

Intraneural Injection – Is it bad?

(Subtitle: *Intra fascicular injection* is everything).

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INDEX

- Introduction
- Background to discussing intraneural injections as cause of nerve injury.
 1. Are all needles and nerves equal?
 2. Are all nerve block drugs equal?
 3. Types of intraneural injection.
- The evidence that intraneural injections occur.
 - A. Origin of the theory that pain occurring with nerve block injection indicates nerve injury.
 - B. Does a signal of pain with nerve block injection always indicate a disaster, and does lack of pain with nerve block injection guarantee safety?
 - C. How close to the nerve does paresthesia technique of nerve location bring the needle?
 - D. How close to the nerve does an electrostimulation technique bring the needle?
 - E. Can using a nerve stimulation guided technique prevent intraneural injections?
 - F. Can using ultrasound guidance techniques prevent intraneural injections?
- The outcomes of intraneural nerve block techniques injections
 - i. Are intraneural injections harmful?
 - ii. Do intraneural injections cause high intraneural pressures?
 - iii. Case reports of non-anesthesia accidental intraneural drug injections.
 - iv. Why do some nerve block injections cause sharp distal radiating pain, or sharp localized pain at the point of injection?
- Evidence and experience of visualized intraneural injections from the era of ultrasound-guided nerve blocks.
- Concluding discussion.

INTRODUCTION

Regional anesthesia creates a rare circumstance where drug has to be applied direct to the target tissue. Local anesthetic drugs have low potency for blocking nerves and low selectivity for nerve tissue. Therefore we have to inject local anesthetics in high concentrations very specifically onto a targeted nerve in order to achieve a sodium channel block of that one targeted nerve only. The injection must be sufficiently close to that nerve that the local anesthetic drug can bathe the nerve. The exact closeness to the needle to the nerve tissue is a critical factor in achieving successful nerve block or not. Furthermore, the intra-axonal concentrations of local anesthetic drug achieved will depend on how long the injected drug lingers in the injection before dispersal into the systemic circulation.

Needle insertion during regional anesthesia was a blind technique for 100 years. Experience revealed nerve blocks to be largely safe, but rarely a nerve injury occurred ASSOCIATED with the nerve block. In the absence of a discoverable alternative explanation for the nerve injury it is usually assumed the nerve block somehow caused the injury. Simple logic invites suggestion that injections into nerves are not a good thing. Observation also shows that some patients experience unusual pain during performance of a nerve block. Simple logic invited assumption that the pain indicated something was wrong with the technique of nerve block injection. Some limited data has shown *correlation* between patients who have nerve deficits after surgery and who had severe pain during nerve block^{1,2}. This correlation could be cause and effect, and has been popularly interpreted as such.

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However it could also be that the pain occurring during the injection of local anesthetic is (i) unrelated to the drug injected, or (ii) simply associated with a third factor such as an *underlying nerve disease* that manifested itself as (a) unusual pain during the block and (b) as a progression of the nerve illness to revealed nerve deficit and for which the actual nerve block had no role in the progression. Either way there is NO proof of cause and effect from an observed pain during injection and a later observed nerve function deficit.

Regardless from late 1970s onwards in regional anesthesia it was generally concluded that pain during nerve block and later nerve deficits were linked. In particular it was Selander who encouraged as far as possible the avoidance of paresthesia during nerve blocks as he regarded this as a sign of intra-fascicular needle placement^{2, 3}. This was in particular from his study of 533 patients undergoing axillary blocks where no significant differences were found between patients who experienced paresthesia during injection or the nerve block success or nerve injury outcomes. Selander despite his own study's inconclusive negative result, felt the need to still condemn using paresthesia as a nerve block technique guide. Selander believed paresthesia could only result from intraneural injection, and he also believed intraneural injection was damaging to nerves. Selander's belief satisfied the "logic test", as weakly scientific as that can be in some circumstances, and fitted other anecdotal evidence at hand. The following three point concept was developed which became dogma from 1980 into the new millennium;

- 1. Intraneural injection was always damaging.**
- 2. Severe pain seen during performance of a nerve block was evidence of intraneural injection.**
- 3. Nerve injury could be avoided by avoiding intraneural injection that could be avoided by repositioning the needle if a patient reported severe pain during needle placement or during drug injection.**

There were ramifications to these beliefs. This all required that the patient be awake in order to report such pain. This meant no nerve block could be safely done under anesthesia. It is observed that in medicine the strongest opinions exist only when there is as little evidence to oppose the dogma as to support the dogma.

BACKGROUND TO DISCUSSING INTRANEURAL INJECTIONS AS A CAUSE OF NERVE INJURY

1. ARE ALL NEEDLES AND NERVES EQUAL?

Much confusion has also occurred in this debate because little distinction was made between sharp needles used in animal study and blunt needle used in practice. Also evidence of injury in the laboratory was never correlated with clinical outcomes. So many wild presumptions were made. Furthermore early researchers did not factor in the differences between rat (small animal) virtual monofascicular nerves and large mammals like humans with large poly-fascicular nerves. Dag Selander and others did research on needle tip design and intraneural injections^{4, 5}. Selander studied 60 rabbit sciatic nerves inserting either sharp 14⁰ bevel needle (long bevel) or a blunt 45⁰ bevel needle (short bevel). He demonstrated a number of things.

1. It was near impossible to impale a nerve fascicle in its natural tissue seat with a needle, and retain the tip within the fascicle during injection.
2. True intrafascicular injection when artificially achieved in vitro only, did rupture the fascicle. It was necessary, in the laboratory, to hold the rat nerve fascicle in an immovable way in order to force the needle into the nerve.
3. Sometimes an injection occurred within the fascicle and then damage was great.

Sharp needles were needed to intentional puncture fascicles in these experimental conditions. Rice, in another study, artificially claimed to validate Selander's work partially in an artificial situation laboratory study showing artificially created forced intrafascicular injections with blunt needles damaged the fascicle more than sharp needles⁶. Hirasawa also confirmed one other of Selander's observations that intrafascicular inserted needles parallel to axon direction regardless of



needle bevel type were less injuring⁷. Reina's study sort of validated Selander's work in a postmortem human electron-microscopic study showing shallow bevel needles for a given force tended to indent nerves without penetration, whereas sharp needles penetrated the epineurium readily⁸.

These laboratory studies were however all contradicted by a series of 883 sharp needle peripheral nerve blocks were done on human children which resulted in zero nerve injury⁹.

In summary, in humans with multi-fascicular nerves the fascicles tend to slide aside when pushed upon by a sharp needle and more so when approached by blunt nerve block type needle. So although needle can be inserted into the gross structure of a human nerve relatively easily, achieving intrafascicular penetration is much harder especially with a blunt needle. Also other evidence suggests penetration of a fascicle with sharp needle is associated with recovery in weeks of the nerve, if a discernable injury should occur. Likely sharp

needle injuries are more often undetected due the small size of tissue one fascicle represents.

Figure number one shows large human nerves although seemingly monofascicular in structure very close to the formation of the nerve, the nerves very soon become more typically MULTI-fascicular. Figure two shows a typical bi-

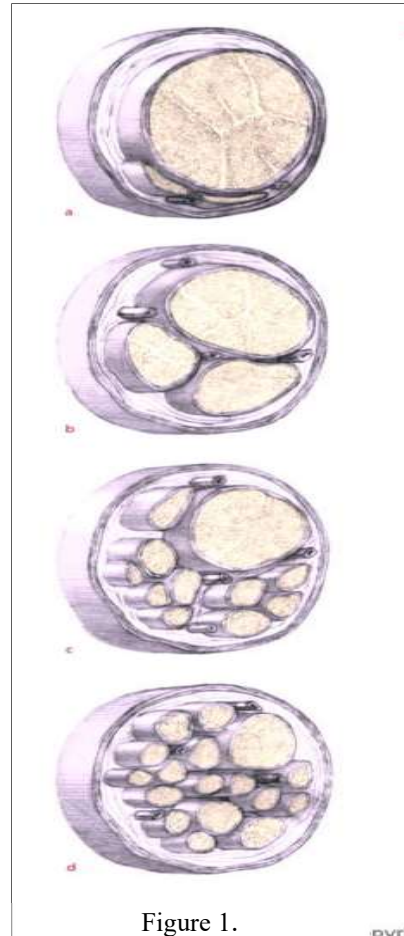


Figure 1.

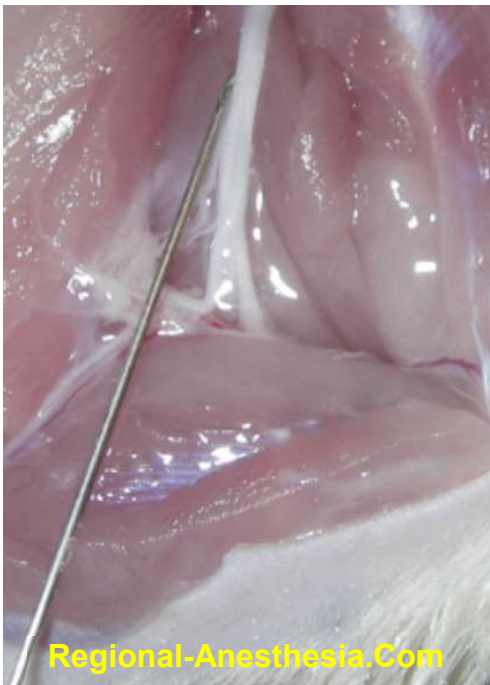


Figure 2.

fascicular rat sciatic nerve. A forced intrafascicular rat injection is very different to an INTER-fascicular injection in humans. Extrapolating rat nerve injection data to human clinical nerve injection needs to therefore be very guarded.

Figure number three is of a human sciatic nerve with in intraneural, interfascicular needle. Notice how across species of different sizes fascial are relatively similar in size. As the species gets larger and has larger nerves, the gain in nerve size is due to increased axons, but contained in increased number of fascicles. The number if axons within a fascicle needs to be



Figure 3.

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relatively constant for physiological reasons fascicles between mammal species.

2. ARE ALL LOCAL ANESTHETIC DRUGS EQUAL?

Some of the earliest case experiences of the association between nerve block, pain on injection and outcome involved drugs no longer in use. This may invalidate the evidence of those case reports in current context. For examples esters and tetracaine popular in earliest days are now known to be more neurotoxic than current popular amide drugs in popular concentrations^{10,11}. Preservatives such as sodium bisulphate were popular before their neurotoxicity was discovered and their presence in a drug solution is not even mentioned in earliest case reports.

Similarly addition of epinephrine and alkalization enhance nerve toxicity with lab-animal intrafascicular injections. Alkalinization increases bleeding potential^{Error! Bookmark not defined.}. As early techniques when paresthesia nerve location was the standard, using sharp needles it is likely *intrafascicular* injections occurred worsening the risks even more. Conversely modern blocks using blunt needles although maybe still allowing intraneural injection, will make intrafascicular injection very unlikely because of the needle bluntness. When locating nerves depending on paresthesia only, it is easier to elicit paresthesia if the needle has sharp (cutting) tip, rather than with blunt tip needle. This is added reason to be extra cautious when interpreting rat nerve regional anesthesia studies performed before about 1990 after which blunt needles for electrostimulation became more popular. Thus drugs injected perineural or interfascicular may act different to drugs injected intrafascicular.

Selander showed that local anesthetics are generally as benign as saline unless injected intrafascicular¹². He however never tested with isotonic salt solutions were different to standard local anesthetic with intentional intrafascicular injections. He in particular showed that the physical anatomical disruptions *intrafascicular* injection itself was the major factor, but when the highest concentration of local anesthetics were used and added adrenaline (epinephrine) was used a slightly higher rate of injury occurred than when just 0.9% saline was injected.

Old case reports must be interpreted contemporaneous to their era's general practices, including the method of nerve localization, needles used drugs injected and additives within the drug solutions.

3. TYPES OF INTRANEURAL INJECTIONS.

Intraneural drug can be injected either in between fascicles under the perineurium (*inter-fascicular*), or within a fascicle under its epineurium (*intra-fascicular*). In general intrafascicular injections are destructive in animal research. Selander never ever showed inter-fascicular or sub-epineural injections to be harmful. Unfortunately it was decided by others that all injections anywhere within the epineurium would be equally harmful. The correct conclusion should have been that it is not an intraneural injection that is necessarily harmful, but an intrafascicular injection that is more likely harmful, but also not necessarily so.

The literature in just over the last decade has become abundantly full of ultrasound and CT scan diagnoses of intraneural gangliomas which may be incidental pathology that interacts with tourniquets, patient surgical positioning, sustained blood pressure changes etc. which may cause neuropathy unrelated to a nerve block. This would seem another reason for early sonographic examination of any acutely neuropathic nerve as soon as possible after recognition of suspected problems.

The evidence that intraneural injections are common.

- A. Pain and nerve block injections.
- B. Does pain signal disaster and lack of pain safety?
- C. How close to the nerve do paresthesia location techniques bring the needle?
- D. How close to the nerve is the stimulator needle?
- E. Does using nerve stimulator stop intraneural injections?
- F. Can using ultrasound guidance techniques prevent intraneural injections?

A. PAIN AND NERVE BLOCK INJECTIONS

Scientific articles and reviewers have not all used the same terminology or even the same meanings for same terms. *Paresthesia* has generally meant any sensory perceptions distal to the point of needle insertion that is not painful. It is typically a mild sensation with variable descriptions like tingling, or “electric” or a “pins-and-needles” type sensation. It can be subtle enough that minimal sedations makes the patient unaware of the paresthesia. Other writers specifically state *pain* while others use the word paresthesias referring to pain. Patient paresthesia is a common experience during nerve blocks and pain is a rare experience during awake nerve blocks. This makes making a scientific conclusions hard when comparing older scientific reports or authoritative books.

It was, and sometimes still is, established basic regional anesthesia teaching dogma that severe pain experienced upon nerve block injection indicates nerve injury is occurring and cessation of injection was recommended. It is also said that fleeting paresthesia is fine but a sustained paresthesia despite the needle being held steady is worrisome. It has also been said that paresthesia during injection is bad. The evidence to support these beliefs is sparse.

A case report by Barutell in 1980 related a lady experiencing severe sharp pain during an 8 ml volume interscalene block¹³. This patient became horse, unconscious and apneic. She subsequently had permanent nerve deficit over three nerve roots (C7, C8 and T1). This case report was used as evidence for needing to perform all nerve block only on awake patients and was used as evidence that intraneural injections cause severe pain. This case clearly could not have had three intraneural injections from one injection. So that refutes the claim that it was an intraneural injection. Alternate plausible explanations such as a wrong drug and tissue toxic drug was never considered. This author guesses a wrong drug was injected, and likely being thiopentone. Thiopentone typically causes immediate severe pain, is severely tissue damaging often causing subcutaneous necrosis when it extravasates, and could also explain the altered consciousness likely from partial intravenous injection resulting from the patient moving upon injection. It can thus be argued had injection been terminated after the first milliliter of injection, perhaps a less severe result could have occurred. This is, all considered, an extreme and rare event to argue for all nerve blocks being done only awake patients. This is also no evidence of link between local anesthetic intraneural injection, pain and neuropathy.

Labat stated in his 1922 translated work of Pauchet of 1921 and reprinted in 1984 by Adriani that intraneural injections are painful and induce syncope and often produce postoperative neuralgia¹⁴. These comments are not validated by evidence or case report details and could represent limited observations of nerve blocks done under direct vision after surgical exposure in pioneer days using drugs no longer available for nerve blocks, e.g. cocaine or others. Moore and Pauchet/Labat’s comments entered folk-lore but now need to be reviewed under modern scientific eyes.

Selander in his axillary block trial found a 1.9% incidence of neuropathy that was likely nerve block associated². Of note all were patients who had experienced paresthesia, sharp needles were used and mepivacaine with adrenaline (epinephrine) too. The Paresthesias were not painful. Selander however regarded those paresthesia as meaningful and emphasized the need for patient to be conscious so as to be able to communicate experiencing paresthesia. Selander, from Europe, strongly criticized paresthesia based nerve block techniques. Paresthesia nerve blocks were however strongly entrenched and trusted in some countries such as the USA and the “paresthesia cautionary” became later redefined to mean a radiating painful paresthesia to distinguish it from the intentional little anesthesia that so many believed in as a legitimate anesthesia technique.

Dag Selander stated that “*painful paresthesia on injection indicates intraneural needle position – worst intrafascicular*”²¹. No evidence is lead to support this pivotal statement.

B. DOES PAIN ALWAYS SIGNAL DISASTER, AND THE LACK OF PAIN SIGNAL SAFETY?

There are abundant case reports of bad nerve block associated outcomes that were done awake without evidence of pain on injection, but where a nerve deficit developed afterwards. Bonner reported an unremarkable sciatic nerve block done on a fully un-sedated 59 year old lady who experienced no pain during the procedure but subsequently lost nerve function for 12 months¹⁵.

Sala-Blanch described intraneural sciatic nerve injection without any pain experience and without any consequence¹⁶. Two patients were studied prospectively. In one a needle was placed at the sciatic nerve with a minimum Stimulating current (MSC) of 0.3 mAmp and the other with a MSC of 0.56 mAmp. Those were pre-chosen MSCs. In a protocol of serial injection, use of contrast and catheter placement the following was observed utilizing CT scans. There was clear evidence in each case that the catheter was intraneural, there was contrast and even incidental air-bubbles intraneural. The flat nerve expanded to a round shape after injection. Most contrast was seen outside the nerve and had spread a total distance of 10 cm about the injection point. In each case minimal sedation and analgesia was used and the patients experienced no unusual discomfort, the blocks lasted a standard duration for the doses and drugs selected and there was no ill consequence relating to the nerves. The conclusion has to be that intraneural catheter placement is common and may be the norm as these cases were entirely routine except for the use of contrast mixed with local anesthetic and the examination by CT scan.

The large prospective French study of Auroy covering 21 278 peripheral nerve blocks revealed 4 neuropathies associated with nerve blocks¹⁷. Unfortunately Auroy did not specify separately whether paresthesia or pain occurred with the performance of the peripheral nerve blocks. He grouped all comments on pain and paresthesia combined with neuraxial block which represented the majority of nerve damage complications.

C. HOW CLOSE IS THE NERVE TO THE NERVE DOES THE PARESTHESIA NERVE LOCATING TECHNIQUE BRING THE NEEDLE?

Elementary logic has to assume that the needle has to at the least be touching the nerve when paresthesia occurs. At the most the needle could even be within the nerve before paresthesia is elicited. It is further well established in practice that it is necessary to perform paresthesia blocks with sharp needles in order to more successfully induce paresthesia. That suggest that many if not most paresthesia based, blind nerve blocks result in an intra-neural needle tip position. This question could be rephrased as how many paresthesia technique blocks are associated with intraneural needle tip positions and injections?

A nerve trunk contains numerous fascicles which contain either all sensory, or all motor axons. A needle agitating a motor fascicle cannot not cause sensations. Thus the needle will need repeated repositioning until a sensory fascicle is agitated if finding paresthesia is the goal. A sensory fascicle lying deep to a motor fascicle require intraneural penetration of the nerve to reach the sensory fascicle.

Paresthesia blocks were also claimed to producer faster onset nerve blocks than nerve stimulator guided nerve blocks¹⁸. This is perhaps because paresthesia guide nerve blocks are more likely to result in intraneural needle positions. No study ever showed paresthesia guided nerve injections produced more nerve injuries than nerve stimulator guided nerve blocks. That would be despite a more likely chance of intraneural injection with the paresthesia technique.

Dag Selander prospectively studied 533 patients undergoing axillary blocks either with an intentional paresthesia technique or a perivascular based technique². There was a 100% paresthesia incidence in the paresthesia group and an unintentional 40% incidence of paresthesia in the perivascular group. There were associated nerve symptoms in both groups and significantly more in the 100% paresthesia group. The interpretation is that a sharp needle based in paresthesia nerve block



technique with its inherent greater likelihood of penetrating fascicle was also the more likely one to cause persistent post-surgical nerve symptoms.

The Selander paresthesia group (100% paresthesias) has 5 times more post-operative nerve deficits, than the arterial pulsation group who had 40% paresthesia incidentally. This was taken as evidence that intraneural injections (more likely with paresthesia) increase the risk for nerve injury. This however must be interpreted in the light of sharp needles having been used. This thus cannot be related to nerve stimulator techniques where blunt sheathed needles are used which don't easily penetrate a fascicles not cut axons. That may be more related to current blunt needle practice, and lastly the trial may be incorrect because of methodological flaws, anyway. The Plevak study reported a similar trend¹⁹.

Daniel Moore in a 1994 editorial defending paresthesia techniques said “ *We believe there is no significant data to demonstrate that eliciting paresthesia (likely intraneural injection) results in neuropathy*”*We believe that authors should not draw conclusions relating to clinical practice and which may have significant medico-legal connotations*²⁰.

Selander later softened his viewpoint, and concluded in 1999 with a middle of the road statement that “*when paresthesia techniques are used, paresthesia should be elicited gently*” as this would avoid intraneural injections²¹. No evidence was offered as to what “gentle” was and how it made a difference.

The conclusion that paresthesia techniques are higher risk techniques for intraneural injections to happen (which *supposedly* cause nerve injury) is supported in studies. That fact of increased intraneural injection incidences is however not matched with good supporting evidence of increase incidences of nerve block associated nerve injuries.

The unrelated studies of 2001 and 2002, for Choyce and Urmey respectively, each presented mutually supporting evidence, and strong evidence that about half of all interscalene nerve blocks performed by paresthesia technique or nerve stimulator technique resulted in intraneural injections. They clearly showed the heterogeneous nature of the distribution of sensory and motor axons within the large human interscalene brachial plexus structures. It would be a random event whether an advancing nerve block needle made first contact with a sensory fascicle or a motor fascicle. If it was the wrong type of fascicle (sensory or motor) for the particular nerve localizing technique (paresthesia or electrostimulation), and that the needle would need to be advanced until it reached the specific target type of fascicle. First contact with the desired nerve response could occur equally intraneural or at the nerve surface. No patient in the studies had a painful experience nor a nerve injury as result of intraneural injections of drugs. We can call this the Choyce and Urmey *paresthesia and motor location discrepancy*.

A further conclusion is that if the paresthesia technique was associated with lower MSC than what is the standard acceptable electro-location goal of 0.5 mAmp then the paresthesia technique likely ends up putting the needle tip intraneural in perhaps 70% of times. Conversely, the observation that 30% of the paresthesia cases had no motor stimulation at 1.0 mAmp were those motor needle they would have been advance further and likely ended intraneural in 30% of cases. The trial thus doubly suggests both paresthesia and electro-stimulation location methods are associated with a very substantial amount of intraneural injections, and paresthesia being the more likely to be intraneural due to use of the sharper needle.

If paresthesia techniques are associated with higher risk for intraneural injection that should correlate with higher block success rates and faster onset of nerve blocks. Paresthesia nerve location technique proponents strongly claimed this. If this were true it would further support the suggestion that paresthesia techniques are mostly intraneural injections. Two trials using slower drugs like bupivacaine support this. Horlocker showed a highly significant faster block onset for the paresthesia technique over the transarterial technique with axilla blocks using bupivacaine local anesthetic.

D. HOW CLOSE TO THE NERVE DOES THE ELECTROSTIMULATION GUIDED TECHNIQUE BRING THE NERVE BLOCK NEEDLE?

Initial researchers simply positioned the needle at high current until they got the maximum size motor response. They then re-positioned the needle to find the position of lowest current giving the same maximum response^{22, 23}. If that lowest obtainable current was 0.5 mAmp the block was generally observed to be successful and if the lowest current obtainable current exceeded that the block had a high failure rate. A minimum stimulating current (MSC) of 0.5 mAmp was then prescribed as the target to achieve before injecting local anesthetic²⁴. This suggest that if the MSC is 0.5 mAmp or less, then the needle tip is at least touching the nerve, but being within the nerve cannot be excluded.

Joe McNeal in a book chapter in 1996 said nerve stimulators had no scientific evidence that they diminished nerve injury over the incidence seen with paresthesia techniques and he recommended locating the nerve first at a current of 3 mAmp to find a desired muscle twitch and then fine adjusting the needle to get the same twitch with a minimum stimulating current set between 0.5 and 1.0 mAmps (200 ms pulse width)²⁵. There was no concept yet, at that time, that a needle could be intraneural nor of recognizing such a fact.

A very popular test for supposed nerve safety in the electro-stimulation era preceding the ultrasounds rise in popularity was the "Raj test". The "Raj test" stated that after locating the nerve if the twitch was lost after injection of 1 ml of lidocaine (lignocaine), which was evidence of the needle being of sufficiently close proximity for the block to be successful. He was unclear on the meaning of failure to lose the twitch after injection in 1980²³. Raj in 1980 studied five dogs' sciatic nerves using unsheathed spinal needles.

Another assumption often made in earlier times was that a nerve was a homogenous structure that (i) could be stimulated to elicit a motor twitch equally with needle approach from any direction at identical distances, and (ii) the entire nerve was stimulated. Early in the new millennium this was commented on by Heble and Horlocker in an editorial with Choyce's axillary nerve stimulation study^{Error! Bookmark not defined.} where they state "*These findings suggest an inconsistency of elicited motor responses despite the needle presumably being near a nerve. Therefore, the illusion that the nerve stimulation allows clinicians to approximate neural structures without the risk of mechanical trauma must be abandoned*"^{Error! Bookmark not defined.} Choyce did axillary blocks with sharp unsheathed needle and after establishing paresthesia then stimulated the needle electrically to establish whether a motor response could be achieved and also at what current. In 23% of the patients a current higher than 0.5 mAmp was needed. The considered minimum stimulating current compatible with effective safe nerve blockade was then considered to be 0.5 mAmp.

William Urmey did a related study in the interscalene brachial plexus and too achieved paresthesia when electrical stimulation of the nerve failed to elicit a twitch in some patients at a current considered a correct minimum stimulating current²⁶. It was a poor study with a critical change from unsheathed sharp needles to blunt sheathed needles half way through but without separation of the data groups. The results however were that only 30% of patients showed a motor twitch at currents up to 1.0 mAmp. The letter discussions that followed were highly emotional and were vigorous. Debate focused largely on defending personal viewpoints with respect to the merits of paresthesia and electrostimulation nerve location techniques. There was virtually little focus on interpreting the clear paresthesia-electrostimulation evidence being evidence of a likely high intraneural injection incidence^{27, 28, 29}. The letter writers were incredulous, questioned the methodology, and made accusations of misinterpretation of the results etcetera. Urmey said in a letter response "*In life you are forgiven your lies, but heaven help you if you attempt to tell the truth*". In addition he said "*It is denial on our part as anesthesiologists to perpetuate and cling to folklore that we can deliberately aim and advance needles at large superficial nerves gently sneaking up on them and never making nerve contact*"³⁰. Urmey also humbly wrote in his response "*We simply described a phenomenon*" and said further "*We do not completely understand nor pretend to definitively explain...*" the paresthesia electrostimulation discrepancy

E. DOES USING A NERVE STIMULATOR GUIDED TECHNIQUE PREVENT INTRANEURAL INJECTIONS?

An early assumption of nerve stimulator proponents was that paresthesia techniques were mostly associated with intraneural injections and that nerve stimulator techniques were not.

There was little quality early research to suggest how low a MSC would indicate intraneural injection before Voelckle in 2005³¹. His modest study based on examination of 5 pigs and 10 nerves looking at histological evidence of inflammation 6 hours after nerve block, suggested that MSCs under 0.20 mAmp correlated with intraneural injection and MSCs between 0.3 and 0.5 mAmp did not.

A related study done by Karaca (2003) studied 64 patients when performing interscalene blocks with targeted minimum stimulating current (MSC) of 0.2 to 0.4 mAmp³². Block success was 95%. No patient spontaneously demonstrated discomfort or reported paresthesia during block performance. On questioning 55% reported a dull electrical tingling upon nerve electrostimulation location with muscle twitch, and 75% reported a mild distally radiating paresthesia during drug injection. No complication occurred within the group.

Shah's sciatic nerve injury case report occurred despite placing a needle onto the sciatic nerve using MSC of 0.38 mAmp³³. Tsui has in an exposed pig nerve model documented an electrical resistance offered by the epineurium. Measured resistance was 12.12 (+- 1.79) kOhm outside the nerve and 23.23 (+- 4.45) kOhms inside the nerve³⁴. Whether this pilot study could translate into a practical effective technology is undetermined. It is unlikely considering the variety of nerves and structures and their different anatomy at every point of their length and other fascial structures (electric current resisters) around nerves, that sensitive thresholds could be described to differentiate intra- and extra-neural needle placement. It is also additionally unlikely as nerve stimulation concerns electrical field density which is unaffected by resisters and modern nerve stimulators are constant current generators.

Tsai (2008) studied exposed pig nerves³⁵. At distances of 2 to 20 mm from the nerve currents of 2 mAmp failed to induce a sciatic nerve specific twitch. They could only elicit sciatic nerve specific responses with needle to nerve distances went down to 1 mm away from the nerve at minimum stimulating currents (MSC) of a mean of 0.92 mAmp (range 0.24-1.48). With the needle against the nerve (0 mm millimeters away) the MSC was 0.39 mAmp mean (range (0.15 – 1.40). when the needle was intraneural the MSC was mean 0.56 mAmp (range 0.08-1.80 mAmp. In 87% of intraneural placements a MSC was under 0.40 mAmp.

If one then assumes that a nerve block will be successfully injected only if the needle is against the nerve at the least as that excludes the presence of an intervening fascia to divert injected drugs, then a MSC of 0.39 mAmp, or more practically **0.4 mAmp** must always be aimed at. Once a needle position is taken that achieves MSC of no more than 0.4 mAmp it can be assumed the needle the needle could also be within the nerve. There is no MSC that can exclude the needle tip being within the nerve and guarantee the tip is close enough to ensure nerve block success. This proved electro-stimulation guided nerve blocks will always be associated with a large fraction of cases experiencing intraneural nerve block injections. The world experience of nerve stimulation guided nerve blocks runs tens or more millions of cases with virtually no practitioner observing pain upon injection nor postoperative nerve injuries despite perhaps 505 of all injections having unknowingly been intraneural.

F. CAN USING AN ULTRASOUND TECHNIQUE RELIABLY PREVENT INTRANEURAL INJECTIONS?

In the opinions of Perlas and Chan^{Error! Bookmark not defined.} and of Sauter⁵¹ there is too much *operator dependence* in ultrasound image interpretational skill required to trust the ultrasound to be absolutely a guide to exclude intraneural injection. In fact all case reports and colleague anecdotes of ultrasound observed intraneural injections are made once injection had already commenced. This implies intraneural needle placement was not recognized at the time of last needle position adjustment. Furthermore the observation of intraneural injection itself is dependent on optimal images which are only rarely obtainable and only for superficial nerves. Also there are many published and anecdotal reports of intraneural injection occurring and only being recognized at a later upon studied review of initially recorded videos of the ultrasound guided procedure, and no ill consequence having



occurred. With deeper nerves such as sciatic, femoral and particularly infraclavicular blocks it is rare to recognize intraneural injection if not impossible to recognize or exclude.

In conclusion ultrasound guidance cannot assist in reliably preventing intraneural injection in all cases.

Outcomes of intraneural injections

- i. Are intraneural injections harmful
- ii. Do intraneural injections cause high intraneural pressures?
- iii. Evidence from accidental non-anesthetic intraneural injections
- iv. Why do some nerve block injections result in sharp radiating pain or marked discomfort at the injection point and others not?

i. ARE INTRANEURAL INJECTIONS HARMFUL?

This is the key question. Indirect broad experience evidence supports the general answer of NO. Urban studied 508 cases and found no evidence that paresthesia techniques caused more neuropathy problems than other techniques³⁶. Dag Selander studied 533 patients, observing 40% incidental paresthesia in the non-paresthesia group, but finding only a trend to more post-surgical neuropathies but without statistical difference in the intentional paresthesia group². He did however casually observe all the patients who had neuropathy had had painful paresthesias during the block. This trial has been much quoted but is limited in scientific perfection, and is poorly validated by other work. In retrospect the fact the paresthesia was painful, suggest there existed prior nerve dysfunction and neuropathic pain.

Gentili injecting various local anesthetics with and without added epinephrine (adrenaline) epineural (extra-fascicular) in test animals found no evidence of nerve damage at 10 days afterwards¹¹. Gentili also studied non-local anesthetic drugs occasionally accidentally injected into the sciatic nerve during deep buttock injections³⁷. He found interfascicular injection, for the study drugs, was minimally damaging, but intrafascicular injection was damaging. That observation does not differentiate whether the drug itself was injurious, or the mechanical effects of fascicle distortion by the injected fluids made the difference. Selander did similar research injecting intraneural fluid, being either interfascicular or intrafascicular, and found no injury from interfascicular injections but did find some modest injury evidence with intra-fascicular injection particular with highest concentrations of some drugs and especially if epinephrine (adrenaline) was added³⁸. Gentili extending his study to intraneural injections (presumably interfascicular) found micro hemorrhage evidence and some myelin changes in the exposed nerves but no axonal damage. Of note, all the changes seen fully regenerated later¹¹. This was not correlated with any long term outcome, but it can still be tentatively assumed the study did not show evidence of permanent injuries.

One case report of two consecutive patients who underwent axillary blocks by the same doctor each time using lidocaine, tetracaine, sodium bicarbonate and epinephrine (adrenaline) and blunt needle nerve stimulator technique, developed alternatively a median nerve and an ulnar nerve palsy afterwards. In each case the block was performed uneventfully without unusual patient discomfort. The nerve fallout in each nerve was substantial for that nerve. Also in each case the injured nerve showed an axilla Tinel sign. The patients also had nerve conduction studies done which localized the injury level to the axilla. In each case the axilla nerve was surgically explored some months later at the site of block. The one nerve explored was scarred internally for 2 cm segment in the axilla. It is likely the injured nerves had intraneural injections and probably interfascicular. It is also likely there were pre-existing patient factors and the combined use of alkalization with epinephrine were critically additive. It is unknown if there were bleeding risk such as aspirin consumption as well or not. A wrong drug or additive error is unlikely as the other axilla nerves were unaffected. The key points for this discussion from these cases is (i) that nothing done wake alerted to any future problems, and (ii) there are potential additional factors that may have prevented injury in another patient with identical nerve block injection technique. In other words the answer is not simplistic.

Gentili in 1980 when reviewing the various substances accidentally injected into nerves in case reports and research studies, re-emphasized that a bigger factor than what substance was injected, rather



than whether it was injected intrafascicular or not that determined the bad outcome³⁹. He also emphasized that nerve regeneration mostly occurred in the research studies.

Sala-Blanch documented two intraneural sciatic catheters with full clinical use and no consequence¹⁶. Russon in 2007 described an ultrasound observed intraneural musculo-cutaneous nerve injection with fully normal outcome⁴⁰.

ii. DO INTRANEURAL INJECTIONS CAUSE HIGH INTRANEURAL PRESURES?

Selander show intrafascicular injection raises the endoneural pressure to 700mm Hg and that returns to a safe level after 15 minutes⁴. Hadzic did a study in exposed dog nerves. He used 25 g sharp point needles which easily penetrated fascicles. He unfortunately did not measure actual intraneural pressure but measured line pressure proximal to the needle. Pressure measured would then also reflect resistance in the flow line distal to the measurement point and this excludes knowing exact intraneural pressures. His drug delivery system and needle had base line pressure of about 90 mm Hg needle exposed to air at a drug flow rate of. He observed in 7 dogs' sciatic nerves a mean "interfascicular pressure" (Hadzic's term was perineural) of 206 mm Hg mean. In the intrafascicular group (Hadzic's term was intraneural) and a pressures ranging from peaks of 1293 to 2483 mmHg pressure when flow was started. Drug flow rate was 240 ml / hour (4 ml per minute). Not every intrafascicular injection resulted in very high pressure although most did. Also of note the pressure all had an early high peak and then a rapid fall in 20 seconds to plateaus around 206 mm Hg. The rapid fall may reflect fascicular ruptures or needle displacements. Only the animal whose pressure peaked over 1293 mmHg got nerve injuries. Hadzic was puzzled why some of the high pressure intrafascicular injection animals got palsy and others not. It is possible the non-paralyzed dogs had sensory intrafascicular injections and thus no motor function injury. Detecting sensory loss in a dog is likely hard to do. It is expected only the fascicle injured would manifest injury beyond the pharmacological block. Hadzic believes it is the combination of high pressure and intrafascicular block that is injurious and wondered whether slow injection rates would be safer. This is unlikely as it is probably the physical distension and internal disruption of the fascicle by volume that is injurious and that volume delivered at any clinically practical slow rate would still cause damage. The flow rate (4 ml / min) used in the study would take 10 minutes to inject 40 ml and at flow rate of say 2 ml / min would take an impossible 20 minutes of keeping both needle and patient still. It is also curious what the "opening pressure" mechanism were for the intrafascicular injections.

Vuckovic, a Hadzic associate in the Hadzic paper, published identical results in a Bosnian medical journal^{41, 42}.

The Shah case report of sciatic nerve block injury case report is intriguing³³. A stimulating needle was located in proximity to the sciatic nerve with Minimum Stimulating Current (MSC) of 0.38 mAmp with muscle responses of the common peroneal nerve portion. That MSC suggests intraneural nerve block. Initial injection met great resistance which was forcibly overcome with 1 ml of injection where-after the remaining 29 ml injected easily. This suggests intrafascicular injection with fascicular rupture. No unusual patient discomfort was noted which suggest a motor fascicle was injected. The drugs were mepivacaine, with added adrenaline (epinephrine), and sodium bicarbonate. There is evidence the additives compound neurotoxicity of local anesthetics. The patient subsequently had common peroneal nerve fall out that was both sensory and motor in the zone of the common peroneal nerve. The mixed sensory and motor fall out suggest more than one fascicle was injured. At 48 hours neurology tentative opinion was one of neuropraxia (nerve conduction studies unknown). She later developed distal radiating pain in the common peroneal nerve distribution. Nerve conduction studies at 4 weeks indicated common peroneal nerve denervation from the level of the block downwards. At one year near full recovery had been made. This implies there was axonal death initially without Schwann cell death and then axonal regrowth. The chronic pain persisted for years subsequently.

A possible explanation for Shah's case is either that the common peroneal nerve had an unusually thick epineurium that ruptured initially, but that is unlikely (i) as 1 ml of drug could likely readily track within the sheath to dissipate pressure, and (ii) no generalized condition of neuropathy associated with nerve thickening nor any risk illness for nerve thickening or was ever discovered on the patient nor any local condition that could have selectively local cause a prior common peroneal



nerve pathology at the site of rupture. An alternative more possible theory is that a motor fascicle was ruptured, an intraneural bleeding resulted from this causing a sustained intraneural pressure increase, and the additives of adrenaline (epinephrine) and sodium bicarbonate worsened the problem causing a metabolic block too with CPN paresis beyond the duration of pharmacologic action of the local anesthetic and also a sufficiently long CPN ischemia to cause axonal death but not long enough for Schwann cell death to occur. Schwann cells based on vascular surgery experience can survive near 8 hours of ischemia. Axons generally are considered tolerant of two hours ischemia. The persistent pain fits development of nerve compression possibly from scarring and scar shrinkage and the lady may benefit from an extra-neural neurolysis and a very limited intraneural neurolysis.

This very rare well documented case report is *compatible* with the following observations;

- Intraneural injections are common.
- Intraneural injection are generally painless.
- Intrafascicular injections are discernable by the great resistance to injection offered.
- Intrafascicular injections may be painless (if it is a motor fascicle)
- Rupturing fascicles are dangerous.
- Additives sodium bicarbonate and adrenaline (epinephrine) are inadvisable to use.

As future more detailed case reports of nerve block associated injuries accumulated, especially with ultrasound supporting evidence the mystery on these problems should become clearer.

iii. ACCIDENTAL NON-ANESTHETIC NERVE INJECTIONS CASE REPORTS

These are almost all sciatic nerve injuries from deep intramuscular injections of various substances. The case reports and specific research on this has value for regional anesthesia. Fibrotic scarring is part of the pathology seen at late surgical exploration and neurolysis has benefit, both when done early and when done late. Research emphasizes that intrafascicular injections (likely due to the sharp needles used) is severely damaging compared to intraneural injections for all of these unintended intraneural injections drugs studied^{43, 44}.

In other non-anesthesia disciplines monthly intraneural injection are intentionally done, for example intraneural steroid injections are used for therapy of leprotic nerve damage^{45,46}.

iv. WHY DO SOME NERVE BLOCK INJECTIONS RESULT IN SHARP RADIATING PAIN OR MARKED DISCOMFORT AT THE INJECTION POINT AND OTHERS NOT?

This is a legitimate question. The scientific literature does not elucidate this well. Author anecdotal experience shows an occasional patient will experience marked discomfort from the moment of needle insertion into the tissues, and greatly marked discomfort at first near nerve contact (touching the nerve?). Final precise nerve location with low current electrostimulation sometimes causes vociferous patient protestation and discomfort (intraneural?). Drug injection causes discomfort. Pausing to let the first milliliters of drug take effect before further injection allows completion of the full nerve block injection. These injection do not have associated resistance to injection. These patients stand starkly different from routine patients. The block outcomes were all benign and beneficial.

This author's observations are that; (1) such patients are overwhelmingly upper limb block patients but not exclusively so, (2) such patients have pre-existing pain from the precise pathology to be operated or have pain from other older pathology in the same limb, (3) they have current allodynia or a history of allodynia in that limb within the preceding twelve months. Conversely they are never patients with fresh pathology (under 24 hours old) or without prior pain. Typically their prior pathology has had multiple surgeries and persistent pain has been a problem. Occasionally they have acute pain but severe injury injuries, for example an arm degloving injury with multiple fracture sites and they are having repeat surgery within the same week.



This is all the picture of early or established chronic pain, and hyperalgesia. These conditions have an unknown pathophysiology and it is unknown why some individuals are prone to it and others not. It is known that there are nerve function changes and there is a dramatic increase in numbers of sensory neurons transmitting pain. Some are typical thin pain type axons that normally are inactive and in reserve but get recruited, and some are thick axons that do not normally transmit pain at all. This kind of patient seems to be the one who is more at risk to develop neuropathy after the procedure based on reading into case reports. This may be due to the effects of surgery, patient positioning, limb manipulation, and tourniquets alone (no nerve blocks done). Neuropathy may also just be simple progression of underlying neuropathy.

The big question is what role do nerve blocks play in these kind of patients? There is no validated scientific answer. Some argue to do no block at all and stay out of the line of malpractice gun fire. That is defensive medicine. Some argue that these chronic pain conditions get therapeutic benefit from nerve blocks, and that these patients need maximum analgesia more than others.

This kind of patient is in fact recognizable beforehand as they are anxious, are scared of pain, have a history of prior injury as described above and OFTEN have a history of allodynia (“just putting on clothing once caused the skin to hurt”). This author’s approach has been to give extra patient information about risk of neuropathy after the surgery (regardless of blocks being done or not), annotate the discussion, and get written consent for the procedure and have the patient ask for a nerve block. A slightly unwilling patient is a contraindication for nerve block. The block is done with standard high care. Use is made of multimodal analgesia including ¼ mg/kg ketamine during the block and another ½ mg/kg ketamine during the surgery. This anecdotal practice had not yet resulted in misadventure for the author nor the author’s patients. It is hope better scientific information will appear in future published literature

THE EVIDENCE AND EXPERIENCE OF VISUALIZED INTRANEURAL INJECTIONS FROM THE ERA OF ULTRASOUND GUIDED NERVE BLOCKS.

The advent of ultrasound guidance for nerve block needles soon produced many case reports, many animal studies and one amazing human study that confirmed all of^{47, 48, 49, 50, 51, 52, 53, 54}.

1. We did more intraneural injections before ultrasound guidance than we ever knew. Perhaps 50% of all nerve blocks ever were intraneural, or much more.
2. That the normal outcome of intraneural injection is no harm to the patient.
3. That intraneural injections are painless and barely recognizable. Newest and to date studies and case reports show many ultrasound guided nerve blocks with intraneural injections and none with any patient bad consequence.

Paul Bigeleisen in 2006 did the amazing human pioneering study where he intentionally injected 74 healthy human volunteer nerves intraneural under ultrasound guidance⁵⁵. In brief, no patient experienced pain upon intraneural injection nor a neurological deficit.

The 2005 Iohom study additionally put Selander’s and other early animal researchers’ laboratory research conclusions to rest. Iohom was the first to investigate in rats whether intraneural injections had any long term consequences⁵⁶. This study used 30g hypodermic type needles to inject into nerves under vision under anesthesia. There was sham surgery done on the opposite sciatic nerve for control, a two ropivacaine strengths studied and also saline and phenol in different groups. Footprint walking patterns were studied to evaluate sciatic nerve function and after 67 days the rats were sacrificed and the nerves were all studied histologically. All rats made full normal recoveries within hours except the phenol injected group which mostly also recovered but only from 21 to 67 days after injection. The rat sciatic nerve has 3 fascicles one being notably large. Intrafascicular injection was tempted in all the rats. At 67 days 77% (n=9) of the group injected with phenol had evidence of intrafascicular histological changes. None of the other groups showed any evidence of having had an intrafascicular injection, despite a similar proportion of them (77%) having likely also

having had intrafascicular injection with saline or ropivacaine. The suggestion is there that even intrafascicular injections are not absolutely neuropathic.

In summary intraneural injections are likely very common and largely harmless.

CONCLUDING DISCUSSION

The incidence of neuropathy of all grades brief, minor to severe, and permanent that are *associated* with a nerve block is different for different nerve blocks. The French Auroy study reported rates per 10 000 cases done as 2.9 for femoral nerve block, 2.4 for sciatic nerve block, 2.9 for interscalene block, 1.8 for axillary nerve block and 1.4 for mid-humerus blocks⁵⁷. As these are only *associated* injuries some neuropathies would likely have occurred in the absence of a nerve block and the true nerve block caused incidence is unknown. The true incidence of nerve block induced injury is likely much lower than that Auroy suggested.

A second issue is that “intraneural injection” can be either interfascicular or intrafascicular. All evidence suggests interfascicular injection in normal patients is harmless and only techniques associated with not penetrating fascicles should still be used. This is perhaps the final death knell of paresthesia techniques. There is sufficient evidence to suggest that intrafascicular injection is disruptive for that fascicle and likely to cause neuropraxia taking some weeks to recover. Furthermore sharp needle penetrating fascicles could conceivably sever some axons which would take months to re-grow. Paresthesia nerve block techniques using sharp needles should thus be avoided.

The regional anesthesia goal should perhaps not be to avoid intraneural injection as a generic goal, but rather to *avoid intrafascicular injection* as a highly specific goal.

Avoiding intrafascicular injection could be established by avoiding sharp needles in nerve blocks which should thus restrict paresthesia location of nerves to selected situations where it is the only option, and all risks considered. The second step to avoid intrafascicular injections would be to never inject if resistance to injection is significant. The needle would need to be repositioned. In this authors experience the “feel” of resistance to injection that is occasionally encountered is dramatically greater than that felt with routine injections. Pressure indicating devices are not needed to recognize this, and are wasted costs. When injection is impossible with standard syringe plunger pressure simply withdraw the needle fractionally millimeter for millimeter until injection suddenly is easier. Complete the injection. In this author’s busy practice, anecdotal experience was that such a need to readjust the needle occurred 1 to 2 times per year. All blocks were successful and no injuries resulted.

It will be good to abandon obsessions against intraneural injections and refocus onto other potential cause of nerve related injury like drug substitution errors, etcetera.

Joe Neal in 2001 commenting on Choyce’s study in an editorial said the conclusion of all data to that date was “*neither paresthesia* (locating techniques) *nor PNS* (peripheral nerve stimulator nerve locating techniques) *protect us from being nearer* (to the nerve) *than we imagined* (intraneural)”⁵⁸.

Recommended reading;

1. Dag Selander's chapter; Peripheral nerve injury after regional anesthesia. Chap. 7. Finucaine; complications of Regional Anesthesia. Churchill Livingstone. 1999. (Note; Read this in the context of the year of 1999 before more recent evidence was available. He has excellent references and good perspectives for the time. This will aid in understanding the evolution of erroneous beliefs in regional anesthesia)

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