Prevention of local anesthetic systemic toxicity

There has been a resurgence in the popularity of regional anesthesia in recent years because of the increasing availability of ultrasound guidance. This journal is receiving contributions from authors administering regional anesthesia, with simultaneous multiple regional blocks in a single patient, using potentially unsafe amounts of local anesthetic (LA) agents. There is a false perception among most surgeons and some anesthesiologists that regional anesthesia is "safer" than general anesthesia. Local anesthetic systemic toxicity (LAST) remains a real danger of regional anesthesia. Though its incidence is less than 0.2%,[1] LAST is difficult to treat and is potentially fatal. Prevention of LAST should be ensured during all regional anesthetic procedures.

LAST affects the central nervous and cardiovascular systems depending on the free plasma concentration of the LA and its rate of change. No single intervention can reliably eliminate the risk of LAST. A number of steps must be taken to avoid intravascular injection and high blood concentration of the LA during the performance of the regional technique. Aspiration prior to injection of LA and the use of an intravascular marker such as adrenaline reduce the likelihood of accidental intravascular injection to a large extent. The American Society of Regional Anesthesia and Pain Medicine (ASRA) Practice Advisory on LAST recently published recommendations for its prevention.[2]

LAs vary in their potential for toxicity and less toxic drugs should be preferred whenever a larger volume of the drug is required. Continuous catheter techniques are better as they allow the use of shorter acting, less toxic drugs such as lignocaine, prilocaine, and mepivacaine.[3] Bupivacaine, levobupivacaine, and ropivacaine are longer acting and more toxic drugs with bupivacaine being the most cardiotoxic and ropivacaine the least.[4] Chloroprocaine is less toxic because it undergoes rapid hydrolysis by plasma pseudocholinesterase, resulting in a short plasma half-life of 1.0–4.5 min. Even when the toxicity occurs with chloroprocaine, it is transient in nature.[5]

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The total dose of the LA drug should be limited to the lowest effective dose. A continuous catheter technique allows titration of the dose and use of minimum amount of drug. Whenever larger doses of LA are required, the total dose should be fractionated with adequate time between doses. The intravascular marker adrenaline also decreases and delays the peak plasma concentration of LAs and thus increases their safety. Addition of opioids also allows the use of lower doses of LA.

Physicians should be aware of and adhere to the maximum dose recommendations of various LA. The present recommendations are not entirely based on scientific evidence. They have been extrapolated from animal experiments, case reports of LAST, and some pharmacokinetic studies, because human randomized control trials (RCT) are difficult to conduct for ethical reasons.[6] Blanket recommendations regarding doses are not valid. Plasma concentration of LA depends both on the amount injected and on the site of injection, as the amount of drug absorption varies from one region to another.[6] For example, the highest plasma concentrations occur with intercostal, epidural, and brachial blocks in that order. There is a need for studies to recommend clinically adequate and safe doses specific for each block and site.

Simultaneous multiple regional blocks in a single patient are being increasingly used today, but the safety of the procedure remains doubtful. There is a possibility of injection of large and toxic amounts of LA. There is also the possibility of complications at multiple sites such as bilateral pneumothoraces. Therefore, multiple blocks should be used only in case of necessity and not as a routine practice. After reviewing the literature for bilateral upper limb blocks, Holborow and Hocking have recommended that steps should be taken to decrease the dose of LA such as the use of ultrasound and nerve catheter and temporal spacing of blocks.[3] In addition, patients should be closely monitored with minimal sedation to allow early detection of any symptoms of toxicity.

It is a common practice to combine an LA with rapid onset of action (e.g., lignocaine) with an LA of longer duration of action (e.g., bupivacaine). This practice is dangerous as the individual safe doses when multiple drugs are used are unknown. The maximum dose of each of the drugs in combination should not be used as their toxicities are not independent of each other.[7] There is experimental evidence in animals that simultaneously administered lignocaine decreases the toxicity of bupivacaine

on ventricular conduction parameters, but does not protect against hemodynamic alterations.[8,9] In the absence of similar evidence in humans, the toxicities of multiple LA should be presumed to be additive.

Certain patient factors also reduce the amount of LA required and should be considered when deciding the dose of LA. In patients with hepatic or renal disease or with low cardiac output there is decreased metabolism and plasma protein binding of LA. Changes occur at extremes of age; the elderly have decreased organ function; neonates and young infants have immature liver metabolism and decreased plasma protein concentration. Various hormonal and mechanical factors affect the doses of LA during pregnancy.[4]

Theoretically, ultrasound-guided (USG) regional anesthesia seems safer than other localization techniques with regard to LAST as the localization of neural tissue and deposition of LA is performed under USG visualization. There is Level A evidence only for a decrease in the incidence of vascular puncture with USG (pooled risk ratio 0.16; 95% CI 0.05–0.47).[10] There is also some evidence that the total dose of the LA required is decreased in case of USG blocks.[11] However, these are only surrogate markers for LAST. There is no evidence that reducing the amount of LA decreases the frequency of LAST. The actual incidence of LAST following USG blocks remains the same as that with peripheral nerve stimulation guided blocks.[12] Large high-quality RCTs would be required to conclusively address the issue of improved safety of USG regional blocks as the incidence of LAST is low.

Successful resuscitation from LAST-induced cardiac arrest by lipid emulsion has been reported in a number of cases. The proposed mechanisms of action include the emulsion acting as a "lipid sink" extracting the lipophilic LA from plasma and tissues and reversal of the LA-induced inhibition of myocardial fatty acid oxidation, thereby restoring myocardial ATP supply. The ASRA Practice Advisory on LAST recommends administering lipid emulsion at the first signs of LAST.[2] However, this is only a Class IIa recommendation based on Level B evidence from case reports and animal experiments. Such evidence carries the risk of reporting and publication bias and suffers from an inability to estimate the incidence of such intervention. A number of other issues regarding use of lipid emulsion remain unresolved including the best formulation, the dose of bolus and infusion, and the timing of administration. In addition, large doses of adrenaline or combination of adrenaline and vasopressin used for resuscitation have been found to impair lipid resuscitation from bupivacaine toxicity in animal experiments because of lactic acidemia.[13]

To summarize, all possible precautions should be taken to prevent LAST whenever LA drugs are used. The practice of using more than one nerve block or more than one LA in a patient is inherently unsafe. Adequate monitoring of the patient throughout the procedure is paramount to detect the toxicity early. There is a need to increase the awareness regarding LAST not only among anesthesiologists, but also among other physicians and medical personnel who use LA drugs. There is also a need to develop and propagate block- and site-specific recommendations for effective and safe doses of LA.

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