

ASRA NEWS

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In this Issue

Mythbusters:

The Use of Epinephrine-Containing Local Anesthetics for Digital Blockade



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President's Message

Parting Words

Two years have gone by quickly. As I leave office in early May, I am again struck by a great sense of honor and privilege to have had the opportunity to serve this society and its members. During my term as president, I had the unique experience of truly understanding ASRA's financial, educational and administrative priorities, and the challenges that lie ahead. I was also fortunate to be able to personally meet many ASRA members and to hear their concerns and valuable feedback about the society. I represented ASRA at many national and international meetings and fostered a closer relationship with our sister societies (ESRA, LASRA, OASRA and most recently AFSRA, the newly created African Society of Regional Anesthesia). I consider myself privileged to have enjoyed these special experiences in the past two years.

At the outset of my term, I pledged to uphold the academic excellence and financial well-being of ASRA and set three main goals to pursue. They are: transparency and openness, enhanced member-society interaction, and membership value. In the past two years, we have embarked on a number of new initiatives to meet these goals – a Member Update session during the Opening Ceremony of the Spring and Fall meetings, member feedback corner on the ASRA website, a member needs-assessment survey, a bimonthly electronic e-News bulletin, an online comprehensive Pain Resource Center, a new Pain Research Fund, a Special Interest Group for Ultrasound for Pain Medicine, the ASRA-ESRA training curriculum document for Ultrasound-Guided Regional Anesthesia, and an update of the ASRA Anticoagulation Guideline. More initiatives are forthcoming.

ASRA is a big “family” with many dedicated men and women working tirelessly for the society. They are the heroes whose contributions are often not publicly recognized. I wish to pay special tribute to the ASRA Board of Directors and the Executive Director who continuously strive to advance the vision and mission of the society. I thank the multitude of talented ASRA members who serve on committees and as organizers and faculty of the annual meetings. I thank Dr. Joseph Neal and the *Regional Anesthesia Pain Medicine* editorial board for making our journal one of the best in our specialty (impact factor of 4.16!).

Under the leadership of Dr. Julie Pollock, our new president, I am sure ASRA will grow stronger and healthier. Your commitment and active participation in the society is an integral part of this growth. Let's give full support to our new president. Together, we will build a solid society that leads the practice and science of regional anesthesia and pain medicine.



Vincent W.S. Chan, M.D., F.R.C.P.C.

President's Message II

A Thank You, and Introduction, From Incoming President

It is a great honor to follow Vincent Chan as ASRA President. It is impossible to convey all the many wonderful things that Vince has done for the practice of regional anesthesia and for the society in anything shorter than a textbook. Many of you are aware of his great contributions to our specialty, but something that has probably been underappreciated is his dedication, hard work and even-handedness as the president of ASRA. Dr. Chan's wonderful leadership has brought ASRA to a great place, and I truly hope to continue the growth of the society for the next two years. I know each of you will join me in giving Dr. Chan heartfelt thanks for the countless hours that he has devoted to the society, not just in the last two years as president, but for the many years preceding his presidency as a member of the Board of Directors.

This is a time of transition at ASRA, not just in the presidency, but as we work to more involve the members of the society in committees and the daily work of the society. The board has been involved for the past year in a very thorough strategic planning process. One of the goals during this strategic planning process has been to conduct a member



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Fraud in Clinical Research: Why We Should Care



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In April 2009, Dr. Steven Shafer, Editor-in-Chief of *Anesthesia & Analgesia*, issued a Notice of Retraction for 10 articles involving perioperative analgesia authored by Dr. Scott Reuben on the basis of fabricated data that was revealed following an investigation at his institution.¹ One additional publication has been retracted,² bringing the total to 20 articles and two abstracts confirmed as fraud. To be honest, life would be simpler if we could all cry out, "Liar, liar, pants on fire," and be done with it. Unfortunately, nothing is ever that simple.

Just as we start putting that business behind us, a recent retraction of another article by *Anesthesia & Analgesia* has led to new series of investigations to evaluate the validity of past publications by a prominent clinical researcher.³

These reports of fraud in clinical research in the past two years have undermined our confidence in the process of research. Researchers are left wondering how often fraud occurs and how much of it goes undetected. Clinicians are forced to question the results of published studies and the knowledge of expert speakers who cite them. Patients may start to doubt the motives of investigators who offer enrollment in research studies and distrust the "evidence-based" recommendations of clinicians.

Although the discovery of fraud in our scientific community is unsettling, clinical research must continue.

Instead of just preaching that cheaters never prosper, it is imperative that we examine our current system and look for ways to improve it collectively. In the academic setting, the process of advancement through research productivity can be incredibly daunting for junior faculty members starting their careers. There is nothing more frustrating than undertaking a project without proper guidance and support. Likewise, it can be disheartening to devote time and resources to a study on a topic of little or no interest. Although there is no convincing evidence to date that mentorship affects future research practice, assigning senior mentors to junior faculty seems to make sense when the match is right.⁴ By connecting like-minded people in the pursuit of the same research goal, ideally the search for answers becomes as satisfying as the answers themselves.

Students in formal research training programs are taught to demonstrate equipoise or indifference with regard to outcomes when designing studies. In fact, the results of any study may turn out to be contrary to what we may have expected. A ground-breaking discovery may even be made by accident. Remember the story of penicillin? However, we will not always find clinically-relevant or practice-altering answers every time we do a study. In clinical research, we formulate questions designed to improve patient care and ultimately study them in the actual population in which we want to eventually apply the results. However, human subjects are not predictable, and the results of a well-designed study often do not go the way we want. As Dr. Shafer says in his editorial, "The perfect study cannot be performed."⁵

Although such times can be personally deflating, we must remember that important and influential lessons may come from studies that fail to prove what they set out to prove.

For clinicians not involved in research who read journals regularly

to update their fund of knowledge and provide their patients with the latest evidence-based care, the retraction of several studies supporting multi-modal analgesia has been discouraging to say the least. Fortunately, the actual impact of these retractions on the results of systematic reviews incorporating data from these studies appears to be limited.⁶⁻⁷ With the start of a new investigation into another researcher's publication history, it seems apparent that we all need to read articles carefully and feel comfortable asking questions. This most recent retraction of Dr. Boldt's article was prompted by the inquiries of three readers.³ We encourage all clinicians to not merely

**"Clinicians should keep the best interest
of the patient in mind and not allow personal motivation
or external pressures to distort our practice.
Our patients deserve it."**

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New Pharmacological Management for Headache Disorders

Of the maladies that afflict the human species, headache is perhaps among the commonest and may at times be one of the worst.

Newly introduced or recently revisited agents are being continually added to the pharmacological armamentarium for combating headache. In this discourse, three pharmacological modalities that have recently emerged as promising remedies for headache disorders will be discussed.

Cosyntropin for Postdural Puncture Headache: An Old Remedy Recently Revisited

As early as 1994, there have been reports on the successful treatment of refractory postdural puncture headache (PDPH) with adrenocorticotrophic hormone (ACTH)¹⁻³ or its analogues.^{4,5} One decade later, a prospective randomized controlled trial (RCT)⁶ reported no difference between tetracosactrin, a synthetic ACTH analogue, and placebo in parturients suffering from PDPH after subarachnoid block or accidental dural tap. However, the implications of that study were difficult to appraise owing to the small number of patients studied (9 per group).

Accidental dural puncture (ADP) is notorious for a disturbingly high incidence of PDPH.^{7,8} Lately, there has been revival in the interest in ACTH analogues as prophylactic options after ADP. A recent RCT⁹ involving 90 parturients who sustained ADP during placement of epidural catheter for labor analgesia were randomized to receive cosyntropin or placebo. The study showed that cosyntropin was associated with significantly lower incidence of PDPH and need for epidural blood patch, as well as significant delay in the experience of headache after dural tap had been sustained.

Cosyntropin is a synthetic ACTH analogue that possesses full hormonal activity of the natural peptide with much less antigenic potential.¹⁰ How ACTH or its synthetic analogues can help PDPH is not entirely understood. One assumption is that these agents stimulate the release of aldosterone with enhancement of salt and water retention and subsequent expansion of blood volume. This could help seal the dural hole by inducing edema of the dura with simple overlay of the torn edges.¹¹ Other suggested mechanisms are promotion of cerebrospinal fluid formation via active secretion of sodium ions, or increase in brain levels of β -endorphin^{1,4} which shares the same precursor with ACTH.¹² Evidence also exists that byproducts from ACTH may bind to opioid receptors,^{13,14} and such an interaction simulates the effects of morphine in-vitro.¹⁵ Although a clinical implication for this ACTH-opioid receptor interaction cannot be claimed

at the moment, it may be surmised that other likely mechanisms of action could be present, and that an ACTH analogue could be more operational for PDPH than direct-acting glucocorticoids which have also been used as treatments.¹⁶⁻¹⁸

A number of question need to be answered including the following: Should cosyntropin be administered exclusively to patients at high risk for

“Could cosyntropin be administered to high-risk patients when they undergo deliberate dural tap for subarachnoid block in order to lessen the chance of PDPH?”

PDPH when they suffer an ADP? Could cosyntropin be administered to high-risk patients when they undergo deliberate dural tap for subarachnoid block in order to lessen the chance of PDPH? Used as such, what would be the optimal dose and route of administration? Should it be used before or after the dural tap? Is there a therapeutic or prophylactic window during which cosyntropin would be effective and beyond which it would not? These and other emerging questions await answers from well-designed RCTs, and until evidence from such trials is available, cosyntropin may perhaps be viewed as a possible remedy for an old problem.

Warfarin for Intractable Chronic Cluster Headache: Still a Place for Serendipity in Medicine?

In 2004, Souza and colleagues¹⁹ presented the first case report of remission from refractory chronic cluster headache (CCH) with the use of warfarin therapy for an unrelated indication. A year later, Kowacs and colleagues²⁰ published a series of 3 such cases. The effectiveness of warfarin^{21,22} or acenocoumarol²³ has also been claimed for migraine, and an observational study²⁴ reported that significantly more patients with migraine underwent reduction in the frequency of their attacks compared with those suffering from other headache disorders when they received acenocoumarol for unrelated ailments. Contrary to these reports, one randomized crossover study,²⁵ failed to demonstrate an improvement



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New Pharmacological Management for Headache Disorders

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in migraine symptoms with acenocoumarol. That study was terminated prematurely after recruitment of only 12 patients, as an interim analysis showed significance level would not be attained with the calculated sample size. Judgment, therefore, warrants that caution be exercised in interpreting the results of that study.

Lately, a randomized double-blind cross-over pilot study²⁶ showed that low-intensity anticoagulation with warfarin (INR = 1.5 – 1.9) in patients with intractable CCH was associated with significantly higher incidence of remission as well as significant reduction in severity and intensity of cluster attacks. Overall impact of CCH on patients' lives was also significantly reduced with warfarin.

How warfarin might improve cluster headache (CH) or other trigeminovascular headaches is not yet clear. The fact that the drug does possess anti-inflammatory effects has been demonstrated experimentally.²⁷ Such an effect may occur in these cases because neurogenic inflammation is believed to underlie vascular headaches.²⁸ However, this seems not to be a likely mechanism considering the extraordinarily high doses of warfarin needed to exhibit appreciable anti-inflammatory action. A seemingly more consistent explanation could be linked to the antagonism of the action of vitamin K on neuronal metabolism.²⁹ In this regard, vitamin K has been shown to promote dendritic outgrowth through activation of protein kinases³⁰ which are also believed to be involved in hypothalamic control of circadian functions.³¹ In fact, evidence exists that hypothalamic activity could be linked to the circadian and circannual phenomena typical of CH.^{32,33} Besides, antagonism of the effect of vitamin K on the induction of nitric oxide synthase in vascular smooth muscle³⁴ could, in theory, suppress nitric oxide-mediated neurogenic inflammation, the hallmark of CH and related disorders.³⁵

Could warfarin offer hope to those patients desperately stricken with refractory CCH? What would be the ideal level of anticoagulation? For how long should the drug be administered? What hazards may arise from such treatment? Current data is far from adequate and future trials are needed to identify if efficacy truly exists.

Calcitonin Gene-Related Peptide Antagonists (the Gepants): A looming Hope for Patients With Migraine

Calcitonin gene-related peptide (CGRP) is a 37-amino acid chain derived from the calcitonin gene by splicing of ribonucleic acid during gene expression. Evidence exists of a potential role for CGRP in the pathogenesis of migraine. A potent vasodilator, the neuropeptide is abundant in trigeminovascular terminals converging on the exquisitely pain-sensitive meningeal arteries, the ultimate arena for neurogenic inflammation.³⁶ Nonetheless, CGRP-specific receptors have been demonstrated on meningeal vessels and trigeminal afferents, as well as in the trigeminal

ganglion and areas of the brain believed to be involved in migraine such as the periaqueductal grey matter.³⁷ A temporal relation has also been substantiated between acute attacks of migraine³⁸ or stimulation of the trigeminal ganglion³⁹ and an upsurge in CGRP levels in venous blood samples drawn from the external jugular vein.

Currently, two non-peptide CGRP antagonists that have exhibited proven efficacy in migraine are available, olcegepant and telcagepant, formerly coded BIBN4096 and MK-0974, respectively. These agents hold promise as remedies for migraine that neither involve serotonergic mechanisms nor induce vasoconstriction, the major drawbacks of triptans. In this respect, olcegepant has been shown to be more effective as an acute treatment for migraine compared with placebo.⁴⁰ Telcagepant, which has the advantage of oral administration, has been demonstrated to exert beneficial effect in acute migraine in one phase IIB⁴¹ and 2 phase III studies.^{42,43}

Available data⁴¹⁻⁴⁴ indicates that telcagepant could be as effective as rizatriptan and zolmitriptan and that, used intermittently to terminate an acute attack, the drug seems to be as tolerable as placebo. There is concern, however, of an untoward effect on hepatic transaminase levels if used for prolonged periods, e.g., for prophylactic purposes.⁴⁵ Telcagepant is expected to be released for clinical use in the near future. Nevertheless, further clinical trials are required for thorough appraisal of the safety and appropriateness of these emerging medications.

Conclusion

New possibilities are being developed that may significantly help sufferers of chronic headache. Further studies are required to determine efficacy and safety of each of these exciting treatments.

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An 1819 caricature by English artist George Cruikshank (born 1792, died 1878) depicting a miserable man tormented by a devilish headache. From the National Library of Medicine, Bethesda, Maryland (in the public domain).

Update on Long-Duration Nerve Blocks From Slow-Release Formulations of Local Anesthetics



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Conflict of Interest: Dr. Strichartz is currently conducting research sponsored by Covidien, Inc. on the actions of local anesthetic-containing degradable microspheres.

One ideal sought by anesthesiologists is a duration of nerve block longer than the surgical procedure. A block that extends into several post-procedural days can minimize post-operative pain and its attendant central sensitization, which is implicated in chronic post-operative pain.¹ Injecting large doses of local anesthetic (LA) at the start of the block, or “topping up” later, to extend the block when it begins to regress, raise several problems, of

which systemic toxicity is the most serious. Indwelling catheters have the advantage of a continuous supply of drug at low dosing rates but raise problems of spontaneous re-location, barrier breach and infection.²

One solution to the need for prolonged nerve blocks has been the use of formulations that slowly release LA at the intended site. The criteria for such formulations include the correct release rate and the total drug-holding capacity; Drug release must occur at a rate that is adequate for the drug to diffuse into the target nerve and to sustain an effective steady-state concentration there³, while competing with diffusion and uptake by surrounding tissues and re-sorption by the local vasculature (Figure 1). If the release rate is too fast, the LA content of the formulation will be emptied prematurely and a rapidly appearing supra-effective local concentration will quickly fall to an ineffective level. Systemic toxicity may also occur. In contrast, too slow a release will be incapable of matching the drug depleting actions of non-neural tissue uptake and vascular removal, and the critical concentration for nerve block will never be reached. Obviously, the drug-holding capacity is also critical; even if a release rate matches removal rates to effect a critical block concentration, the resulting block will only last as long as the drug is available. Two parameters limiting the drug capacity of formulations are the fraction of the formulation that is composed of LA and the total mass of formulation that can be placed at the target site.

Local anesthetics are released slowly from drug-containing lipid-composed materials, from degradable microspheres and from solid matrices.⁴ The first two are usually injectable formulations, but the last needs to be implanted, which limits its applications to surgical sites, or requires a separate procedure for implanting. The two basic mechanisms controlling release are; 1) diffusion of LA molecules through and out of a relatively constant delivery structure, or 2) degradation of the structure, by hydrolysis of the bonds at the surface for example, and resulting release of the contained LA. In the first strategy, the diffusion of the LA is dependent on the molecule's lipophilicity (hydrophobicity), its size, and the fluidity of the membranes formed by the lipid constituents.⁵ High capacity “liposomes” are formed by multi-lamellar structures composed of many concentric spheres of lipid bilayer membranes. LA molecules partition into all the membranes, with distribution coefficients of 100-1000, allowing for a high capacity and potentially long-lasting block.⁶⁻⁸ Blocks from such liposomal formulations containing lidocaine or bupivacaine can persist for up to several days.^{9,10}

Diffusion from solid matrices is controlled by the molecular composition of the solid and the use of “release modulating” additives, as well as the LA's physico-chemical properties.^{11,12} Release rates of LA from degradable carriers, such as biodegradable microspheres, are largely dependent of the rate of degradation,¹³ much less so on LA properties, although these properties still govern the rate at which drug enters the nerve or is locally absorbed, plus the confounding factor of a dynamic vaso-activity of LAs, dilating or constricting the local circulation in a concentration-dependent manner.^{14,15} Biodegradable microspheres can block peripheral nerves for up to one week, but only when co-constituted with dexamethasone or a comparable NSAID.^{16,17} It appears that local inflammatory reactions to the injected microspheres produce conditions, such as low pH and hyper-perfusion, that disfavor LA delivery to the nerve target.^{18,19}

Recent work in our laboratory has investigated a solid formulation based on a bone wax substance originally designed for hemostasis after bone graft. We found that lidocaine composed into this solid putty could be released over several days, and that peripheral nerve block by implants shaped next to a rat sciatic nerve lasted for about a day.¹¹ Interestingly, the longest duration block corresponded to an intermediate *in vitro* release rate,¹² confirming the theoretical viewpoint that too fast or too slow a release results in a shorter duration block (cf. Figure 1). Although the block of nociceptive functions of the rat sciatic nerve lasted less than one day, the same sciatic implant was able to suppress the post-operative pain from paw incision in the blocked nerve's receptive field for 2-3 days, reducing integrated pain intensity by up to 75%.²⁰ Identical implants at the contralateral sciatic nerve had a

smaller effect in reducing post-incisional pain, suggesting that some of the actions of drug from the implant might be due to systemic uptake. However, measurements of plasma concentrations after identical implants showed that blood levels had returned to undetectable levels ($<0.2 \mu\text{g}/\text{mL}$) by 12h, as had the neural levels of lidocaine (unpublished data), showing that the prolonged anti-hyperalgesic effect did not depend on the continued presence of LA.

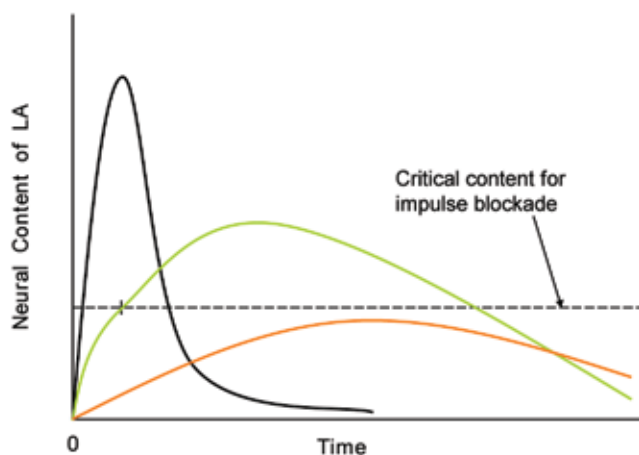
This observation confirms the notion that there is a “critical period” after surgery or trauma where the actions of a LA, injected around a nerve or delivered systemically, are effective, but if given afterwards have acute effects of much shorter duration. An effective post-operative local anesthetic, therefore, need not be present in the body for the entire period that post-operative hyperalgesia would exist without any analgesia or anesthesia; its presence during this critical period may be sufficient. In this light, a briefer, more dense block that suppresses all afferent input may be more effective than one that lasts longer but is incomplete.

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Figure 1



Schematic illustrating the dependence of block duration on the release rate of local anesthetic. Very rapid release rates (black line) quickly load the nerve to concentrations well above the critical block level (dashed line), while very slow rates (orange line) are not able to deliver enough drug to nerve to reach the critical block. An intermediate release rate, while slower in onset than the very rapid release, will provide a block that is sustained for far longer.

*Mythbusters:***The Use of Epinephrine-Containing Local Anesthetics for Digital Blockade**

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The use of epinephrine in local anesthetic (LA) preparations for digital nerve blockade is controversial. Medical students and residents are frequently taught to avoid injecting epinephrine-containing solutions into the digits (or the ears, nose or penis) due to concerns of vasoconstriction-induced ischemia or necrosis.¹ While many experienced clinicians follow this advice, there are those that oppose this view, and believe that epinephrine at the digit is safe and improves operating conditions.² The purpose of this review is to summarize the evidence surrounding this topic with the aim of either supporting or debunking the commonly held belief that epinephrine should not be used for digital blocks.

**Potential Advantages**

Clinicians who favor epinephrine for digital blocks often point to advantages of the vasoconstrictive effect during hand surgery. Examples include a prolonged duration of LA action through reduced vascular absorption, decreased bleeding, and a reduced need for mechanical tourniquets, a factor that has itself been implicated in digital necrosis.³ In addition, the need for additional injections to the digit are decreased, theoretically reducing the potential for neurovascular injury.

**Effect on Blood Flow**

The effect of epinephrine-containing LAs on digital physiology and hemodynamics has been investigated in several studies. Sönmez *et al.* assessed fingertip capillary blood gas values after randomizing 20 patients to digital block with either 2 percent plain lidocaine or 2 percent lidocaine with 1:80,000 epinephrine.⁴ Both PO₂ and SaO₂ increased significantly after injection with plain lidocaine, whereas there was no change in these values in the epinephrine-containing group, suggesting that a clinically significant reduction in oxygen delivery to fingertip tissues did not occur.





In one study, digital blood flow (as measured by color duplex ultrasonography) was shown to be reduced significantly following blockade with 2 percent lidocaine and 1:100,000 epinephrine.⁵ However, the effect was short-lived, with flow velocities returning to normal by 60-90 minutes. Another prospective Doppler ultrasound study of 100 patients receiving 2 percent lidocaine with 1:80,000 epinephrine for hand surgery demonstrated that the mean reduction in digital blood pressure was 20% (range -63% to +15%).⁶ Taken together, these data suggest that epinephrine in LA solutions results in a “low-flow” (rather than “no-flow”) state in the digit that is reversible in a timely manner. Indeed, experimental data has shown that catecholamines preferentially vasoconstrict cutaneous shunt flow rather than nutritive flow, which helps to explain why the skin is generally tolerant of epinephrine injection.⁷

“This myth is BUSTED! The oft-repeated dogma that epinephrine should never be used in digital blockade is based on very scant, old and misleading evidence.”

Effect of Concentration

The safe range of epinephrine concentration is unknown. Accidental administration of 1:1000 epinephrine via auto-injectors and subsequent digital ischemia has been reported,⁸ although treatment with phentolamine almost always results in prompt resolution of the vasospasm. Commonly used concentrations range from 1:100,000 to 1:200,000, with little apparent difference in operating conditions or adverse outcomes.⁹ In a study of plastic surgery patients, Siegel *et al.* injected 1 percent lidocaine containing one of four concentrations of epinephrine (1:100,000, 1:400,000, 1:800,000, or 1:1,600,000) and asked blinded surgeons to assess the effect on hemostasis and blanching. All but the weakest concentration resulted in blanching and equal hemostasis, suggesting that strong concentrations are not required for adequate operating conditions.

Adverse Outcomes

An exhaustive review of the worldwide literature back to 1889 revealed only 21 cases of digital gangrene following injection of LA with epinephrine.¹ In contrast, there are 27 cases of digital gangrene associated with plain LA injection. All but six of these cases occurred prior to 1950, when the LA of choice was procaine. In the late 1940s, it became apparent that as procaine underwent hydrolysis to para-aminobenzoic acid, the pH dropped to as low as 1. This was especially true in older vials, and since expiry dates were not mandated by the FDA until the 1970s, it is likely that outdated acidic procaine was the culprit in many if not the vast majority of these cases of tissue necrosis.² Toxic batches of procaine were indeed recalled in 1948, the same year that lidocaine was introduced. Six of the 48 cases involved cocaine as the local anesthetic, which has intrinsic vasoconstrictive properties.

In contrast, there is not a single case of digital ischemia following infiltration of lidocaine and epinephrine for digital block. Only two randomized controlled trials could be found comparing lidocaine with and without epinephrine for this purpose, and both showed no difference in outcome.^{9,10} Several case series and prospective observational studies have been reported and to date over 200,000 cases of lidocaine (or bupivacaine) plus epinephrine injection for digital block have been described in the literature, none of which were associated with ischemia or necrosis.^{6,11-16}

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This supports the notion that lidocaine, by far the most common LA used for digital blocks at present, is safe when combined with epinephrine for this purpose, and that it is, in fact, the presence of more toxic LAs such as procaine or cocaine that are at fault.

Other Factors

Other surgical factors that may play a role in the development of ischemia and necrosis following digit surgery include the use of tourniquets,¹⁷ although this is common practice and is generally safe unless accidentally left inflated for a prolonged duration. The practice of hot soaks is associated with thermal injury and intraluminal digital artery thrombosis.⁹ Circumferential injection may also cause compression of the structures in the digit and predispose to ischemia and/or nerve injury.¹⁸ Clearly, consideration should be given to avoiding vasoconstrictive agents in patients with comorbidities such as pheochromocytoma, severe uncontrolled hypertension, cardiac disease, diabetes, and collagen vascular disease such as Raynaud's phenomenon.

Conclusion

This myth is **BUSTED!** The oft-repeated dogma that epinephrine should never be used in digital blockade is based on very scant, old and misleading evidence. Moreover its safe and effective use is supported by nearly a quarter of a million *documented* cases with no ischemic or gangrenous outcome. However, despite the drive towards increased use of evidence-based medicine, this may be a challenging practice to change: for example, an informal poll of orthopedists at our own institution revealed that 10 of 10 surgeons would **not** use epinephrine in digital blocks. The reason that this myth is so engrained is not entirely clear in the face of the evidence, and may deserve investigation in the future.

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survey, which many of you have recently completed. We will review the specific results of the survey in the next newsletter, but it has been obvious from both the strategic planning process and the survey that the members of ASRA would like to be more involved in the society. One of the best ways to accomplish this will be to move to a society structure that allows for more of the decisions and work of the organization to occur in committees rather than just with the Board of Directors. In order to accomplish this, we will be starting a process similar to that currently conducted by the ASA where members are allowed to review available committee assignments and job descriptions and then either self-nominate or nominate a

colleague to serve on that committee. Committee members will be selected by the committee chair and then be available for re-appointment. The Board of Directors believes that it is very important to harness the many talents and skills of the ASRA members and utilize that creativity and energy to improve ASRA and what it is able to offer our members. As we roll out this process over the next year, I encourage each of you to review available committees and consider where your talents can best be used to make the society even better in the future. I look forward to working with each of you as we continue the great work that Dr. Chan has begun.

Fraud in Clinical Research: Why We Should Care

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accept an author's conclusion at face value but to develop a systematic approach to regularly and critically evaluate published articles so results can be judiciously applied to our patient population.

A major concern with falsifying data is that unreliable, or even potentially harmful, results may be applied to our patients. As clinicians, we have an obligation to provide the highest level of care to those who entrust us with their lives. At every level of evidence-based clinical care, from the inception of a clinically-relevant research question to the application of published study results, clinicians should keep the best interest of the patient in mind and not allow personal motivation or external pressures to distort our practice. Our patients deserve it.

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Volumes, Concentrations, Doses and Neurolocation Techniques: Where Are We Bound?



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In the past three decades, there has been considerable evolution of neurolocation techniques for regional anesthesia. This has influenced the recommended drug doses for peripheral nerve blockade substantially. In particular, the emergence of ultrasonographic guidance has led to reconsideration of how much drug should be delivered to accomplish the desired anesthesia.¹ Understanding the relationship between pharmacologic parameters of local anesthetics and their clinical effects is essential to balance patient safety, efficacy and desired block onset and duration.

Relationships of Volume and Concentration:

A number of pharmacologic principles have been well substantiated, with regard to the clinical effects of local anesthetics. These include the importance of physicochemical properties of the molecules themselves in determining potency, onset and duration of sodium channel blockade.² Other pharmacologic manipulations, such as the addition of vasoconstrictors and adjunctive medications may serve to affect duration as well,³ while changing the pH of the solution has the potential to influence onset.⁴

However, once an agent (and any additives) is selected for injection, other parameters play an important role in clinical aspects of nerve blockade. Onset and duration of effective nerve blockade are determined by distribution and dissipation of drug at the site into which it is injected, which relate in turn to the flow characteristics of the solution, diffusion of the drug into the nerve, and binding of the agent to sites of activity⁵; local blood flow patterns also play a role in this process.

Some of these determinants can be affected by the regionalist in the performance of nerve blocks through manipulation of volume, concentration and overall drug dose. These variables represent a simple arithmetic arrangement, but studies have not consistently supported the impact of each parameter on characteristics of nerve blockade. It is likely that mass of drug is the most important among these—as dose of drug increases, the duration is expected to be prolonged and the onset of block shortened.⁵ However, the manner in which volume

and concentration interact with each other to produce these effects is not always simple, even when the overall drug dose is constant.

In epidural block, this relationship of drug mass to quality and depth of nerve blockade, as well as to onset and duration, is reasonably well established.^{6,7} Similar drug doses, even with variable concentration and volumes tends to result in similar block characteristics.⁸ Large variations in volume may, however, result in significant differences in spread or ascension of block in the epidural space.⁹

In peripheral nerve blockade, however, the simple adage of “larger mass of drug leads to faster onset and prolonged duration” is not so consistently evident. As with neuraxial block, concentration has been held to be an important determinant of block onset,¹⁰ though not all studies have supported this.¹¹ Pharmacokinetically, it is logical to suppose a higher drug concentration, with all other factors being equal (they often are not), would lead to faster onset, since drug uptake through the connective tissues that separate axons from drug (epineurium, perineurium and possibly connective tissue septations) is passive, from high to low concentration.⁵

In studies investigating peripheral nerve block characteristics, such as onset, success and duration, authors have utilized different block sites and nerves, different nerve localization techniques and a variety of local anesthetic agents, while varying volume, concentration and overall drug dose. Unfortunately, the results have not been completely consistent or offered a simple, unifying principle. Furthermore, as precision of needle tip placement and local anesthetic delivery have progressed in the past three decades, some research has contradicted earlier reports.

Early investigators frequently made use of large volumes of local anesthetic solution, placed in anatomic spaces, in an attempt to gain optimal proximity of drug to nerves. DeJong in 1961 calculated that 42 ml of local anesthetic solution (1% lidocaine with epinephrine) should be utilized to fill an average-sized neurovascular compartment, or sheath, in the axilla.¹² Vester-Anderson further explored this idea two decades later, by varying the volumes of axillary block while maintaining a fixed dose of mepivacaine.¹³ The authors reported that anesthesia in several peripheral nerve territories improved with increasing volumes, while motor block was intensified with lower volumes/higher concentrations. In a somewhat different manner, Vester-Anderson et al assessed the importance of volume and total drug dose in axillary block, injecting three different volumes of 1% mepivacaine with epinephrine, and found that sensory and motor block onset was similar in all three groups, though a better quality of sensory block was evident with higher volumes. The authors recommended that 50 ml of this solution was an optimal dose for axillary block.¹⁴ In

an evaluation of optimal volumes for the orthogonal two-needle technique of axillary block, Rucci et al utilized three different volumes of a mixture of a fixed concentrations of bupivacaine and lidocaine with epinephrine, and reported a direct correlation between injected volumes and spread of anesthesia to all the major nerves of the brachial plexus.¹⁵

The accuracy of needle tip placement in relation to target nerves improved with the widespread adoption of electrical nerve stimulation. In an investigation of the effect of the precision of nerve localization on required drug mass and volume for axillary block, Koscielnak-Nielson et al compared a four-nerve targeted nerve stimulation technique to a single injection into the neurovascular bundle (guided by transarterial needle placement) of a similar local anesthetic solution.¹⁶ Despite a four-fold increase in volume and drug dose with the single-injection approach, the four-nerve stimulation proved superior in terms of block setup time as well as success, requiring markedly fewer supplemental blocks for an adequate effect. Bertini et al¹⁷ evaluated the effect of two different concentrations of ropivacaine, 0.5% and 0.75%, as well as 0.5% bupivacaine, for nerve stimulator-guided axillary block, and found that there was little difference between 0.5 and 0.75% ropivacaine. Both formulations were more rapid in onset of effect than bupivacaine; there was no difference among the three in block success or duration. In comparing three different volumes of mepivacaine 1% for axillary block with the four-nerve stimulation technique, Seradell et al found no difference in block success, block duration, or onset times, despite the escalating drug doses.¹⁸ For interscalene brachial plexus block, Casati et al compared similar volumes of 0.5%, 0.75% and 1% ropivacaine with 2% mepivacaine, and reported the fastest onset of block occurred with the highest ropivacaine concentrations, but no difference in effectiveness of anesthesia or block duration (except for the markedly shorter duration of mepivacaine).¹⁹

In an assessment of lower extremity blockade with nerve stimulation guidance, Casati et al evaluated femoral-sciatic blockade guided by nerve stimulation with a total dose of 225 mg of ropivacaine in two different concentrations (0.5 and 0.75%) or with mepivacaine 500 mg.²⁰ The authors noted a slower onset with the lower concentration of ropivacaine than with the other two solutions, as well as a 14% shorter duration of analgesia, when compared with the higher concentration. In assessing the import of volume and concentration, with

fixed drug dosage in the Labat sciatic block guided by nerve stimulation, Muniz reported a higher success rate (96.6%) utilizing 20 ml of 1.5% mepivacaine, than with 30 ml of 1% mepivacaine (68.7%), as well as a faster onset.¹⁰ The authors did not evaluate the impact of the variable volumes and concentrations on duration. Bertini, et al¹¹ injected a fixed dose of 400 mg of mepivacaine for four-nerve axillary block guided by nerve stimulation, in a variable volume of 20, 30 or 40 ml. There was no significant difference in success rates of the blocks, or of rate of onset; however the concentration/volume that produced a significantly longer sensory and motor blockade was the intermediate one (30 ml of 1.5%), rather than the highest or lowest concentrations.

Prior to the ultrasound era, accurate placement of local anesthetic was difficult to confirm. While peripheral nerve stimulation ensures accurate needle tip placement, it does not confirm appropriate distribution of local anesthetic

solution around the nerve. Ultrasound provides visual confirmation of this phenomenon, though it is somewhat limited by its two-dimensional plane of section. However, dynamic appraisal is made possible by moving the transducer along the axis of the nerve, to evaluate spread of injectate outside the plane of the needle.

Diffuse spread about the nerve, in a "halo" fashion, has been recommended for optimal effect.²¹ Recent data corroborates this for the sciatic nerve, with an approximately 33% decrease in onset time when complete circumferential spread was demonstrated,²² as compared to incomplete spread.

With the ability to more precisely confirm local anesthetic proximity to the nerve in clinical studies through the use of ultrasound, one might expect rigorously conducted research into the pharmacodynamics of local anesthetics. A number of authors have demonstrated lower dosing requirements, primarily lower volumes of a fixed concentration of drug, in order to obtain equal or greater block success rates. Marhofer et al evaluated both nerve stimulation and ultrasound guidance for 3-in-1 blockade in the femoral triangle, and reported that a 33% lower dose of 0.5% bupivacaine could be utilized with the ultrasound technique, with a higher success rate in sensory blockade.²³ Similarly, Casati et al investigated the minimal effective anesthetic volume (MEAV) necessary for femoral nerve block with ropivacaine 0.5%, using

"With the ability to more precisely confirm local anesthetic proximity to the nerve in clinical studies through the use of ultrasound, one might expect rigorously conducted research into the pharmacodynamics of local anesthetics."

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Volumes, Concentrations, Doses and Neurolocation Techniques: Where Are We Bound?

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the Dixon up-down methodology, an increasingly popular means of determining minimal effective dosing in regional anesthesia.²⁴ The authors reported MEAV50 for femoral block of 15 ml in the ultrasound group and 26 ml in the PNS group, with a calculated MEAV95 of 22 and 41 ml respectively. McNaught et al compared interscalene block guided by either ultrasound or nerve stimulation, by a similar methodology,²⁵ with PACU pain scores as the primary end point for determining success (patients underwent general anesthesia for surgery). The authors found that ultrasound guidance allowed a greater reduction in volume of drug while preserving postoperative analgesia than did nerve stimulation-0.9 ml versus 5.4 ml. In a meta analysis of randomized, controlled trials comparing these two guidance techniques, Solomon reported that ultrasound imaging resulted in faster onset, lower drug doses and significantly prolonged block durations.¹

Not all investigators have reported an advantage of ultrasound in reducing drug dosage when compared to nerve stimulation. Ponrouch et al evaluated median and ulnar nerve blocks in the humeral canal for carpal tunnel surgery, randomizing patients to either technique, while utilizing 1.5% mepivacaine as a local anesthetic solution.²⁶ A sequential up-down technique was utilized, with an end point of complete sensory blockade in the respective nerve territories. While the MEAV50 for the median nerve was lower in the group with ultrasound guidance (2 ml vs 4 ml), there was no difference in this value for the ulnar nerve. In assessing the impact of ultrasound guidance on dosing in supraclavicular block, Duggan et al likewise utilized the up-down approach.²⁷ The authors reported that the MEAV95 of 42 ml was similar to the recommended volumes for this block using nerve stimulation, though this was not a direct comparison of two neurolocation techniques.

Some authors appear to have refined the technique of ultrasound guidance even further, reporting extremely low volumes/doses of required local anesthetics for successful nerve blockade under ultrasound guidance. O'Donnell, et al, reported that only 1 ml of 2% lidocaine was required for anesthesia of each nerve in a four-nerve axillary block,²⁸ and in a subsequent study corroborated this finding, while reporting a mean duration of approximately 160 minutes.²⁹ While also utilizing the up-down methodology, Eichenberger et al attempted to measure the volume of 1% mepivacaine required for blockade of the ulnar nerve in the forearm to produce sensory anesthesia in the hand.³⁰ The authors indexed the required dose to the cross-sectional area of the nerve, and reported an effective dose of 0.11 ml per mm² of nerve area, as determined by ultrasound imaging. As noted above, McNaught et al were able to provide effective postoperative analgesia after shoulder surgery by utilizing only 0.9 ml of ropivacaine 0.5% for interscalene block.²⁵

These studies underscore the importance of the accuracy of drug delivery as a major determinant of required drug volumes/doses to provide successful nerve blockade.

Thus, the exact requirements for drug dose, concentration and volume remains somewhat ill-defined for a variety of blocks. Certain aspects of an individual block site may exert influence on the dose of drug required, such as a "sheath" to fill, or a tight compartment lined by the fascia of surrounding muscles. For instance, one nerve, at two different sites of blockade, may have different dosing requirements for successful nerve blockade. Taboada, et al, examined the ED95 (MEAV95) of 1.5% mepivacaine for the sciatic nerve at both the subgluteal site and the popliteal fossa site.³¹ The authors reported a nearly two-fold increased requirement for volume of drug/mass of drug (17 vs 30 ml) for the popliteal fossa, in order to obtain the same degree of blockade.

The amount of adipose and/or connective tissue within or surrounding a nerve or plexus may also affect local anesthetic disposition and effects.³² In a unique study design, Fredrickson et al explored the idea that thresholds may exist for effective blockade in terms of volumes and concentrations, below which either parameter could lead to an ineffective block. This was demonstrated by the authors for interscalene block.³³ Upper thresholds, or ceilings, may exist as well, above which further drug dosing produces no significant increase in rapidity of onset or duration of effect. These upper thresholds may also be dictated by the potential for local anesthetic systemic toxicity.

This suggests that an ideal range of volumes and concentrations may exist (as well as total drug dosage) below which block success, onset or duration is judged to be inadequate, and above which nothing is to be gained or patient safety is compromised. In such a framework, concentration and volume are dynamic variables that may change significantly in relationship to one another, as long as the thresholds are met, and ceilings not exceeded. Such a phenomenon may explain some of the variability noted in the studies reviewed above, and the failure to find a meaningful difference for some dosing parameters of a local anesthetic agent for a given block.

Conclusions:

Most studies support the idea the total drug dose is a primary determinant of block effect, but the ideal volumes and concentrations with which the mass of drug should be delivered has been difficult to specify. It is apparent that greater precision of local anesthetic deposition in proximity to nerve targets minimizes the drug volume/dose necessary to carry out effective blockade.³⁴ Thresholds and ceilings may exist for each local anesthetic and each nerve block, which permit the use of a range of effective dosing strategies. As investigators continue to evaluate local anesthetic dosing in the context of greater accuracy of drug delivery, these ranges may be determined more precisely for a variety

of peripheral nerve blocks, allowing greater patient safety and an assurance of optimal effectiveness.

REMINDER:

This month marks the initiation of the "Ask the Experts" column, which features questions directed to researchers or instructors in regional anesthesia, answers to which will be published in ASRA news. Please direct questions to: Steve Orebaugh, M.D. c/o ASRA news at this e-mail address: newsletter@asra.com.

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The intervertebral disc (IVD) has been implicated as the primary pain generator in 30 to 50 percent of chronic lumbosacral pain cases. Although the exact mechanism of injury for IVD degeneration is still being determined, genetic, biomechanical, and nutritional factors all play a role. The treatment of IVD degeneration ranges from conservative management to interventional pain procedures to surgical intervention. Interventional pain procedures for diagnosing and treating discogenic back pain involve annular puncture. Recently, clinical studies have been published in the spine literature suggesting that a relatively minor annular puncture has clinical and biological

consequences. Here, I will discuss the concerns for needle puncture stimulating the degenerative disc cascade.

As early as the 1950s, de Sèze and Levernieux and Goldie raised concerns about changes observed in the IVD following discography.^{1,2} de Sèze and Levernieux discovered areas of necrosis at the time of surgical intervention within the discs of 13 of 59 individuals who had discography. Goldie demonstrated hyaline droplets in 28 of the 53 discography discs. The hyaline droplets were attributed to the interaction between the nucleus pulposus and Dijon D35 percent contrast (diathanolamine diiodopyridon-N-acetas and diphenhydramine chloride).

Lately, two clinical studies have been published implicating needle penetration in the acceleration of disc degeneration. In 2009, The International Society for the Study of the Lumbar Spine Award went to the project titled: "Does discography cause accelerated progression of degenerative changes in the lumbar disc: A 10 year matched cohort

PRO Interventional Disc Procedures Are Not CON



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Needle puncture occurs during provocative manometric discography as utilized by interventional pain physicians to confirm the painful nature of abnormal discs identified on imaging studies. While not innocuous due to its purpose of causing discomfort, the procedure has been abandoned by some practitioners because of studies highlighting it as a source of future disc degeneration.¹⁻⁴

Objectivity and caution need to be exercised when analyzing research results. Many have pointed to a recent ten-year matched cohort study to question the safety of discography.¹ If discography leads to degeneration, it should do so in all patients. Although

35 percent of patients developed greater progression of disc degeneration vs. 14 percent of the control patients after discography, universal progression did not occur.¹ Contrarily, after the 10 year follow up, the authors found that more than 50 percent of patients who had Grade I or II (normal) degeneration at the time of initial discography, remained at the same level 10 years after an initial injection! Hence, in this subset of patients there was no change in the degree of degeneration in the injected discs. Previously, 188 patients followed 10-20 years after discography and chemonucleolysis demonstrated no progression of disc degeneration on serial radiographic evaluation.⁵

The astute examiner of the Carragee study will ask, how certain are we that patients in the study were not predisposed to developing degeneration?¹ Evaluated subjects had prior cervical or lumbar disc disease with or without pain. The possibility exists that these patients are

study.”³ 50 subjects who underwent discography at the L3-S1 discs and 52 matched control subjects were analyzed. An MRI prior to discography and a repeat MRI performed 7 to 10 years later were evaluated for quantitative (disc height and disc signal) and qualitative (herniation, endplate changes, disc grade progression, and annular fissures) degenerative changes. When examining the subset of discs that underwent needle puncture, the percent of individuals with progression of disc degeneration (35 percent) was significantly greater than control (14 percent). The discography group had a significantly greater incidence of new herniations with the herniations disproportionately occurring on the side of the annular puncture (foraminal and far lateral). No differences in degeneration patterns between the groups at the non-punctured discs (L1-L3) were observed.

Nassr et al.⁴, in retrospective radiographic analysis of 87 patients who had undergone anterior cervical discectomy and fusion, examined the influence of incorrect needle localization in the adjacent disc on the rate of disc degeneration. 17.8 percent of patients had incorrect needle localization with a 22-gauge spinal needle placed above

the planned surgery level. Incorrectly punctured discs had a 3 fold increase in the risk of developing degeneration.

Both the Carragee et al.³ and Nassr et al.⁴ studies bring into question the conclusions from the animal models of Elliot et al.⁵ that suggested significant degenerative changes do not occur with a needle diameter to disc height ratio of less than 40 percent. Both the 22-gauge and 25-gauge needles used in these studies are below the proposed “safe” 25 percent needle:disc height ratio. Korecki et al.⁶ also demonstrated that even small needles (25-gauge) have mechanical and biological consequences in bovine discs.

Are we to believe the above human studies? All of the above studies have limitations including patient selection from a group of individuals that had a history of greater than average risk of disc degeneration and surgical dissection around the studied discs. In vitro and in vivo animal models for disc degeneration providing further insight into the effect of needle puncture on disc biomechanics, degeneration, and cell viability would

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“Recently, clinical studies have been published in the spine literature suggesting that a relatively minor annular puncture has clinical and biological consequences.”

Without Clinical Consequences

predisposed to developing disc degeneration, as there is a natural tendency for the progression of disc degeneration to occur over time.⁶

A second study suggested a three-fold increase in disc degeneration with 22 G spinal needle puncture adjacent to an anterior cervical discectomy and fusion after a minimum follow-up of 21 months.⁴ Many factors may cloud the results from this report, but most obvious is the progressive risk of disc degeneration that occurs at the level adjacent to a fusion.

Interventionalists should seek to determine if any factors inherent in discography might lead to degeneration and not just assume that patients who have discography develop degeneration due to the procedure. Needle size and procedure technique may play a role. The authors of the above study describe the use of a 22 or a 25 G needle technique.¹ Elliott et al.⁷ have noted the importance of needle size (diameter) to disc height as a factor in the development of degeneration after annular puncture in animal models. Needle diameter greater than

25 percent of the disc height may lead to biochemical, mechanical, and subsequent histologic alterations in punctured discs. A smaller sized needle lowers the risk of subsequent degeneration. This finding has been corroborated in another animal study evaluating the histologic changes after annular puncture.⁸ The authors also highlighted the differences between needles utilized, noting mechanical factors relevant to the risk of tissue injury during needle puncture. The findings of this paper suggest that annular defects caused by 22G or 26G needles are reversed during normal repair with annular healing. The often-quoted study by Carragee¹ also does not highlight whether a one-needle technique or a two-needle technique was utilized to access the discs, as

the risk of skin-flora contamination could lead to discitis and degeneration. The difference between the techniques may have ramifications on the findings gleaned from the study.

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“The astute examiner of the Carragee study will ask, how certain are we that patients in the study were not predisposed to developing degeneration?”

Table 1: Needle Punctures Effects on Disc Biosynthetic and Structural Properties Based on Animal Data^{6,7,10-13}

Structural Properties	Biosynthetic
↓ Disc rupture pressure	↑ Cell death at annular puncture site
↓ Elastic stiffness	↓ Production of matrix components (proteoglycans & glycosaminoglycans)
↓ Disc height	↑ Production of matrix metalloproteinases
↑ Leakage pathway	↓ Cellularity
Change in microscale shear strain	Chondrogenic differentiation
Nucleus pulposus depressurization	Collagen II accumulation
Annulus Fibrosus damage	Activation of cytokine pathways

Table 2: Areas for Future Investigation on Needle Puncture and Injectate Effects on the Degenerative Cascade in Human Disc Tissue

Needle gauge
Needle design (e.g. bevel)
Location and direction of needle puncture
Injection pressure
Injection volume
Chemical composition of the injectate
Population vulnerability to needle puncture
Development of repair strategies for annular puncture (e.g. chemical cross-linking & cross-linked scaffolds)

indicate that we should be concerned. Animal models involving disruption of the annulus with a needle are used to study disc degeneration. Annular punctures have negative consequences including changes in biochemical and structural properties, cell viability, and biosynthesis (Table 1). In a bovine model, needle puncture with a 25 gauge needle demonstrated harmful changes in dynamic modulus and creep (i.e. tendency of the material to the form).⁶ Cell viability was decreased at the area of needle insertion. The validity of an animal model in understanding human disc degeneration is still unknown. The cellular composition of animal discs is different than human discs. The nucleus pulposus of rats has a more gelatinous composition and is composed of notochordal cells.⁷

Concerns have also been raised about the effects of the injectate on nucleus pulposus viability. Analgesic discography which involves the injection of local anesthetic has been proposed as a way to increase the sensitivity of diagnostic discography. In an in vitro control study on bupivacaine's effect on rabbit IVD viability, 0.5 percent bupivacaine exerted greater cytotoxic effects on cultured nucleus pulposus cells in comparison to articular chondrocytes, demonstrating 51 percent vs. 28 percent cell death, respectively.⁸ A time dependent response was seen with 0.25 percent bupivacaine. Additional in-vivo studies are needed.

Since disc degeneration is multifactorial, this leads to the next question: "Are certain individuals or discs more vulnerable to the effects of needle puncture?" Furthermore, if this degeneration occurs, does it lead to further pain? Carragee et al.⁹ suggested that discography performed in subjects without pre-existing low back symptoms but with significant emotional and chronic pain problems may experience low back symptoms for at least 1 year following discography.

The studies presented above are concerning. As we continue to investigate the appropriate role for disc diagnostic, repair, and regenerative procedures, we need to continue to further clarify the effects of needle puncture on human IVD health. The IVD is a vulnerable structure that lacks a blood supply, depends on diffusion for nutrition, and possesses poor repair mechanisms. Since a majority of interventional disc procedures are performed by pain physicians, it is imperative that we take a leadership role in examining ways to minimize disc damage. If the degenerative cascade is clinically determined to be activated by needle puncture, additional emphasis needs to be on repairing the consequences to the disc. Table 2 lists areas for future research. This topic will become even more important as we hopefully develop biological therapies for IVD disease, for which delivery depends on annular puncture.

Both authors currently perform discography and the above PRO/CON statements are to bring healthy debate to recent clinical and animal studies implicating needle puncture in the advancement of degenerative disc disease.

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CON

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Disc degeneration is a complex and multi-factorial process that deserves in-depth investigation and review to ascertain if needle puncture is a risk factor for further degeneration. MRI studies suggest that degeneration develops when the decrease in nutrient supply produces inadequate levels for metabolic demand.⁹ The supply interruption leads to degeneration and is heralded by calcification of the hyaline cartilage end plate zone. This altered nutritional status (as opposed to mechanical change) is thought to be responsible for the majority of cases of disc degeneration.¹⁰

Degeneration of discs is seen clinically with a loss of nucleus pulposus disc pressurization, leading to strain at the annulo-nucleo junction.¹⁰ The injection of material into the nucleus of a degenerated disc could logically serve to counteract this pressure decrease that leads to degeneration.

Proponents of the role of discography in causing disc degeneration suggest that a single procedure is responsible for chronic discal changes. The response of an intervertebral disc to a stimulus however, should be evaluated by noting the intensity and frequency of the occurrence.⁸ Basic science studies commenting on creep compression (degeneration) of the disc study the breakdown after multiple, repetitive injections.^{7,8} In discography the disc is typically only punctured once. It is not logical that one injection to a disc at a relatively low pressure can lead to a lifetime of clinically significant degeneration.

The future evaluation of needle puncture on disc health should involve study at the cellular level to determine the effect of an injection of non-irritating contrast on disc cellular structures.⁹ Miniaturized technology can describe pressure and structural changes occurring from an injection. The knowledge obtained may assist in our understanding of what happens at the cellular level during discography.

Let us assume for a moment that needle puncture associated with discography in an isolated clinical setting does lead to degenerated discs as visualized on follow-up imaging studies. What is the clinical significance of the degeneration? The proponents of decreasing needle puncture and discography use have not characterized the incidence and occurrence of prolonged discomfort that results from the procedure.¹⁻³ The presence and the degree of degeneration in a disc also have not been shown to correlate with a patient's symptoms.¹² The end result of such logic proposed against the use of interventional disc procedures that involve annular puncture may lead physicians to abandon these potentially useful diagnostic and therapeutic tools for patients suffering from discogenic back pain.

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Perspectives:

Views on 'Double Crush' Syndrome From a Surgeon and an Anesthesiologist



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The Surgical Viewpoint:

While the concept underlying the double crush syndrome seems attractive, it remains debatable whether or not the condition actually exists and, if it does, whether it has clinical relevance.^{1,2} Much of the investigation of this condition has been done electrophysiologically and the most recent data is inconclusive. For example, Kwon et al³ concluded that there was no neurophysiologic basis to link the electrophysiologic findings in patients with cervical radiculopathy and symptoms of carpal tunnel syndrome. This conflicts

with previous studies suggesting that median nerve compression can co-exist with neuropathic symptoms, clinical findings, and imaging data consistent with cervical nerve root compression.⁴ However, even if a temporal association between cervical radiculopathy and carpal tunnel syndrome can be demonstrated, it by no means indicates that the two sites of nerve involvement are pathophysiologically related, which is the basis of the double crush concept. There is also no evidence to suggest that treatment should be adjusted to take this possibility into account, although this has been proposed frequently in the past.⁵

Although the focus in investigations of the physiology of double crush syndrome has been on electrophysiologic evaluation, diagnosis and treatment of peripheral nerve compression is usually based on clinical assessment. It has been shown that electrophysiologic findings do not contribute in a clinically meaningful way to decisions about diagnosis and treatment in the vast majority of cases of carpal tunnel syndrome.⁶ Therefore, even where there may be electrophysiologic findings suggestive of multiple sites of compression, these may not correspond to the clinical findings and, as a result, it is highly dubious whether these merit intervention. Usually the suspected site of additional compression is proximal in the extremity, either at the thoracic outlet or the cervical spine. If the clinical complaint is one of a sensory disturbance in the hand and this is at least partly due to an easily identified site of peripheral nerve compression, for example at the carpal tunnel or the cubital tunnel, it is clearly a safer, easier and more effective strategy to only treat the more accessible area. In the rare instance in which adequate treatment has failed to address the symptoms, consideration of another

site of nerve pathology should be entertained. Patients with clinically significant cervical nerve root compression will often present with painful dysesthesiae radiating from the neck into the involved area of the hand, which can usually be easily distinguished from symptoms of median or ulnar nerve compression more distally in the limb. When the additional site of compression is at the thoracic outlet, surgical treatment is rarely indicated anyway.

In general, diagnosis should be thought of in probabilistic terms because certainty about most diagnoses will almost never be complete. It is implicit in determining the best management for the patient's symptoms that treatment success will depend in large measure on the accuracy of the diagnosis, and so the condition with the highest probability of explaining the symptoms should be the one to which treatment is directed, at least initially. On this basis alone it is difficult to accept the double crush concept because it implies that multiple site surgery would be required in many or even all instances and this is both impractical and unnecessary. Most surgeons have anecdotally recognized that, even where a double crush phenomenon has been suspected, most patients are successfully treated with decompression of the nerve in one site only. Given this experience, the usefulness of the double crush concept is questionable. In other words, if standard treatment is usually successful, does it matter if there was an additional abnormality identified electrophysiologically before treatment? This finding only has significance if prior treatment proves to be ineffective, which would most likely stem from inaccurate diagnosis and/or the wrong site having been given priority. The idea that all possible sites of pathology be surgically addressed regardless of their significance is simply not tenable. It is entirely appropriate to treat the most obvious cause of the symptoms and to reserve additional, often inherently more complex, intervention at another site for the rare individual who does not improve and has a clear site of additional nerve compression. Obviously this means that a very few patients will end up having undergone more than one intervention, but it also means that the overwhelming majority of patients hypothesized to have a double crush syndrome will be successfully treated with a single, small procedure. Even in the absence of evidence, it seems clear that, for patients with peripheral nerve compression, this is a better approach.

From the standpoint of the anaesthetist administering regional anaesthesia the presence or absence of multiple sites of compression should only be relevant where surgery at more than one site is being considered. Even if the double crush phenomenon is a possibility it is difficult to see how this would have an impact on the provision of a safe, effective regional anaesthetic.

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The Anesthesiologist Viewpoint:



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Nearly 40 years ago, Drs. Upton and McComas coined the phrase “double-crush syndrome” to hypothesize that synergistic neural insults may lead to severe nerve injury.¹ Their study demonstrated that 81 of 115 (70 percent) patients with entrapment neuropathy also had proximal cervical-root lesions. They suggested that proximal compression and subsequent reduction of axonal flow could make the nerve more vulnerable to injury at another site. They also hypothesized that “sick” neurons produce less “trophic” substances and thus are more susceptible to permanent injury from an insult.

Since its inception, the double crush syndrome continues to be a major source of debate in the practice of regional anesthesia. Double crush syndrome has been difficult to prove or refute since nerve injury is a rare and

complex phenomenon. A variety of factors contribute to nerve injury for patients undergoing anesthesia: mechanical factors such as stretch and compression; impaired oxygen supply from tourniquets or vascular conditions; metabolic abnormalities; toxins such as local anesthetics; surgical factors; and patient factors.² A retrospective study by Welch examined 380,680 anesthetics (general and regional) over a 10 year period and found the risk of perioperative peripheral nerve injury to be 0.03% percent.³ Peripheral nerve injury was associated with hypertension, tobacco use, and diabetes. All three of these conditions can affect oxygen delivery and could provide the first crush, predisposing to nerve injury from a second crush in the perioperative setting.

There are several large retrospective studies of patients with preexisting neurologic conditions which suggest an increased risk of nerve injury following regional anesthesia. In a retrospective study of 567 patients with preexisting neuropathy undergoing neuraxial blockade, Hebl and colleagues demonstrated a higher risk of severe nerve injury (0.4 percent vs. 0.008-0.03 percent) compared to previous studies that examined neurologic injury following neuraxial techniques in the general population.⁴ Another recent retrospective study by Hebl and colleagues examined 937 patients with spinal stenosis or lumbar radiculopathy undergoing neuraxial anesthesia.⁵ This study demonstrated an increased rate of neurologic complications of 1.1 percent in this specific patient group compared to historical rates in patients without these preexisting conditions.

Several case reports have also been published which describe patients with preexisting neurologic conditions who develop severe nerve injury after a peripheral nerve block. Hebl and colleagues described a patient who had undergone chemotherapy with cisplatin prior to an interscalene block and developed a severe brachial plexopathy.⁶ Another report described a patient with a previously undiagnosed neuropathy who underwent placement of a femoral nerve catheter and developed prolonged quadriceps weakness.⁷ Lastly, Koff and colleagues, from my home institution, described a patient with multiple sclerosis who underwent an interscalene block and developed a severe brachial plexopathy.⁸ Taken together, these data may signal a cause and effect relationship between preexisting nerve damage and block-related nerve injury.

At my current institution we have done nearly 12,000 ultrasound-guided peripheral nerve blocks and indeed, have seen a handful of severe nerve injuries in patients with acknowledged risk factors. I suspect that double crush syndrome may have been involved in these injuries, and we are in the process of reviewing these cases. It remains to be seen whether double crush syndrome may

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Perspectives on 'Double Crush' Syndrome From Both a Surgeon and an Anesthesiologist

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be better named triple, quadruple, or even quintuple crush, since multiple factors variably align and contribute to nerve injury.

Double crush syndrome influences my practice of regional anesthesia. During my pre-anesthetic evaluation, I perform and document a focused history and physical exam to reveal possible neurologic conditions and deficits that could predispose to nerve injury. If a patient has a preexisting sensory or motor deficit in the area to be blocked, I typically will not offer a regional anesthetic due to the potential for worsening the deficit. However, in patients undergoing amputations that are already suffering from neuropathy, I will still offer regional anesthesia. In this scenario, the risk of nerve injury from the block likely poses no greater risk than the surgery itself. Further, the benefits of regional anesthesia in this demographic can be tremendous. Similarly, in patients with multiple sclerosis, Charcot-Marie-Tooth disease, Guillain-Barré or other generalized neurologic disorders I will not perform a regional anesthetic unless there are major contraindications to general anesthesia. In surgeries that have a high risk of neurologic complications, such as an elbow arthrotomy, I typically only offer post operative rescue blocks so that a neurologic exam can be performed post operatively. Lastly, the consequences of nerve injury from a peripheral nerve block become magnified in specific patients (i.e. professional athlete or concert violinist). Under these circumstances, I counsel these patients against peripheral nerve blocks. Although subtle neurologic

deficits are more common than severe injury after regional anesthesia, the impact of even a subtle deficit could be professionally catastrophic.

In summary, nerve injury occurs in regional anesthesia and preexisting neurologic deficits and diseases appear to be risk factors. I do not offer nerve blocks to all patients. A careful evaluation of the risk and benefits helps guide my decision making.

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