block provides an additional block of the axillary nerve, suggesting that for the sub-omohyoid approach, the local anesthetic may reach at least the superior or intermediate trunk or the posterior division of the brachial plexus, which confirms the results reported by Siegenthaler et al. [2].

Concerns regarding the novelty of the DiSC block are disconcerting. The DiSC block is a novel, potentially safer and simpler anterior approach that involves a diagonal view of the SSC through which the SSN travels [1]. The approach proposed by Tran et al. [5] cannot be performed using an anterior approach because the clavicle conflicts with the ultrasound beam, preventing correct visualization of the SSC during the puncture; thus, the needle is inserted at a posterior entry point in the anterior medial direction using ultrasound visualization that is completely different from that with the DiSC block.

To date, the sub-omohyoid SSN block has either been referred to as an anterior or supraclavicular SSN block. Given the introduction of this novel anterior approach, the term "anterior SSN block" cannot be used as a synonym for the sub-omohyoid SSN. Although anterior SSN block approaches have clear advantages, the sub-omohyoid SSN block is a less selective "anterior SSN block" than the DiSC block [3,4] and may be riskier. Therefore, although the sub-omohyoid SSN block may be the first option in most patients, it must be avoided in high-risk respiratory patients [3]. In conclusion the diagonal suprascapular block is a simple, more selective in some scenarios and a safer anterior SSN block.

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## Lipophilicity of drugs, including local anesthetics, and its association with lipid emulsion resuscitation

Local anesthetics are commonly used to provide pain relief during the peri-operative period. However, there is a risk of local anesthetic systemic toxicity (LAST) when these anesthetics are accidentally injected into the bloodstream or administered in excessive amounts. This can lead to cardiovascular depression and central nervous system symptoms, such as seizures. Currently, a treatment approach for LAST involves the use of lipid emulsion [1]. Lipid emulsion has also shown effectiveness in mitigating the cardiovascular depression caused by a toxic dose of non-local anesthetic drugs that have high lipid solubility [1]. The underlying mechanism associated with the use of lipid emulsion for treating drug toxicity is known as the 'lipid shuttle' [1]. This concept suggests that the lipid and surfactant components of the emulsion interact with drugs with high lipid solubility (defined by a log P value greater than 2) [1]. Subsequently, the lipid emulsion containing these lipid-soluble drugs, such as bupivacaine, is transported to the liver, muscle, and adipose tissue for detoxification and storage [1]. Furthermore, lipid emulsion can also alleviate severe vasodilation induced by a toxic dose of aminoamide local anesthetics, and the extent of this effect is dependent on the lipid solubility of the specific local anesthetic used (with bupivacaine having a higher log P value than ropivacaine and mepivacaine) [2]. Currently, the log P (or log $P_{o/w}$) value is widely used to indicate the lipophilicity of drugs, such as local anesthetics (log P [PubChem] values: bupivacaine = 3.41; ropivacaine = 2.9; lidocaine = 2.44; and mepivacaine = 1.95). Moreover, the octanol/water (o/w) partition coefficient is only a surrogate indicator regarding lipophilicity of drugs including local anesthetics that may be used as one of several factors to predict whether intractable cardiovascular collapse induced by a toxic dose of a drug

**Table 1.** Physiochemical Properties of Local Anesthetics

| Local anesthetic | Log P* | $pK_a$ † | Estimated log D‡ at pH 7.4 | Estimated log D‡ at pH 7.1 | Non-ionized fraction§ (%) at pH 7.4 | Non-ionized fraction§ (%) at pH 7.1 |
|---|---|---|---|---|---|---|
| Bupivacaine | 3.41 | 8.1 | 2.63 | 2.37 | 16.6 | 9.1 |
| Ropivacaine | 2.9 | 8.1 | 2.12 | 1.86 | 16.6 | 9.1 |
| Lidocaine | 2.44 | 7.8 | 1.89 | 1.66 | 28.5 | 16.6 |
| Mepivacaine | 1.95 | 7.9 | 1.47 | 1.25 | 33.4 | 20.1 |
| Levobupivacaine | 3.6 | 8.1 | 2.82 | 2.56 | 16.6 | 9.1 |

*Log P: log octanol/water partition coefficient from PubChem (https://pubchem.ncbi.nlm.nih.gov/). †$pK_a$: negative logarithm of acid dissociation constant ($K_a$) from PubChem. ‡Estimated log D (distribution ratio in octanol and water phase) is calculated using the following equation: $\log D = K_D + \log K_a - \log (K_a + 10^{-pH})$. §Non-ionized fraction of local anesthetics is calculated using Henderson-Hasselbalch equation.

is well responsive to lipid emulsion resuscitation. However, the o/w partition coefficient is not the best indicator regarding lipophilicity for drugs undergoing lipid emulsion resuscitation because of following reasons: First, the o/w partition coefficient is a distribution ratio of the non-ionized form of drugs in the octanol and water phase [3]. However, since drugs, including local anesthetics, exist in both ionized and non-ionized forms *in vivo*, the use of the distribution coefficient (log D) becomes clinically more relevant for assessing the lipophilicity than log P [3]. Log D indicates the distribution ratio of both forms (ionized and non-ionized) of drugs between the octanol and water phases [3]. Log D is dependent on the acid dissociation constant ($K_a$) and the pH value of the surrounding medium [4]. Moreover, as a patient with severe hemodynamic depression or cardiac arrest due to LAST or drug toxicity of non-local anesthetics shows acidosis, which can affect the distribution coefficient [4]. Thus, the log D of weak bases such as local anesthetics ($pK_a$: 7.7 to 8.1) is estimated using the following equation: $\log D = \log K_D + \log K_a - \log (K_a + 10^{-pH})$ where $K_D$ is the logarithm of the o/w distribution ratio of the compound, and $\log K_a$ is the logarithm of the acid dissociation constant ($K_a$) of the compound. The $pK_a$ is the negative logarithm of the acid dissociation constant ($K_a$) when the ionized and non-ionized forms of the drug exist in the solution at equal amounts (50%). For example, the non-ionized form of bupivacaine at pH 7.4 is only 16.6% of the total concentration of bupivacaine, calculated using the Henderson-Hasselbalch equation: $pH = pK_a + \log_{10} ([A^-] / [HA]$, where $A^-$ is the concentration of the conjugate base and HA the concentration of the acidic form of the compound. Therefore, the log P is not a good indicator to evaluate the lipophilicity of local anesthetics because the log P value considers the distribution ratio of only 16.6% non-ionized form of bupivacaine in the octanol and water phase (Table 1). Furthermore, acidosis at pH 7.1 that is commonly observed in patients undergoing lipid emulsion resuscitation for LAST or drug toxicity of non-local anesthetics further reduces the non-ionized form of bupivacaine to 9.1% (Table 1). The log D of local anesthetics is lower than log P because the ionized molecules of the local anesthetics are mainly distributed in the water phase (Table 1) [3]. The order of log P of local anesthetics is similar to that of log D of local anesthetics (Table 1). However, log P of bupivacaine that reflects only the non-ionized form of bupivacaine is 3.41 (Table 1), but the (calculated) estimated log D of bupivacaine that reflects all forms (ionized and non-ionized) of bupivacaine is decreased to 2.63 (Table 1). Second, in the clinical practice using lipid emulsion resuscitation for LAST or drug toxicity, the lipid to water distribution ratio of drugs including local anesthetics that indicates the distribution ratio of both forms (ionized and non-ionized forms of local anesthetics) in the lipid and water phase has more clinical relevance than octanol to water distribution ratio because octanol is different from lipid. Thus, although the order of log P in the local anesthetics is similar to that of log D, further studies to compare the distribution ratio of drugs including local anesthetics in lipid and water phases with that in octanol and water phase are needed [5].

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