Literature Review

Ketamine and Postoperative Pain – A Quantitative Systematic Review of Randomised Trials Elia N, Tramer MR. *Pain*. 2005; 113:61-70.

Ketamine, an *N*-methyl-D-aspartate (NMDA) receptor antagonist that has been used as an analgesic for several decades, is associated with psychomimetic effects that have limited its use clinically. Its NMDA antagonist properties have interested investigators because of the possibility of a beneficial impact on the neural sensitization/wind-up phenomena. In this article, the authors present a comprehensive review of the literature on ketamine to evaluate whether existing data can be used to calculate a risk/benefit ratio for the use of ketamine to treat postoperative pain.

Fifty-three trials from 25 countries were found that compared ketamine to an inactive control in a randomized design in surgical patients. These studies reported on pain outcomes, sparing of opioid consumption and adverse effects. In these studies, ketamine was administered via the intra-articular, intramuscular, subcutaneous, oral, transdermal or caudal routes. Ketamine also was added to a local anesthetic for brachial plexus blockade and added to intravenous morphine for patient-controlled analgesia (PCA). Hallucinations were a common side effect of the drug, although no relationship could be found between the dose of ketamine used and the risk of psychomimetic changes.

Key findings include:

- In studies of intravenous (I.V.) ketamine, the pain intensity score decreased but only by 1 cm on a 10 cm visual analog scale.
- The studies of ketamine through other routes of administration had such disparities that the authors determined that meta-analysis was inappropriate. There were an equal number of positive and negative trials for the addition of ketamine to an opioid PCA, epidural administration of ketamine and prolonged I.V. ketamine infusion. Ten trials of a variety of other regimens (intra-articular, intramuscular, subcutaneous, oral, transdermal, etc.) were grouped together and had five reports suggesting a benefit, with the other five suggesting no benefit.
- The quantity of morphine consumed to obtain adequate pain relief was reduced by 27 percent to 47 percent, but this did not result in a decrease of morphine-related adverse effects.
- The time to the first request for analgesia was reduced by only 16 minutes, which is not of great clinical significance.
- The risk of ketamine-induced hallucinations was minimal in patients who underwent general anesthesia rather than monitored anesthesia care. The hallucinations were even greater when the agent was used for procedures that were not particularly painful.

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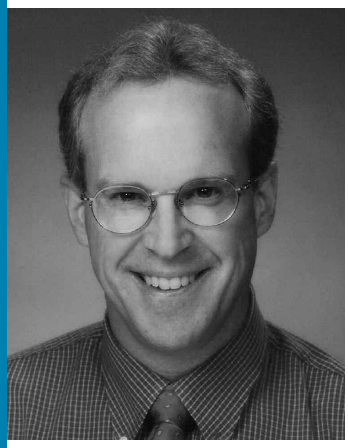
Most of the studies reviewed were too small to have adequate power to determine if the reduction in opioid use is a benefit worth the risk of mental status change associated with ketamine. While the authors have provided an excellent review of the literature, there are no convincing data to support the postoperative use of ketamine.

On the Cover

2005 ASRA Officers, from left, Julia E. Pollock, M.D.; Vincent W.S. Chan, M.D.; Richard W. Rosenquist, M.D.; F. Michael Ferrante, M.D.; and Terese T. Horlocker, M.D.

ASRA's Founding Fathers, from left, L. Donald Bridenbaugh, M.D.; Harold Carron, M.D.; Jordan Katz, M.D.; P. Prithvi Raj, M.D.; and Alon P. Winnie, M.D.

C6 Paratracheal Cervicothoracic Sympathetic Block: Safety, Comfort and Reliability Reside in the C6 Approach



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What is wrong with the following sentence?

"When performing a stellate ganglion block for diagnosis of sympathetically mediated pain of the upper extremity, it is best to place the needle closer to the stellate itself, i.e., at the C7 level, to allow a minimum amount of medication to be used – thus avoiding inadvertent somatic blockade while insuring that the sympathetic block of the upper extremity is complete."

In addition to its length and boredom, the sentence errs in four assumptions. In fact:

- The aim is not to block the outflow of the stellate ganglion.
- It is not a diagnostic block.
- Neither placement site nor specific volume injected will ensure *complete* interruption of sympathetic outflow at these levels.
- No placement of the needle, no type of anesthetic and no specific volume injected will ensure *only* a block of sympathetic outflow at these levels.

Freed of these beliefs, we also are free from concern over the best needle placement site (there isn't one), and the "correct" volume to inject (there isn't one) to ensure a "pure" stellate ganglion block that will allow us to diagnose "sympathetically mediated pain" (we cannot). We can, however, use this block to successfully aid the treatment of patients with such diverse diseases as complex regional pain syndrome, congestive heart failure, vasculitis, gangrene and cerebral vascular insufficiency.[1,2]

It is not a stellate block? Moore, who advocated placement of the needle at the level of C7, stated that:

The term "stellate ganglion block" is now used merely because the needle is inserted in the region of the ganglion. The block … is actually a block of … the entire cervicothoracic sympathetic nervous system.[3]

In fact the stellate ganglion may be the only structure we are not blocking.[4] The various portions of the cervicothoracic sympathetic chain are notably undependable in their shapes, sizes and locations.[5,6,7] The best theoretical construct for the practitioner is to consider this set of structures as a "tangled trunk" rather than a "chain" of discrete and identifiable ganglia, some of which may actually exist only in a minority of humans.[8]

Although computed tomography scan and fluoroscopy have proven to be useful adjuncts that may increase the efficacy of the paratracheal block, no approach can ensure that the stellate ganglion is blocked.[9] Rather it is probable that successful sympatholytic paratracheal injections at any level only block the upper sympathetic chain, but not the lower (i.e., the stellate ganglion). Instead caudal flow of medication instilled in that area appears to be too anterior to block the lower sympathetic trunk. It has been suggested that effective blockade is more likely achieved by action of the anesthetic at other loci such as the sympathetic fibers to the upper extremity that accompany both the subclavian and carotid arteries.[10]

If the stellate ganglion is not the target, logic evanesces for any and all the arguments for a low approach (at C7). Even if we did want to reach the stellate, however, the C7 approach is not reliable for that anyway.[11] In truth we should choose our technique based upon three criteria: safety, comfort and reliability. They are important because this block most often must be employed repeatedly and frequently in order to be an effective adjunct to patient recovery. So we should go where it is safest, most comfortable and most reliable. That's right: C6!

Safety

The paratracheal area abounds with easy opportunities to inject local anesthetic of significant toxicity into vessels and the neuraxis.[12,13] For this reason, I recommend the C6 level where Chassaignac's tubercle usually (but not always![14]) provides a clear indicator of the bony

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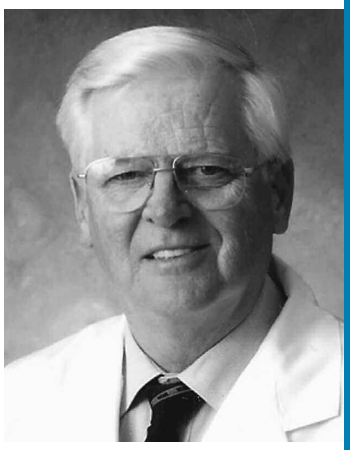
"… this block [C7] most often must be employed repeatedly and frequently in order to be an effective adjunct to patient recovery. So we should go where it is safest, most comfortable and most reliable. That's right: C6!"

I Use Only the C7 Approach to the Stellate Ganglion



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The stellate ganglion is located at C7, T1 and usually lies in front of the neck of the first rib. Anterior C6 and C7 approaches have been described. Overall safety considerations clearly, without doubt, favor the C7 approach. For this approach, the neck is placed in a slightly flexed position, and the cricoid cartilage is palpated. One finger breadth below the cricoid, the left index finger is gently pressed next to the trachea. The fleshy part of the fingertip easily palpates the carotid pulse. A groove is created between the trachea and the carotid artery, and a 1.5-inch, 22-guage B-bevel needle is passed in a slightly medial direction. Bony contact is made when the needle tip reaches the ventrolateral side of the body of C7. At this point, the hub of the needle is held between the left index finger and thumb, and a syringe, which should not contain more than 5 ml of local anesthetic solution, is connected to the needle. Following negative aspiration, injection is initiated. If there is significant resistance to injection, the tip is withdrawn slightly, and the 5 cc volume is deposited. The onset of the block is rapid, and Horner's sign becomes visible. The needle is removed, and slight pressure is applied.

The technique just described is for the blind technique. For the fluoroscopy-guided technique, a right-angle, short, flexible connecting piece and a 22-gauge, 2.5-inch needle is used. The needle is placed in the same way as it is for the blind technique. The C7 vertebral body, however, is located with fluoroscopy and is marked externally with an instrument such as a long hemostat [Figure 1]. The needle is placed a fingerbreadth below the cricoid cartilage between the trachea and the carotid artery. After bony contact is made, the hub of the needle is held with an instrument; this reduces exposure of the fingers to radiation. The needle tip location on the ventrolateral aspect of the C7 body is verified by fluoroscopy. Omnipaque® 240, approximately 1 ml, is injected [Figure 2]. The contrast will spread from C7 to the top of T1 and toward C6. Next, 5 ml of local anesthetic is injected during continuous fluoroscopy. The local anesthetic should disperse the contrast [Figure 3].

The C7 approach to stellate ganglion is clearly a technique that can be used even in patients with radical neck dissection. It is very effective when the radial or median nerves are involved in sympathetically maintained pain. The 5 ml volume is adequate to cover the stellate ganglion and the middle cervical sympathetic ganglia. Therefore the block is effective for sympathetically maintained pain affecting facial structures — such as supraorbital shingles, or vascular problems such as Reynauld's Disease — and shoulder pain where often there is a significant sympathetically maintained component. The spread does not go to T2 and T3, which is essential when the ulnar nerve is involved, in which case the T2-T3 sympathetic ganglia needs to be blocked rather than the stellate. To produce a long-lasting block, we use 2.8 percent phenol under fluoroscopic guidance. The illustrations in this article are from a patient who received phenol stellate ganglion block on two occasions at a two-year interval along with 100 units botulinum toxin injected into the biceps. The combined treatment relieved pain and muscle contracture.

Our experience using the C7 approach to the stellate ganglion spans 20 years, during which more than 2,000 injections have been performed. There was one case of hoarseness that lasted four and a half to five months with full recovery.[1]

I am aware of many disasters resulting from the C6 transverse process approach, including seizure from vertebral artery injection, total spinal from intraneural injection at the C6 nerve root, several delayed onset respiratory arrests leading to death that clearly resulted from subdural spread of local anesthetic and infarcted spinal cord

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"Our experience using the C7 approach to the stellate ganglion spans 20 years, during which more than 2,000 injections have been performed. There was one case of hoarseness that lasted four and a half to five months with full recovery."

C6

vertebral transverse process' exact location, thereby usually guiding the operator and the needle away from the vertebral artery and access to the central neuraxis. At the C7 level, the sympathetic elements are often *posterior* to the artery, and it is therefore a site of greater risk.[15] Finally the lung is almost never in play at C6 yet can be punctured with even scrupulously careful placement of a needle at C7.[16]

Comfort

Two aspects of the use of the C6 level enhance patient comfort. When present, a prominent Chassaignac's tubercle enhances operator confidence, so there is less time spent grinding around on the patient's neck in preparation to strike. Also the transverse process is rapidly encountered at a more shallow level with passage through less tissue, speeding up needle placement and diminishing its painful nature.

Reliability

Paratracheal injection is not a diagnostic test for sympathetically mediated pain. When this procedure provides pain relief of sympathetically mediated pain, it is only variably associated with production of clinical signs of altered autonomic function.[17] Even the largest volumes of injectate may not completely abolish sympathetic activity in the upper extremity.[18,19] As well, no injection site will reliably produce a purely sympatholytic block because the sympathetic structures are not sufficiently segregated from the brachial plexus and epidural space. Neither of these failings should dissuade its use, however, as a therapeutic adjunct. In most cases, the frequent outcome of only partial sympatholysis and some degree of somatic block are still valuable.

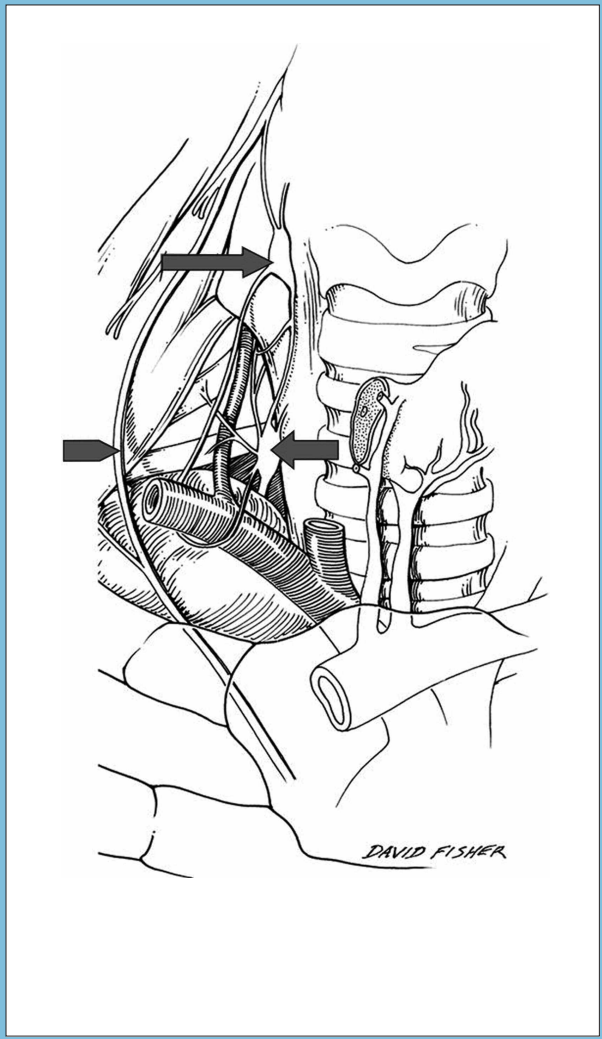
In conclusion paratracheal injection at any level is not a stellate ganglion block, and it is not a diagnostic block. It is, however, a therapeutic tool that may save a limb or even a life. It also is apparent that no one site of injection or specific volume of injectate is completely reliable in producing the desired sympatholytic block. For that reason, I advocate that the initial plan should always be to inject 10 to 15 cc of local anesthetic at the C6 level, as this is usually the safest, easiest and most comfortable approach. If you find that sympathetic outflow is not sufficiently blocked at C6, I would first increase the volume of injectate before moving the needle "south."

Anterior neck:
Tip of long arrow is on the middle cervical ganglion at C6.

Tip of short arrow is on the inferior cervical ganglion.

Arrowhead points to the phrenic nerve.

Note the vertebral artery traveling cephalad and posterior to the middle cervical ganglion.



Used by permission of the publisher, Lippincott Williams & Wilkins. Source: Tubbs RS. et al. Anatomic landmarks for nerves of the neck: A vade mecum for neurosurgeons. Neurosurgery. *2005; 56(4):256-260.*

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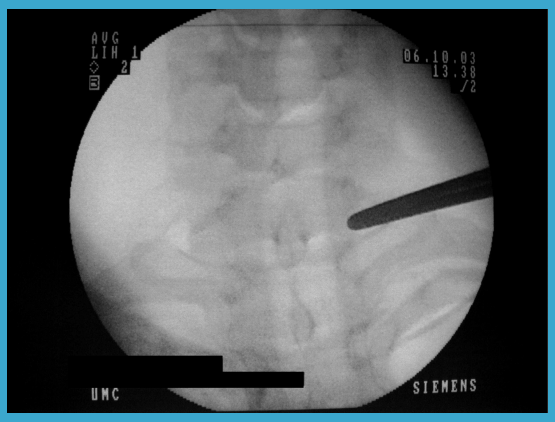
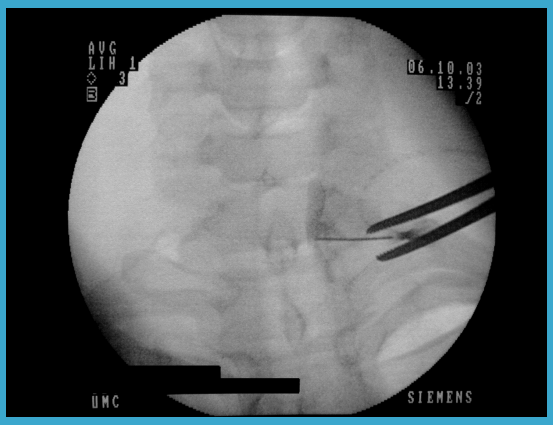
Figure 1



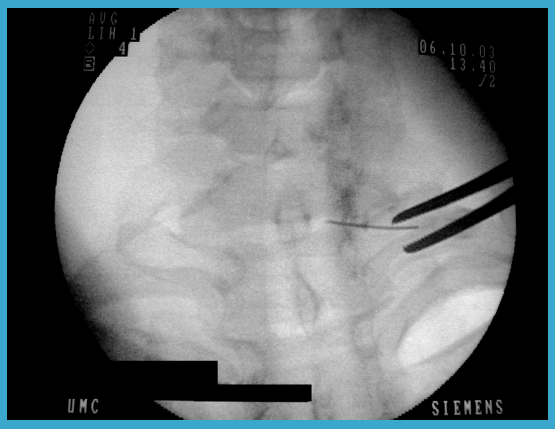
Radiopaque instrument marking the target site.

Figure 2



Spread of contrast after injection.

Figure 3



Dispersion of contrast following phenol injection

C7

from intravascular injection. All of these cases come from the medical-legal arena and have not been reported in the medical literature. Kyzelshytin (personal communication) presented anatomical dissections done after injection of contrast and methylene blue. He found that, with C6, dye spreads to the mediastinim and across to the contralateral side because the injectate is deposited behind the longus colli muscle. Volumes recommended for stellate ganglion blocks using the C6 approach are in the 10-15 ml volume range. Injections are made in the vicinity of not only the vertebral artery and the nerve roots but also near arteries in the posterior neuroforamin. The C6 transverse process may be absent, allowing the needle to enter the posterior wall of the neuroforamin canal and reach the arteries described by Huntoon. Chassaignac's tubercle generally is easily recognizable, but clearly the tip of a sharp needle can enter structures leading to the disasters that occur with an unacceptable frequency. Landmarks are more certain, which makes injection into blood vessels less likely, and smaller volumes of local anesthetic are required for the C7 versus C6 approach. Thus the C7 approach is safer. I recommend the C7 image-guided technique for stellate ganglion block.

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How I Do It: *Ultrasound-Guided Axillary Block*

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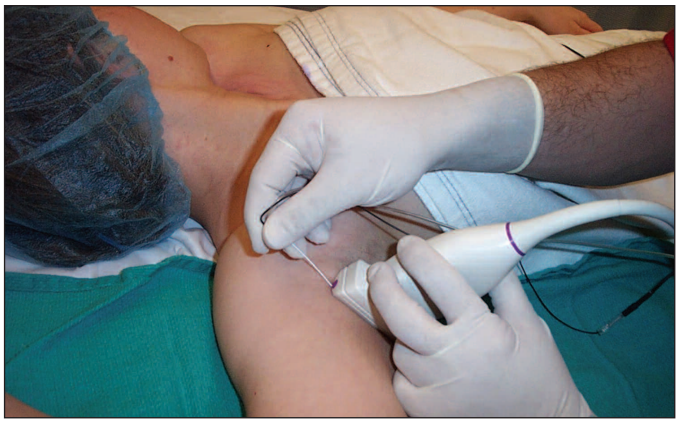
Ultrasound guidance is being promoted as an aid for performing various regional anesthesia blocks. When used as an aid for performing axillary block, the actual performance of the block itself is similar to the classic perivascular approach. The patient is positioned in the usual manner, i.e., supine, with the arm to be blocked abducted and the forearm flexed at 90 degrees. After applying routine monitors and establishing intravenous access, the axillary anatomy is examined under aseptic conditions with ultrasound imaging. A linear probe of up to 10 MHz or 12 MHz is recommended since the axillary artery and nerves are very superficial at this location.[1] Compound imaging, if available, may provide better-quality images. The probe is placed transverse to the long axis of the arm to obtain a transverse or short axis view of the relevant anatomy [Figure 1]. The axillary artery, veins and nerves to be blocked are then identified. The median nerve is most commonly located lateral to the axillary artery. The ulnar nerve is most commonly located medial to the axillary artery. The radial nerve is usually situated posteriorly or posteromedial to the artery [Figure 2]. As there is significant variability from these typical locations, concomitant use of nerve stimulation may help ascertain the identity of each specific nerve. Finally the musculocutaneous nerve is seen as it leaves the neurovascular bundle and travels laterally toward the body of the coracobrachialis muscle [Figure 3]. Once the nerves to be blocked are identified, a two-inch insulated needle is inserted from the lateral end of the probe and advanced under real-time guidance toward each nerve. After confirmation of the nerve's identity by elicitation of a motor response, local anesthetic is administered in small increments. The total amount is divided into equal volumes for each nerve to be blocked. As the local anesthetic solution is being injected, the desired spread is confirmed under real-time imaging. Local anesthetic solution appears hypoechoic on ultrasound imaging, and it is common to see the nerves more clearly demarcated once the solution is injected.[2] As previously shown in anatomical and clinical studies, the neurovascular bundle in the axilla is usually divided into more than one compartment by different fascial planes, and therefore it is important to target each individual nerve separately to obtain a complete block of all the terminal nerves.

Figure 1



Probe and needle position

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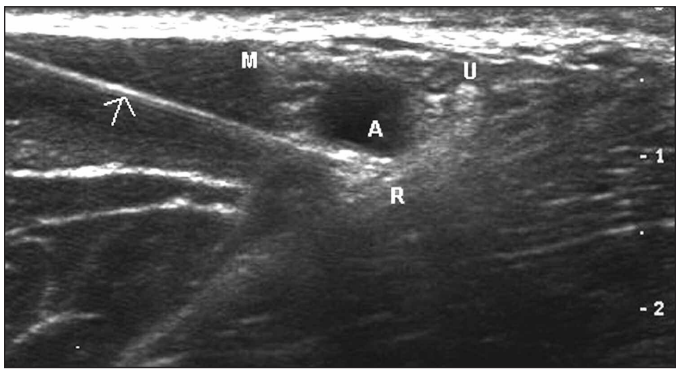
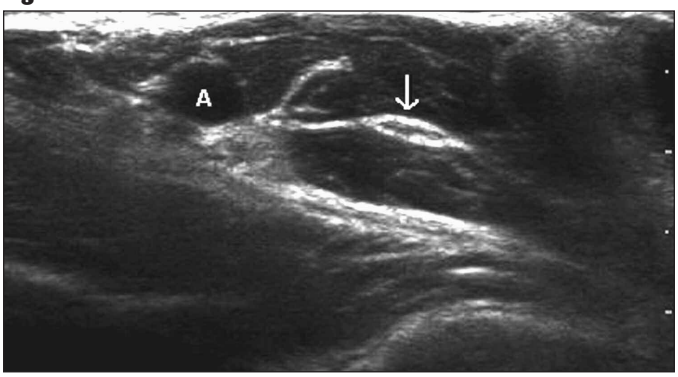
Figure 2: Axillary anatomy (transverse view)



M = median nerve, U = ulnar nerve, R = radial nerve, A = axillary artery. The arrow indicates the needle shaft.

Figure 3: Musculocutaneous Nerve



A = axillary artery. The arrow indicates the musculocutaneous nerve.

RESEARCH UPDATE

Increased Efficacy and Duration of Lidocaine and Bupivacaine When Combined With Ephedrine for Rat Sciatic Nerve Block

We recently reported that ephedrine, an adrenergic drug used frequently to treat hypotension and bradycardia, inhibits Na+ current in cultured cells stably expressing Na+ channels and provides dose-dependent reversible rat sciatic nerve blockade.[1] Ephedrine 0.2 ml of 1 percent produced partial blockade of motor and sensory functions similar to that of 0.125 percent bupivacaine. Histological evaluation of nerves treated with these two drugs ruled out ischemic changes induced by ephedrine.

The relatively high concentration of ephedrine (2.5 percent, 5mg) needed to achieve complete nerve blockade more than likely would prevent clinical use as a sole agent. The dose required to achieve complete blockade (due to the relatively thicker peripheral nerve in humans) may cause systemic side effects such as hypertension, tachycardia and possibly ischemic nerve degeneration. Using ephedrine as an adjuvant with local anesthetics (LAs), such as lidocaine and bupivacaine, might be beneficial, however. In particular the presence of a synergistic effect, one in which the combined effect of two drugs is greater than the sum of the effect of each drug given alone, would allow for dose reduction and, therefore, limitation of side effects while at the same time improving efficacy.

In preliminary studies, ephedrine generally enhanced motor and nociceptive-blocking properties of bupivacaine and lidocaine in the rat subfascial sciatic nerve block model. When ephedrine is combined with bupivacaine, however, there is a nonsignificant synergistic drug interaction for nociceptive block and sub-additive interaction for motor block; when ephedrine is combined with lidocaine, there is statistically significant sub-additive interaction for both nociceptive and motor functions.

Discussion

Although the combination of ephedrine and bupivacaine revealed only a nonsignificant synergistic interaction, even while a sub-additive interaction with lidocaine was observed, this addition of ephedrine, nevertheless, appears to be clinically important. For all types of nerve blockade, at least some of the LA dose could be substituted by ephedrine, decreasing the amount of LA needed, thereby reducing the risk of cardiotoxicity. In addition, as clinically relevant cardiotoxic concentrations of bupivacaine and levobupivacaine have been found to cause profound blockade of norepinephrine release from cardiac sympathetic nerve endings contributing to the cardiodepressant effect.[2] The presence of ephedrine in an LA combination could counteract this effect as it is known to be a direct and indirect sympathomimetic drug.

Synergistic interaction for nociceptive blockade by ephedrine with bupivacaine and not lidocaine could be due to ephedrine and bupivacaine having a similar time of onset and duration of action, as has been shown before. Ephedrine, in addition to having intrinsic analgesic action due to Na+ channel blockade, might confer part of its effect by vasoconstriction, thereby decreasing vascular absorption of the co-injected LA, similar to epinephrine.[4] Since lidocaine combined with ephedrine was found to be sub-additive, however, it is unlikely that a vasoconstrictive effect of ephedrine contributed to the overall efficacy as determined by intensity of blockade. Nevertheless vasoconstriction occurring at a later time point, i.e., after the peak of action, could have had an effect on the overall duration, as ephedrine prolonged the duration of both lidocaine and bupivacaine (in general, lidocaine is thought to be vasodilatory in higher concentrations but also vasoconstrictory, similar to bupivacaine, in lower concentrations).[5-7]

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Although ephedrine clearly has potent vasoactive properties, the overall effect on nerve blood flow (NBF) is not known because the vascular supply of peripheral nerves is very complex, consisting of an extrinsic circulation (affected by adrenergic stimulation) and an intrinsic circulation (responding only passively to changes in systemic blood pressure).[8] Furthermore LAs are known to severely decrease NBF when assessed by laser Doppler flowmeter; e.g., at the relatively low concentration of 0.2 percent, ropivacaine reduces NBF by 70 percent.[9] Finally, at least for epinephrine, there appears to be a disconnect between a potential aggravation of existing nerve injury in animal models and an excellent safety profile in humans.[10]

Given the relatively high doses required for ephedrine alone to achieve sciatic nerve block in a 200-300 gram rat (ED50 of 1.4 percent for sensory blockade corresponding

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C6

Paratracheal Cervicothoracic Sympathetic Block: Safety, Comfort and Reliability Reside in the C6 Approach

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How I Do It: *Ultrasound-Guided Axillary Block*

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RESEARCH UPDATE *Continued from page 11*

to approximately 3 mg), the potential clinical applications of ephedrine in regional anesthesia will be limited to an adjuvant role by its untoward cardiovascular side effects. Since a relatively low dose is needed for epidural, and particularly intrathecal administration, future studies should be directed toward its spinal administration. In addition the lack of neurotoxic effects when up to 50 mg of ephedrine was injected intrathecally alone[11] or in combination with tetracaine[12,13] for spinal anesthesia, and the accidental use of ephedrine epidurally on several occasions without toxicity,[14,15] should hasten institutional review board/Food and Drug Administration approval, provided that rigorously conducted preclinical toxicity studies[16,17] confirm the safety of ephedrine.

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The Bonica Award Committee for the 2005 Annual Fall Meeting is seeking nominations from the members of the Society for this award. Nominations should be sent to Oscar A. de Leon-Casasola, M.D., Chair of the Bonica Award Committee, at <oscar.deleon@roswellpark.org>.