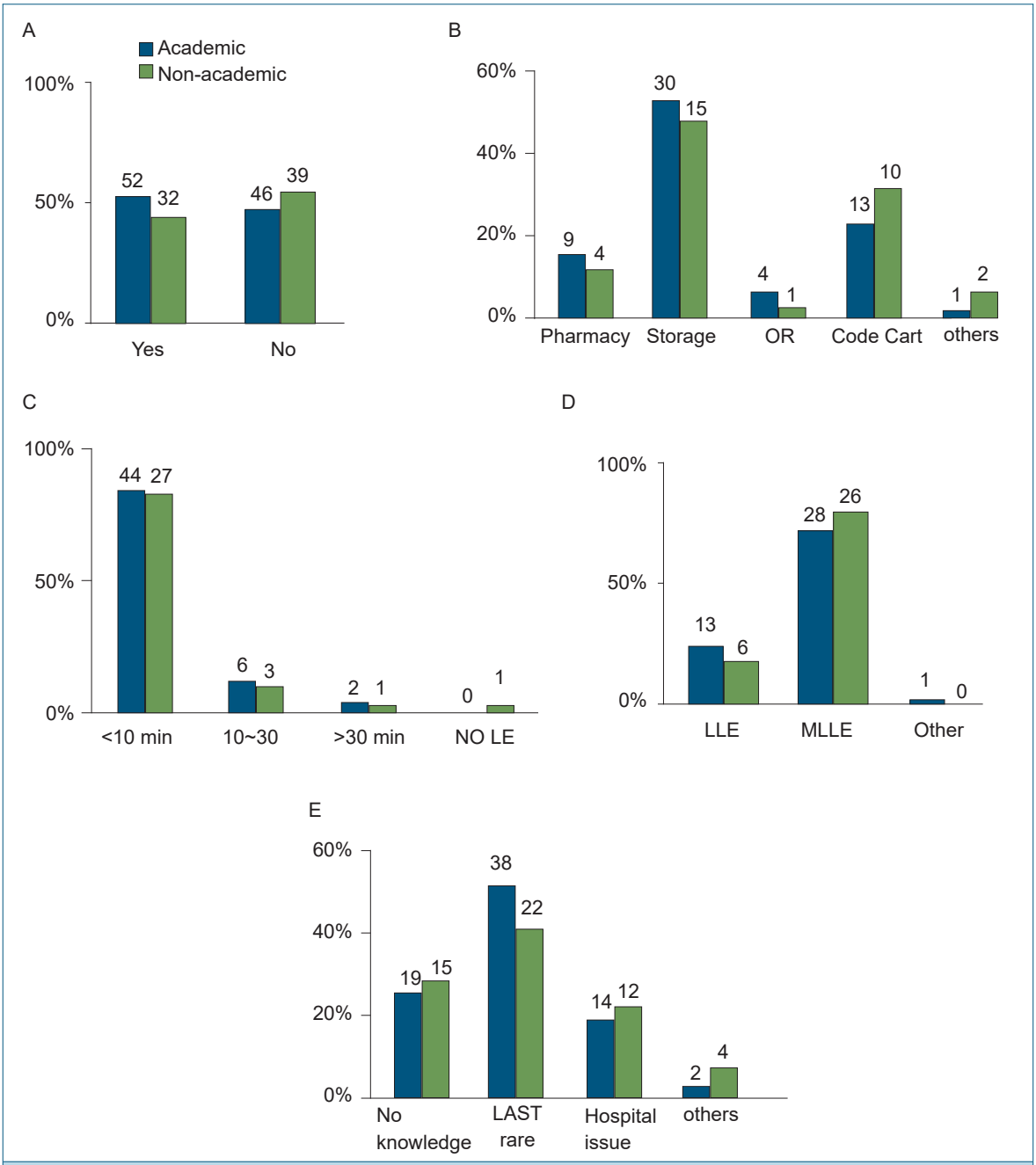

Figure 4. Lipid Emulsion (LE) Storage and Availability in Academic and Non-academic Hospitals.
A. Percentage of hospitals in which LE is available for local anesthetic induced systemic toxicity (LAST) resuscitation; B. Locations of LE storage; C. Time consumption for obtaining LE for LAST resuscitation; D. Types of LE for LAST resuscitation in academic and non-academic hospitals; E. Reasons for LE unavailable for LAST resuscitation. Numbers on top of the bar chart shows the exact amount of the hospitals. LE: lipid emulsion; LAST: local anesthetic induced systemic toxicity; LLE: long-chain emulsion; MLLE: middle-long-chain emulsion.

LAST and Epinephrine Resuscitation

LAST is a severe complication of clinical LA used and can lead to CA in serious situations (3, 4). Epinephrine is the preferred drug for cardiac resuscitation and is recommended to treat LAST induced CA. However, the safe and effective dosage that should be used in these situations is still a subject for debate (14). In a rabbit model of bu-

pivacaine-induced CA resuscitated with LE, high-dose of epinephrine (100 μg/kg) was associated with a significant increase in coronary perfusion pressure but was subsequently associated with declining hemodynamic variables (15). Furthermore, epinephrine overdose might cause severe pneumorrhagia, oedema and acidosis, which argues against using traditional doses for resuscitation, particularly in anesthetized patients (16). ASRA has recommended that the epinephrine dosage used to treat LAST should be decreased to 1 μg/kg (7). In our survey, the most common dose that Chinese anesthesiologists used was 1mg (with weight about 70 kg), which is the common dose in general cardiopulmonary resuscitation (not LAST induced CA) and ten times more than the recommended dose for LAST (7).

LE for LAST Resuscitation

In addition to epinephrine, LE is also considered as an effective treatment for LAST resuscitation (6). The optimal timing for epinephrine administration is also immediately after the bolus of LE, which produces better outcomes of successful cardiopulmonary resuscitation (17). In 1998, Weinberg et al (18). reported the usage of LE for resuscitation during bupivacaine- induced cardiac toxicity in dogs. In 2006, Rosenblatt and collegues (4) successfully used LE to save one patient with bupivacaine-induced cardiac stroke. So far, LE has been established as an effective assistant for resuscitation and accepted worldwide and recommended by the American Heart Association guideline for LAST (19). However, the knowledge of this delivery method is still sparsely known by Chinese anesthesiologists, especially in the non- academic hospitals, as revealed in our survey. More academic hospitals have established precise procedures for the LE resuscitation during LAST, while fewer non-academic hospitals. What's more, fewer non-academic hospitals have developed precise delivery methods in their procedures. Emphasis should be made to establish or refine continuing medical education programs and increase the awareness and use of modern treatment techniques, including LE resuscitation.

Different Types of LE for LAST Resuscitation

At the very beginning, LAST resuscitation with LE ignored the types of the LE preparations (20). Nowadays, studies revealed that different types of LE may have different effects on LAST resuscitation, especially for reversing LA induced cardiotoxicity (21). LLE may be superior to MLLE as it was associated with fewer asystole recurrences after resuscitation and lower myocardial bupivacaine concentrations (22), hence the patients awaked and arrhythmia disappeared quickly (23). However, results have also indicated that MLLE has higher affinity than LLE for LA extraction from human serum (24). Also, another in vivo experiment indicated that MLLE and LLE have no difference in its effects on blood pressure and cardiac index for ropivacaine- induced LAST in swine (25). These arguments all calls to determine the appropriate LE preparation for LAST resuscitation. In particular, different LA has different outcome based on their characteristics. In vitro experiments revealed that long- acting LAs have a high affinity for LE, and the extraction capability of LLE for these LAs is 2.5 times higher than MLLE (26). Bupivacaine was more effectively extracted than ropivacaine by lipid agents, with a 40% and 20% reduction in initial concentration, respectively (27). And the magnitude of LE mediated reversal of vasodilatation appears to be correlated with the lipid solubility of the LA (28). In our survey, MLLE is the most common type of storage. Unfortunately, the survey did not determine the cause.

LE Availability

As LE bolus combined with basic life support benefits LAST resuscitation, LE availability in operation room determines the speed of the onset of recovery. In our survey, LE is available for LAST resuscitation within 10 min in most surveyed hospitals, both academic and non-academic, which allows for the most optimal treatment timing (17). However, an alarming number of hospitals, academic and non- academic hospitals viewed LAST as a rare event and did not store LE for LAST. The LE availability was even worse in a recent survey in the orthopaedic anesthesia group of academic hospitals (29). This situation greatly impacts the safety of the LA delivery in the clinic.

Center Nerve System (CNS) Toxicity and LE Treatment

CNS toxicity and cardiotoxicity are two major signs of LAST. A seizure is a common sign of CNS toxicity during LA administration and might be aggravated without treatment (1). LE is sufficient to treat LA induced CNS toxicity, in addition to cardiotoxicity (30), hence it is the recommended course of treatment when seizure occurs (18). The academic hospitals in our survey were 1.6 times more likely to choose LE for LA-induced seizure than non-academic hospitals. However, the proportion of all the responders is still low in both types of hospitals, and signals the needs to modernize and standardize treatment protocols for LAST induced seizure. Moreover, nearly 30% of the responders, both academic and non-academic hospitals, thought that propofol can be used for LAST resuscitation, even though its LE component is just 10%. It should be noted that propofol can be used for sedation to control seizure, but large doses are required for LAST resuscitation, which can only worsen the hemodynamic stability and cardiac function of the patients.

Limitations

The limitations of our survey are as followed. First, the survey was conducted by an academic hospital and questionnaires were designed based on the researchers' attitude and knowledge of LAST and LE resuscitation. Hence there could be bias against non-academic hospitals, which might have not been revealed in the survey. Second, there is no guideline for LE resuscitation in China, and providers in academic hospitals are more likely to be exposed to updated treatment procedures through continued medical education while providers in non-academic hospitals are less likely to participate in conferences or training classes. This factor may lead to bias against non-academic hospitals in their understanding of LE use for resuscitation. Third, although the understanding of LE for LAST resuscitation has been validated by many clinics across the world, the misunderstanding between medical providers and patients might impact the usage of LE for LAST resuscitation when it's not recommended by the expertise consensus in China. In spite of this, we're glad that some doctors and medical providers turn to us for LE resuscitation details when they encountered LAST, by days after the survey conducted. In this way, the survey has its practical meaning to spread the idea of LE resuscitation for LAST.

In conclusion, the survey of the 250 hospitals, including academic and non-academic hospitals, revealed the poor practice procedures for regional anesthesia and LE use for LAST resuscitation in China. This alarming situation calls for improvements in education especially in non-academic hospitals.

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The authors declare no other potential conflicts of interest.

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Appendices. The survey questionnaire

Note: Completion of the survey indicates consenting of participation in our survey.

Please select the appropriate answer or fill in the blank:

1. Is your hospital academic or non-academic?
☐Yes ☐ No

2. What's the most often used long-term local anaesthetic (LA) and dosage during regional anaesthesia in your department? (including epidural anaesthesia and all peripheral nerve blocks)
☐Bupivacaine Hydrochloride
☐Ropivacaine Hydrochloride
☐Levobupivacaine
☐Others, please info:___

3. Do you use the test-dosing for epidural anaesthesia?
☐Yes ☐ No
If you checked the "Yes" box, please info the drug and dose:___

4. Have your department ever used lipid emulsion (LE) for the resuscitation during caridiac arrest (CA) which induced by LA?
☐Yes ☐ No

5. If CA happens due to the usage of LA, do you use epinephrine for resuscitation?
☐Yes ☐ No
If you checked the "No" box, please jump to question "7" directly.

6. What's the initial dosage for you to treat the CA induced by LA? (Take the body weight of 70 kg for example)
☐1 mg i.v
☐0.5mg i.v
☐0.06-0.1mg i.v
☐If others, please info:___

7. Does your department have the procedure for LAST treatment?
☐Yes ☐ No
If you checked the "No" box, please jump to question "10" directly.

8. Is LE included in the LAST procedure in your department's procedure?
☐Yes ☐ No
If you checked the "No" box, please jump to question "10" directly.

9. Is the precise delivery method of LE included in the LAST procedure in your department? (such as the bolus dosage and maintenance dosage)
☐Yes ☐ No
If you checked the "No" box, please jump to question "11" directly.

10. Do you know that LE can be used for LAST resuscitation?
☐Yes ☐ No
If you checked the "Yes" box, please continue the survey; for "No" box, end the qustionnaire.

11. Is it suitable to use Propofol instead of LE for CA resuscitation during LAST? (as Propofol has the LE component)
☐Yes ☐ No ☐ Uncertain

12. If seizure happens during LAST (no CA), will you choose LE for treatment?
☐Yes ☐ No

13. Is LE available for LAST resuscitation in your department or hospital?
☐Yes ☐ No
If you checked the "Yes" box, please jump to question "15" directly.

14. What's reason for LE unavailable in your department or hospital?
☐Do not know that LE can be used for LAST resuscitation
☐The Committee do not approveLE as the resuscitation method
☐LAST is a rare event, no need for preparation
☐Others, please info:___
Then end the survey.

15. Where is the locarion for LE stoage in your department?
☐Pharmacy in the hospital
☐Operation room-pointed one
☐Storage room in theatre
☐Code cart
☐Others, please info:___

16 What's the preparation type of LE in your department?
☐Long-chain LE
☐Others, please info:___
☐Middle-long-chain LE

17. How long does it take to obtain LE when LAST occurs in your department?
☐No LE available
☐ < 10 min
☐10-30 min
☐ > 30 min
End the survey.