INTRA-VENOUS REGIONAL ANESTHESIA: SHOULD WE ABANDON OR IMPROVE IT?

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Intravenous Regional Anesthesia (IVRA) was discovered more than 100 years ago by August Bier (born exactly 150 years ago). Meanwhile little has changed with respect to the technique. It cannot be ignored that during the last decade the popularity of this block is fading mostly in Western Europe where peripheral nerve blocks under ultrasonography have become the techniques of first choice and anesthetists unable or not willing to use this apparatus are considered as dinosaurs. Most publications during the last 10 years were based on studies performed in Eastern Europe, the Middle East and the Far East while also in South America this block is still a mainstay in regional anesthesia procedures. As a consequence it is still premature to consider IVRA as 'anesthetic archeology' only worth to be mentioned in historical books or a museum.

Its effects results from the local anesthetic in the first place but also in a later phase being related to nerve compression and ischemia. By using a double tourniquet the patients will feel more comfortable with respect to possible tourniquet pain. Many centers still use the commonly recommended 40 mL Lidocaine 0.5 % (i.e. 200 mg) as catastrophies have been reported with other more toxic substances and concentrations.

IVRA has some advantages such as the presence of a tourniquet which orthopedic surgeons would require anyhow. By its simplicity (at least a block not under discussion for ultrasonography assistance) IVRA may be considered as a technique for the dummies resulting in doubts whether there is a real need that anesthetists should do them their selves. Besides intra-operative anesthesia it has also been used for complex regional pain syndromes (CRPS).

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On the other hand several dangers and disadvantages may argue the latter point of view (1). As opposed to some other blocks it cannot be performed in an adjacent area to win time. The tourniquet may deflate too early inducing local anesthetic (LA) toxicity. Seizures have been reported with tourniquet times of 60 minutes. With lidocaine the lowest dose in a seizuring patient was 1.5 mg/kg, in fact the anti-arrhythmic dose. Cardiac arrest has been reported with a lidocaine dose as low as 2.5 mg/kg which is even lower than the recommended 200 mg total dose. Even with high tourniquet pressures there may be leakage of blood via the blood supply in the deeper layers between the two bones of the forearm while the venous outflow is obstructed. Several cases of compartment syndrome have been described as well. An IV line is required at the non-operative side while the IV cannula at the operative side needs to be removed as it may hinder the surgeon. When used for traumatic insults wrapping the arm may not be a pleasant experience for the patient. In ultra-short surgery the tourniquet needs to remain inflated for at least 30 minutes which is not cost-effective. Finally after deflation motor and sensory function will recover rapidly so will pain.

As a consequence anesthetists have tried to make IVRA safer but also to enhance comfort to the patient by prolonging the pain free interval with preservation of the motor function. This may be due to mainly by selecting another local anesthetic, concentration or the addition of adjuvant substances hoping upon a synergistic, additive or potentiating (when a substance is used without known anti-nociceptive properties) effect. Actually more than 10 kind of substance groups have been tested in IVRA (2). Some centers have become specialists in their search for the most exotic adjuvant.

Most studies have compared groups containing 20-25 patients while focusing upon tourniquet tolerance, need for intra-operative supplementation, time interval to the first postoperative analgesic, analgesic requirements after surgery and hospital stay. Although it will be tried to discuss the several adjuvants separately, the confusing design of some studies comparing adjuvants of all kinds and pharmacological origin may complicate correct interpretation of the value of the additives reported up to date.

In the present overview only those references not older than 10 years will be mentioned.

Another local anesthetic?

Although bupivacaine as induced cardiac arrests as well and due to all commotion with respect to its huge toxicity, prilocaine seemed to be an alternative for lidocaine despite a similar pharmacodynamic profile with respect to onset and duration. Also because of the risk of methemoglobinemia, though

IVRA doses are in fact below the doses at risk, there is no major advantage to be expected by changing to prilocaine. Nevertheless it seems to be the most widely used LA after lidocaine for IVRA. Ropivacaine 0.2 % and 0.25 % has also been compared with lidocaine 0.5 % resulting in longerlasting tolerance of the tourniquet, better analgesia and lower requirements, especially with the ropivacaine 0.25 % concentration (3). Despite similar findings with ropivacaine 0.375 %, the total analgesic consumption during the first 24h was similar (4). Levobupivacaine 0.125 % resulted in slower onset of the block but somewhat longer duration, though not clinically relevant (5). Ester-type local anesthetics such as chloroprocaine, used more than 20 years ago but being preservative free now, may be used as well but its fast action (do few minutes matter?) and rapid enzymatic elimination may seem beneficial but surely not interesting when postoperative analgesia is the focus.

NSAIDs and corticosteroids

Especially in orthopedic surgery one of the first adjuvants tested were NSAID's also inspired by the knowledge that there are peripheral receptors present. Therefore it seemed logical not to waste these substances in other tissues not involved in the surgical action. NSAIDs used up to now are ketorolac, parecoxib, tenoxicam and lornoxicam (6-11). The dose of ketorolac, the mostly extensively studied, ranges between 10 (fore-arm tourniquet) and 60 mg (!) while tenoxicam is given in a dose of 20 mg. Based on a majority of studies NSAIDs prolong the interval to the first analgesic (prolongation of 3-7 hrs has been reported) and reduce analgesic requirements or supplementation. NSAIDs do not seem to have a significant effect upon the onset or severity of tourniquet pain. However, wound infiltration with ketorolac did not seem to be inferior to its addition to the IVRA mixture.

Combining dexamethasone 8 mg, though beneficial when used as the sole adjuvant (12), with ketorolac did not result in spectacular additional benefit (13). However there are some concerns to be raised. In the first place it may be questioned whether such a large dose restricted to the operative extremity is without harm with respect to causticity. Secondly, there is a lack of studies comparing the same NSAID given intravenously and if so in similar doses. Some studies could not find arguments to add NSAIDs to the local anesthetic as compared to systemic use.

Paracetamol and Acetaminophen

The doses used were 200-300 mg and some studies compared both the IV and IVRA route. Especially when added to lidocaine, paracetamol seems to offer benefit in terms of intra-operative (tourniquet) discomfort and post-

operative analgesia and requirements although the interval until the first analgesic request was only 10-25 min longer and one oral tablet could be spared during the first 24 hours for similar pain scores (11,14,15). It remains unclear whether IV administration differs significantly from either the placebo or regional injected substance.

Weak and potent opioid substances

Morphine 0.1 mg/kg, fentanyl 100-200 µg, sufentanil 25 µg and tramadol 50 mg and 100 mg have been added to the local anesthetic (16-19). Onset of the block was faster with all substances except fentanyl. Meperidine 100 mg, having local anesthetic effects has been used instead of lidocaine offering similar surgical conditions. When added in a dose of 30 mg (but not less) to lidocaine it was found to provide better postoperative analgesia but at the expense of more sedation, dizziness and PONV (nausea also with fentanyl). Tourniquet and postoperative pain was obviously less in some but not all tramadol studies and probably with the 100 mg dose only. In addition tramadol has been found to cause more rash/pruritus and both tramadol and meperidine are painful during injection. Overall benefit of opioid addition is poor and they should not be recommended for IVRA use.

Alfa-2 Adrenoreceptor agonists

Similar to their use in neuraxial and peripheral nerve blocks it was within expectations that also these substances would find their research in IVRA. Clonidine (1-2 µg/kg) and to a lesser extent dexmedetomidine (0.5-1.0 µg/kg) have been tested and compared with other adjuvant substances for surgery (10,16,20-25). For clonidine the available studies offer quite controversial results ranging from no effect at all to all possible benefits (mostly tourniquet pain) as mentioned for some previously mentioned adjuvants. Delay in first analgesic postoperative request ranges from minutes to 6 hrs. IVRA administration seems to be superior in comparison with systemic use. Although dose finding studies have not been done, a clonidine dose of 2 µg/kg seems far too high. The mostly widely accepted benefit in terms of onset, tourniquet and postoperative pain seems to be obtainable with dexmedetomidine. Systemic administration, either before IVRA or at tourniquet release offered quite similar effects as compared to inclusion in IVRA but at the expense of more sedation, bradycardia and hypotension (25). Finally there is a growing interest in the use of clonidine in IVRA treatment of Complex Regional Pain Syndrome which is not the subject of the present review.

Nitroglycerin

The reason why nitroglycerin might be effective in IVRA is not very clear. Doses of 200 μg have been added to lidocaine resulting in faster onset times and slower recovery times (few minutes), less tourniquet pain and better postoperative pain scores and control (up to 3 hrs longer interval to first request) (26-28).

Ketamine

The NMDA receptor antagonist ketamine has been added to lidocaine in a dose of 0.1 mg/kg . It was found in one study that following its addition the onset was faster, recovery slower, tourniquet pain less, superior to clonidine and nitroglycerin (21,28) and pain scores lower during the first 4 hours (28) while in another comparison with systemic administration no specific benefit was found by mixing ketamine with lidocaine (29).

Neostigmine

Neostigmine (500 μg-1 mg), a cholinergic substance with anti-nociceptive properties at the spinal level has been found to decrease onset times more particularly the motor block and possibly pain scores, and analgesic requirements and to prolong the interval to the first analgesic with 20 minutes (30-32). Tourniquet pain does not seem to be affected.

Others

Some other substances have been studied although it concerns mostly a single or rather old report. A little bit difficult to understand may be the benefit reported with **ondansetron** 4 mg when added to the LA in IVRA (33). Its addition improved intra- and postoperative analgesia with a prolongation of the pain free interval (1.5 h difference). The setrons have an anti-serotoninergic effect which seems difficult to fit with the more comprehensible benefit observed with clonidine and tramadol.

Magnesium (which may have NMDA receptor antagonist properties) may accelerate the onset of sensory and motor block and lower tourniquet pain (34,35). However its injection was considered to be painful in 2 out of 3 patients. Analgesia may last 1 hour longer while one diclofenac dose may be spared.

Midazolam may have analgesic effects mediated by the GABA receptor. In a dose of 50 μg/kg it decreased tourniquet pain, NSAID requirements and postoperative pain scores while it prolonged the pain free interval to 12 hours with more sedation during the first 2 hours (36).

Neuromuscular blocking agents such as atracurium 2 mg and mivacurium 0.6 mg have been added as well to improve the quality of the motor block. Besides this no major additional benefit was demonstrated.

Sodium bicarbonate for alkalinisation of the mixture and **potassium** have also been studied more than 20 years ago but despite reported potential benefit especially with sodium bicarbonate their use seems to be abandoned.

Conclusion

IVRA is still commonly used. Therefore it is too early to abandon a simple and useful technique. Due to possible untoward effects, its application should remain in the hands of the anesthesiologist or at least under his/her direct supervision.

Despite the numerous studies performed in search of the ideal adjuvant substance or local anesthetic, the actual literature is quite controversial. A delay of postoperative pain appearance expressed in minutes or 1-2 tablets of an analgesic less during the first 24 hrs cannot be considered as clinically relevant. There is a lack of dose-finding reports and studies looking at the safety when injecting similar doses in a restricted environment and studies including a control group in which the substance to be tested is also administered systematically. As opposed to neuraxial techniques and fortunately only few authors have mixed more than two substances.

Faster onset and few minutes delay in recovery of sensory and motor function may not be clinically relevant. When respecting a sufficient time interval until the most distal tourniquet is inflated may also significantly affect the onset and severity of tourniquet pain, more than the addition of an adjuvant. The most promising substances for IVRA for surgery or Complex Regional Pain Syndrome (not the focus of this review) at the present time, may be ketorolac and dexmedetomidine (even more than clonidine) as these drugs may cause more side-effects when given intravenously but even intravenous systemic or local (wound) administration may offer quite comparable or intermediate effects. Opioids and other less frequently used adjuvants are rather disappointing with regards to their clinically relevant benefit despite statistical significant differences in comparison with the use of the local anesthetics alone.

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