12 Complications of Intravenous Regional Anesthesia

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Intravenous regional anesthesia (IVRA) of the limb was first described by Bier in 1908.[1] The original technique involved the surgical exposure of, and direct injection of local anesthetic into, an antecubital vessel, of an exsanguinated and isolated upper limb, thereby rendering the tissue below the applied tourniquet insensitive to pain. IVRA is a simple and effective method of providing anesthesia to peripheral tissues that anatomically have a blood supply which can be occluded by a pneumatic cuff. The technique in use today consists of the placement of a catheter in a suitable vein before exsanguination of the surgical site by gravity or compression, the inflation of a pneumatic double tourniquet, and the injection of a local anesthetic into the venous system of the isolated limb. Serious IVRA-related complications are rare and can be classified as drug and tourniquet related.[2]

Drug-Related Complications

In IVRA, drugs are injected directly into a contained vascular space. The integrity of this compartment is dependent on the ability of a pneumatic occlusion cuff, applied externally, to occlude the venous system. Systemic complications arising from drugs used in IVRA can occur when this occlusion fails. Failure of occlusion can occur because of inadvertent deflation of the cuff, cuff failure, an increase in venous pressure within the occluded tissue to a value greater than cuff pressure, or where there is an intact interosseous circulation that bridges the cuff. In each of the aforementioned circumstances, drug-related complications result from the inadvertent spillage of drug into the general circulation. Drug is also released into the systemic circulation with deflation of the cuff at the end of the procedure and under certain circumstances this can also lead to complications.

A number of different classes of drugs have been used in IVRA with varying degrees of success including local anesthetics, opioids, NMDA (N-methyl D-aspartate) inhibitors, neuromuscular blocking agents, and sympatholytic compounds.

The drugs used, and therefore the drugs capable of causing complications, can be classified into two groups, the primary agents and the adjuvant agents.

Primary Agents

The primary agents used for IVRA are the local anesthetics. In North America, lidocaine is the predominant choice, whereas in Europe prilocaine is a popular choice.

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Local Anesthetics

Mechanism of Action

Local anesthetics inhibit action potential propagation within neuronal tissue by binding to receptors in Na^+ channels located on the nerve cell membrane. Na^+ channels have widespread cellular distribution, providing a significant potential for unintended sites of action and associated clinical complications. The major clinically relevant locations of extra-neuronal Na^+ channels susceptible to local anesthetic (LA) blockade are those found in cardiac and central nervous system (CNS) tissue.[3,4]

Normal functioning of the Na^+ channel is required for appropriate Ca^{++} entry and egress across the myocardial cell membrane, which in turn is essential for the preservation of normal ventricular contractility and propagation of the cardiac action potential in pacemaker tissue. Local anesthetics exert negative inotropic effects on ventricular myocytes, the degree of contractile depression correlating with the potency of the LA.[5-7] In contrast, alterations in cardiac electrophysiology are less predictable, are more dependent on Na^+ channel kinetics, and can occur in the absence of a marked reduction in contractility.[5,8,9]

CNS toxicity of local anesthetic solutions is more predictable than cardiac toxicity and correlates relatively closely with the potency of the drug selected.[10] It is important to note that CNS and cardiac toxicity vary between local anesthetics, and that local anesthetics are not a homogenous group in regard to the complications they may produce.

Lidocaine

Lidocaine IVRA is safe and effective and is associated with a rapid onset (4.5 ± 0.3 minutes) of anesthesia after injection and termination of analgesia (5.8 ± 0.5 minutes) once the tourniquet is deflated.[11] Release of the tourniquet 5 minutes after the administration of 2.5 mg/kg of 0.5% lidocaine resulted in no signs of cardiovascular or CNS toxicity; however, symptoms of tinnitus were noted between 20 and 70 seconds after deflation.[12] Approximately 70% of lidocaine remains within the tissues of the previously isolated limb following tourniquet release, the remainder entering the general circulation in the subsequent 45 minutes.[13] Release of tissue-bound lidocaine is increased if the limb is exercised, emphasizing the importance of keeping the previously anesthetized limb quiescent immediately after tourniquet deflation.

The cardiovascular safety of lidocaine is attributable to the characteristics of its interaction with the sodium channel in the conduction system. Lidocaine does not accumulate significantly at the Na^+ channel at therapeutic plasma concentrations,[13-17] and rapidly binds to (time constant <500 ms) and dissociates from (time constant = 154 ms) the channel, preventing toxic accumulation of the drug.[18] Consequently, electrophysiologic disturbances do not occur at heart rates less than 150 bpm.[7] Excessive plasma lidocaine levels are associated with peripheral vasodilatation and reduced contractility which is manifest as hypotension, particularly in the volume-depleted patient.

Bupivacaine

Bupivacaine was first used for IVRA in the 1970s with Ware[19] reporting its use in 50 cases without major complication. The use of bupivacaine in IVRA was initially met with enthusiasm because it offered a more prolonged period of pain relief after the tourniquet release than lidocaine. However, it was not long after Ware's report that the first reports began to come to light of serious problems associated with the use of bupivacaine in IVRA, with seven deaths occurring between 1979 and 1983.[20-22] Bupivacaine binds to activated Na^+ channels at low plasma concentrations (0.2 mg/mL) displaying fast on/slow off kinetics (time constant of 1.467 seconds) facilitating accumulation of bupivacaine at the Na^+ channel, at heart rates as slow as 60 bpm.[18] This

provides a significant risk of electrophysiologic disturbance, including ventricular fibrillation resistant to conventional therapy, on the release of a bolus of bupivacaine into the circulation when the tourniquet is deflated at the end of IVRA.

Levobupivacaine

A study by Atanassoff et al.[23] in 2002 demonstrated in eight volunteers that onset of sensory block was delayed with levobupivacaine (12.5 versus 1.5 minutes) and pinprick sensation return was delayed after tourniquet release (15 versus 4.5 minutes) when compared with lidocaine. They also reported >50% incidence of CNS symptoms on tourniquet release with lidocaine, and a 0% incidence with levobupivacaine. No cardiac adverse events were observed, but the numbers involved are too small to draw any firm conclusions. Levobupivacaine has been compared with bupivacaine in a sheep model. The numbers of animals studied were few, but although convulsions were produced with both drugs, the ventricular dysrhythmias produced by levobupivacaine were relatively more benign and no sheep died during the levobupivacaine infusion.[24]

Ropivacaine

Ropivacaine (0.2%) has a favorable CNS profile relative to lidocaine.[25] Ropivacaine 0.375% provided superior analgesia in the first 2 hours after surgery versus lidocaine 0.5% with no reported local anesthetic side effects.[26] In a direct comparison in a dog model among bupivacaine, levobupivacaine, ropivacaine, and lidocaine, the most frequent cause of collapse was cardiac depression, with arrhythmias being more common in the bupivacaine-treated animals.[27] Resuscitation was successful in 100% of the lidocaine dogs, 90% of the ropivacaine group, 70% of the L-bupivacaine group, and 50% of the bupivacaine group. Most concerning, there was no difference between the unbound plasma concentration of bupivacaine and L-bupivacaine at collapse, whereas the concentration for ropivacaine required to produce collapse was significantly higher. This suggests that ropivacaine might be a better choice than L-bupivacaine or bupivacaine, but that none of these drugs are ideal for IVRA.

Prilocaine

Prilocaine is metabolized by the liver. Dose-related formation of methemoglobin occurs 4–8 hours after prilocaine administration.[28–30] As a result, prilocaine is not used for IVRA in North America. However, significant methemoglobinemia has *not* been reported when prilocaine has been used in IVRA. The large experience with prilocaine in Europe without reported adverse effect brings into question the choice to limit its use in North America. The main advantage of prilocaine over lidocaine is a reduction in the incidence of symptoms of CNS toxicity. Prilocaine 0.5% upper limb IVRA is associated with onset of analgesia in 11.0 ± 6.8 minutes and termination of analgesia after tourniquet deflation in 7.2 ± 4.6 minutes.[31] Prilocaine IVRA is extremely safe.[32] Bartholomew and Sloan[33] reviewed a series of 45,000 IVRA blocks and reported no serious side effects and no deaths related to the use of prilocaine in IVRA. Prilocaine IVRA is equally effective in terms of anesthesia to lidocaine IVRA.[34]

Chloroprocaine

Chloroprocaine is rapidly metabolized by ester hydrolysis to nontoxic metabolites and theoretically should be a very safe local anesthetic to use in IVRA. Local ester hydrolysis should produce a very low risk of release of a toxic concentration of local anesthetic into the general circulation. Unfortunately, chloroprocaine formulated with preservative is damaging to the vascular endothelium[35] and elicits severe pain on injection. The use of chloroprocaine with preservative in IVRA is contraindicated. There has been limited but successful performance of IVRA with preservative-free

solutions of chloroprocaine.[36] However, venous irritation, even with preservative-free solutions, remains a problem.[37]

Articaine

Articaine has been used in dentistry since the 1970s. It is an amide local anesthetic with a thiophene rather than a benzene ring. It is metabolized to inactive articainic acid by plasma carboxyesterase and this adds to its safety. It is short acting and has a similar onset of analgesia to prilocaine, and is faster than lidocaine. Both its CNS and cardiovascular side effect profiles seem to be favorable.[38] Despite all these apparent benefits, it has not come into widespread use. This may be attributable to the propensity of articaine to cause an erythematous rash in the area where the drug is injected.

Mepivacaine

An interesting development has been the investigation of mepivacaine for IVRA. Mepivacaine in a dose of 5 mg/kg was compared with lidocaine in a small (n = 42) double-blind study.[39] Mepivacaine provided better intraoperative analgesia than lidocaine with no difference in side effects. Of note, mepivacaine levels after deflation were less than expected for the dose injected, but they also did not decrease significantly over the following hour, unlike lidocaine levels.

Ketamine

Ketamine is an NMDA antagonist with local anesthetic qualities which has been studied as a sole agent for IVRA. Whereas it provided some, although inadequate, pain relief during IVRA, it was associated with the occurrence of hallucinations on tourniquet release and in some cases the loss of consciousness.[40,41] Ketamine is not a suitable drug as the sole agent for IVRA. However, ketamine when used in combination with local anesthetics has been shown to be very effective in reducing the incidence of tourniquet pain. When ketamine is used in IVRA for this purpose, the recommended dose is 0.1 mg/kg and there are no CNS symptoms when used in this dosage.[42]

Sympatholytic Drugs

The intravenous regional administration of guanethidine and reserpine inhibits sympathetic nervous system outflow in the isolated area.[43] Sympatholytic therapy is used in the treatment of reflex sympathetic dystrophy, causalgia, chronic regional pain syndrome,[44,45] rheumatoid arthritis,[46] frostbite,[47] and to improve blood flow in tissue flap procedures.[48] Despite widespread use of this technique and many anecdotal accounts of its success, randomized, controlled trials have not supported this optimistic conclusion in the area of chronic pain syndrome management.[49] The original work took place in the early 1970s, but it was not until the 1990s that a true double-blind study was conducted. The results of this study found that the placebo medication (in this case normal saline) was an effective therapy, and that there was no benefit in adding guanethidine in treating chronic pain syndromes.

Guanethidine acts at the terminal portion of the nerve fiber and interferes with the normal release and storage of norepinephrine.[50] Guanethidine evokes pain on intravenous injection and consequently it is usually coadministered with a local anesthetic. There is some limited evidence suggesting that repeated doses of guanethidine can permanently reduce norepinephrine reuptake and induce nerve end retraction, the latter being associated with a widening of the synaptic gap.[51] The major systemic complication of guanethidine intravenous regional sympathetic block is the frequent occurrence of hypotension, which can be prolonged in nature and in susceptible patients can be associated with apnea and angina.[52–54]

Adjuvant Agents

The ideal IVRA agent would be simple, safe, give excellent intraoperative analgesia, both at the surgical site and at the tourniquet, and provide prolonged postoperative pain relief. It should also provide the best possible surgical conditions. From the discussion above it can be seen that no single agent achieves this aim, as yet. The only way to attempt to provide these conditions is to use adjunctive agents. Many drugs have been studied in this role (see comprehensive review by Choyce and Peng[55]).

Opioids

The aim of opioid administration in IVRA is to prolong analgesia after cuff deflation and, although many have been studied, including fentanyl, morphine, sufentanil, and meperidine, none have proven to have any clear advantage over the administration of a local anesthetic alone. Indeed, the coadministration of an opioid in IVRA is associated with an increased incidence of unpleasant side effects, especially nausea and vomiting, after cuff deflation.[56,57] Opioids administered as sole agents for IVRA are not therapeutically effective.

Neuromuscular Blocking Drugs

The administration of neuromuscular blocking drugs including atracurium (2 mg) and pancuronium (0.5 mg) with local anesthetics in upper limb IVRA improves surgical conditions in adults undergoing fracture reduction.[58,59] There have been no reported complications from using adjuvant neuromuscular blocking drugs in IVRA. Atracurium is probably the best choice if regional muscle relaxation is required, given the role of Hoffman degradation in its elimination from the body. The use of neuromuscular blocking agents alone cannot be recommended.

Nonsteroidal Antiinflammatory Drugs

Ketorolac has been extensively studied as an adjuvant in IVRA. Reuben et al.[60] found that the addition of 60 mg of ketorolac to local anesthetics improved intraoperative analgesia and reduced the intensity of pain in the first hour after deflation and the demand for analgesics in the first postoperative day. This dose of ketorolac raises some concerns, and Steinberg et al.[61] conducted a dose finding study which showed a linear dose response up to 20 mg and then no additional benefit. There were no reported side effects of ketorolac use.

Tenoxicam and acetyl-salicylate at a dose of 20 and 90 mg, respectively, are also effective adjuvants, although the duration of postoperative analgesia is shorter than that reported for ketorolac.[62,63] It seems reasonable, if no contraindications exist, to use nonsteroidal antiinflammatory drugs as adjuvants in IVRA.

Alpha-2 Agonists

Clonidine, in a dose of 1 μg/kg added to the IVRA solution, has been shown in a double-blind study to prolong the time to request for first postoperative analgesia significantly (460 versus 115 minutes) and reduce overall analgesic requirements in the first 24 hours.[64] Clonidine has also been shown to decrease tourniquet pain.[65] However, the reduction in the severity of tourniquet pain and the prolongation of postanalgesia by clonidine may only be replacing one set of complications for another. At doses of 2 μg/kg, hypotension and sedation have been noted on tourniquet release.[66]

Dexmedetomidine is about eight times more selective for α_2 receptor than clonidine. A dose of 0.5 μg/kg is associated with reported improvements in the onset time of sensory and motor blockade, intraoperative analgesic requirements, onset of tourniquet pain, and duration of postoperative analgesia (564 versus 129 minutes).[67]

In contrast to high-dose clonidine, no side effects were observed. These data are very promising and dexmedetomidine may well become a valuable and standard adjuvant in IVRA.

Anticholinesterases

Neostigmine has been found to improve anesthesia in some regional techniques; however, the evidence for its benefit in IVRA is unclear.[68]

Tourniquet-Related Complications

Tourniquets have a long history of use in medicine. They have two basic functions: 1) isolation of the limb from the systemic circulation, as when preventing blood loss in limb trauma or in the isolated arm technique for monitoring anesthetic awareness, and 2) isolation of the systemic circulation from the limb as in IVRA. The shared feature of both scenarios is the loss of oxygenated blood supply to the limb that has the tourniquet applied. There is consequently the possibility of significant harm even in the case of a properly applied and fully functioning tourniquet.

An intact tourniquet is essential for the establishment and maintenance of IVRA. Inadvertent deflation of the tourniquet or the presence of a vascular communication across an intact tourniquet can lead to serious local anesthetic-related complications. Loss of limb isolation can result in both neurologic and, in extreme cases, cardiovascular collapse if the systemic vascular concentration of the local anesthetic exceeds the safe range. Consequently, the tourniquet, manometer, and inflation equipment should undergo regular maintenance to minimize the risk of equipment failure. Before each use, the competency of the tourniquet should be visually assessed. Where automated dual-cuff devices are used, it is essential that staff are trained in the appropriate use of the equipment and are familiar with the technique of IVRA. Equipment malfunction or misuse is an important and avoidable cause of morbidity in IVRA.[69,70] An intact and properly functioning cuff has a number of common side effects or complications associated with it. Local pressure effects usually evoke discomfort and pain in patients. Prolonged tourniquet time is associated with an increase in systemic blood pressure, often into the hypertensive range.

The presence of an intact tourniquet does not completely prevent drugs injected into the isolated limb from entering the systemic circulation.[71,72] Location of the tourniquet has a role. Almost 100% of IVRA lower limb blocks are associated with detectable leakage of local anesthetic, compared with 25% of upper limb IVRA procedures.[73] Increased drug leakage following IVRA occurs with fracture manipulation,[74] particularly in the lower limb. In addition, IVRA lower limb blocks require a high dose and volume of local anesthetic to achieve satisfactory analgesia. Lower limb IVRA is also associated with a high incidence of poor-quality block (36.8%).[75]

Many factors apart from the location of the tourniquet may be responsible for leakage of drug past an intact cuff. The occurrence of an interosseous circulation, not amenable to occlusion by a tourniquet, has been demonstrated angiographically,[76] but does not seem to be a major factor in IVRA-related morbidity. Of greater clinical relevance is the association between the rate of fluid injection into the isolated segment and the development of an increased venous pressure within the isolated segment. Venous pressure values greater than 250 mm Hg have been recorded 1 minute following bolus injection of 66 mL of saline in volunteers.[77] These data underscore the importance of avoiding rapid injection of drug solutions during IVRA.

The tourniquet pressure required to completely occlude blood flow in a limb is considerably greater than systolic blood pressure as there is considerable attenuation of the applied tourniquet pressure by fat, muscle, and connective tissue within the

limb.[78] Tourniquet use is associated with an increase in systolic blood pressure over time[79]; this increase may be excessive, particularly in hypertensive patients.[80] The inflation pressure of the tourniquet must be adjusted appropriately to account for these alterations.

Deflation of the Tourniquet

Symptoms of local anesthetic toxicity (tinnitus and perioral paresthesia) are frequently reported following elective deflation of the tourniquet.[72] These symptoms correlate with the concentration of local anesthetic in the arterial[81–83] rather than venous circulation.[14,84] No safe time interval between local anesthetic drug administration and tourniquet deflation has been established. The current recommendation is to wait 20 minutes from the time the drug has been injected, but this is not based on any scientific evidence. Intermittent deflation rather than a single deflation has been proposed to minimize risk of LA toxicity[81]; however, this does not alter the peak concentration of local anesthetic achieved on tourniquet release but merely prolongs the time for it to be achieved.

Tourniquet Pain

Tourniquet pain is a common complication of IVRA.[72] A double-cuff tourniquet reduces the incidence of tourniquet pain and should be used if the duration of the surgical procedure is anticipated to be longer than 30 minutes. Other less effective treatment options include intravenous sedation/analgesia and temporary deflation, then reinflation, of the cuff. The evidence presented above would suggest that this complication may be reduced by the use of adjuvants such as dexmedetomidine, clonidine, ketorolac, and ketamine or some combinations of these adjuvants to the IVRA.[42,60,64,67] Dexmedetomidine seems to have the best safety profile, but it is also the drug with the least investigation in this role. Tourniquet pain has also been reduced by lidocaine priming with 1 mg/kg given intravenously 5 minutes before IVRA[85] and by using a forearm rescue cuff.[86]

Paralysis

The incidence of neuromuscular dysfunction (a reduction in preoperative motor or sensory function, whether temporary or permanent) following the use of pneumatic tourniquet for a bloodless field is estimated at 1 in 8000.[87] Sporadic case reports exist of damage to ulnar, median, and musculocutaneous nerves associated with IVRA.[88,89] The common etiology of these injuries is direct pressure to the nerves, which exhibit histologic changes of crush injury. Tourniquet time should not exceed 2 hours to avoid capillary and muscle cell damage secondary to tissue acidosis.[87]

Compartment Syndrome

Compartment syndrome[90,91] is an increase in pressure within a muscular compartment to a value greater than perfusion pressure, leading to tissue ischemia. IVRA, particularly when used for reduction of long bone lower limb fractures, is associated with an increased incidence of compartment syndrome.[92] This may well reflect the large volume of drug solution required to provide effective lower limb IVRA and inadequate exsanguination of the limb before IVRA. Compartment syndrome secondary to hypertonic saline instillation, mistakenly used as a diluent for local anesthetic, has been reported.[90,93]

Loss of Limb

Loss of a forearm following IVRA has been reported in a 28-year-old female patient.[94] In the case described, the tourniquet time was 25 minutes, and signs

of severe ischemia were apparent on release of the tourniquet. One week after the procedure, the 28-year-old patient had her arm amputated. Histologic examination of the excised limb demonstrated thrombosis of the radial and ulnar arteries. This catastrophic event may have been caused by inadvertent intraarterial drug injection, an idiosyncratic drug reaction, or a drug administration error.

Reducing Complications

Appropriate Drug Selection

Prilocaine (3–4 mg/kg of 0.5%)[95–99] or lidocaine (1.5–3 mg/kg)[100–102] are appropriate and safe local anesthetics to administer in IVRA. Levobupivacaine and ropivacaine may become suitable choices in the future, but more studies are required to establish safety. At this time, the evidence is that these drugs are safer than bupivacaine. It remains to be seen if that is safe enough.

Reduce the Quantity of Drug Used

Consider use of a forearm tourniquet technique. This allows use of half as much local anesthetic, thereby reducing the incidence of complications while still providing adequate analgesia.[103–105]

Minimize Leakage of Drug Across the Tourniquet

1. Ensure adequate exsanguination of the limb before tourniquet inflation, a process facilitated by the limb elevation and the application of an Esmarch bandage.[72]
2. Maintain the tourniquet pressure at a level sufficient to prevent venous congestion in the isolated segment of the limb.
3. Do not use excessive volumes of local anesthetic solution. A volume of 0.5 mL/kg (40 mL total volume) is adequate for upper limb IVRA. In forearm IVRA, a volume of 20 mL has been shown to be adequate.[103]
4. Inject the local anesthetic solution over at least 90 seconds.
5. Inject the solution as far distal to the tourniquet as practical.[106]

Reduce the Incidence of Tourniquet Pain

A double-cuff tourniquet is preferable to a single-cuff device.

Prevent Ischemia

1. Ensure that the drug injection cannula is placed in a vein.
2. Do not allow the total tourniquet time to exceed 2 hours.[87,89]

Deflate the Tourniquet Appropriately

An interval of at least 20 minutes between drug administration and tourniquet deflation is suggested.

Conclusion

IVRA is a safe, simple, and effective regional anesthetic. Repeated evaluations have found success rates in the 95% and above range.[107] Careful attention to detail and a thorough understanding of the limitations and potential complications of the technique are essential to achieve the optimal outcome.

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