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Intravenous Regional Anesthesia: A Historical Overview and Clinical Review☆,☆☆

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ABSTRACT

Intravenous regional anesthesia (IVRA) is an established, safe and simple technique, being applicable for various surgeries on the upper and lower limbs. In 1908, IVRA was first described by the Berlin surgeon August Bier, hence the name "Bier's Block". Although his technique was effective, it was cumbersome and fell into disuse when neuroaxial and percutaneous plexus blockades gained widespread popularity in the early 20th century. In the 1960s, it became widespread, when the New Zealand anesthesiologist Charles McKinnon Holmes praised its use by means of new available local anesthetics.

Today, IVRA is still popular in many countries being used in the emergency room, for outpatients and for high-risk patients with contraindications for general anesthesia. IVRA offers a favorable risk-benefit ratio, cost-effectiveness, sufficient muscle relaxation and a fast on- and offset. New upcoming methods for monitoring, specialized personnel and improved emergency equipment made IVRA even safer. Moreover, IVRA may be applied to treat complex regional pain syndromes.

Prilocaine and lidocaine are considered as first-choice local anesthetics for IVRA. Also, various adjuvant drugs have been tested to augment the effect of IVRA, and to reduce post-deflation tourniquet pain. Since major adverse events are rare in IVRA, it is regarded as a very safe technique. Nevertheless, systemic neuro- and cardiotoxic side effects may be linked to an uncontrolled systemic flush-in of local anesthetics and must be avoided.

This review gives a historical overview of more than 100 years of experience with IVRA and provides a current view of IVRA with relevant key facts for the daily clinical routine.

Historical Overview

Cocaine was extracted from coca leafs in 1855 by the German chemist Friedrich Gaedicke (1828-1890) which he called erythroxylin, long before Bier had introduced "venous anesthesia" into clinical practice. [1] Five years later, erythroxylin was purified by the German chemist Albert Niemann (1834-1861).[2] Later, in 1884, the discovery of cocaine's properties as a topical anesthetic for ophthalmologic surgeries by the Austrian ophthalmologist Carl Koller (1857-1944) marked an important milestone for the development of local and regional anesthesia.[3]

In 1886, the New Yorker neurologist James Leonard Corning (1855-1923) described a new method of regional anesthesia.[4] He observed a prolonged insensibility of the limb after subcutaneous injection of cocaine hydrochloride by applying a tourniquet, proximally to the injection site. For this anesthetic technique he designed a new type of tourniquet (Figure 1). For the limb's exsanguination Corning used an elastic band (Esmarch's elastic bandage).[5] It was introduced into clinical practice by Friedrich von Esmarch who was a well-known surgeon and chair holder at the Universities of Kiel, Bonn, Greifswald and Berlin.

In 1908, the Berlin surgeon August Bier (1861–1949, Figure 2)—the former assistant of Friedrich von Esmarch—reported on a new type of conduction anesthesia, the so-called "Venous Anesthesia" (Figure 3). Later, this method became known as "Bier's Block" or "Intravenous Regional Anesthesia" (IVRA).[1] IVRA was described as an

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anesthetic technique, which can be applied for short surgeries and for longer surgeries, such as amputations. For this original method of "Venous Anesthesia" August Bier used an "Esmarch's bandage" for exsanguination, a proximal (on the arm or thigh) and a distal (on the forearm or leg) tourniquet for garroting (Figure 4).[1] After dissection of a vein ("venae sectio"), typically of the basilica, cephalic, median cubital or great saphenous vein, appropriate ligatures were placed and a venous cannula was inserted. Subsequently, a local anesthetic (LA) solution was injected. The distal tourniquet was removed when the desired anesthetic effect was achieved. The proximal one was deflated after surgery by intermittent pressure release. This application allowed flushing out any unfixed drug with saline solution prior to the release of the main tourniquet. Bier used the LA procaine (0.5% solution),[1] which has been introduced by the German chemist Alfred Einhorn (1856-1917) in 1904. In 1909, Bier presented a series of 134 cases in which the anesthetic effect was described as "good" in 115, "satisfying" in 14 and "insufficient" in 5 patients. His method was even applied for amputations.[1]

In 1909, Bier's assistant, Fritz Momburg (1870-1939), reported on a modification of Bier's technique: To reduce pain caused by garroting, he used a third tourniquet which was placed distally to the first upper tourniquet. Subsequently, the first upper tourniquet was released to reduce tourniquet pain.[6]

In 1885, the American surgeon William Halsted (1852–1922) performed the first brachial plexus block via a surgical approach, while the first percutaneous supraclavicular block of the brachial plexus was performed by the German surgeon Diedrich Kulenkampff (1880-1967) in 1911.[7,8] Meanwhile, the German surgeon Georg Hirschel (1875–1963) described a percutaneous approach to the brachial plexus from the axilla[9] and, in 1898, August Bier performed the first operation under spinal anesthesia. During the following years, percutaneous plexus blockades and neuroaxial blockades became more popular and sophisticated and after a short period of enthusiasm, Bier's technique of IVRA fell into disuse. Even in monografts and in the most renowned textbooks of the 1950s, like "*Lokalanästhesie und Lokalanästhetika*" edited by Hans Kilian, the procedure of IVRA was not mentioned at all.[10]

A striking point of criticism against IVRA was the fear of possible side effects due to high dosages of intravenously applied LA. In those times, physicians were very cautious when using drugs intravenously. This fear was intensified when using LA. Other concerns included the risk of producing air embolism as well as the fear of insufficient drug purity and sterility. The lack of reliable monitoring equipment and experience contributed to the disuse of IVRA.

In seeking a better LA, lidocaine was discovered by the Swedish chemists Nils Löfgren (1913-1967) and Bengt Lundquist (1922-1953) in the 1940s.[11] Other amino amide LAs, like chloroprocaine, mepivacaine, prilocaine and bupivacaine, were synthesized between 1898 and 1972. They were intended to be less toxic than cocaine. In 1957, bupivacaine was synthesized, and in 1996, ropivacaine, a pure S-enantiomer, was introduced to the market.

It took approximately half a century until the idea of IVRA was rediscovered. This revisit was not only promoted by new discoveries regarding LA drugs, but also by relevant improvements and simplifications of the technical approach. Surgical vein dissections and ligatures were abandoned, and it became common to insert small intravenous cannulas in a distal vein with the tip directed proximally and to apply pneumatic tourniquets with pressure control (eg, double parallel chambered pneumatic tourniquets). Most authors omitted the additional distal tourniquet. The Brazilian anesthesiologist Flavio Kroeff-Pires performed IVRA together with the Uruguayan orthopedist José Luis Bado (1903-1977), who had visited Bier's medical school in Berlin during the 1920s. In 1954, the results were published in Portuguese.[12,13]

An important pioneer for the rediscovery of IVRA was the New Zealand anesthetist Charles McKinnon Holmes (1932-2011) (Figure 2). In 1963, he published a case series of a simplified, revised method of IVRA in *The Lancet*. Holmes used a single sphygmomanometer cuff, which was situated high around the upper arm and inflated above the systolic blood-pressure. A fine needle was placed into a convenient vein, which was typically located at the dorsum of the

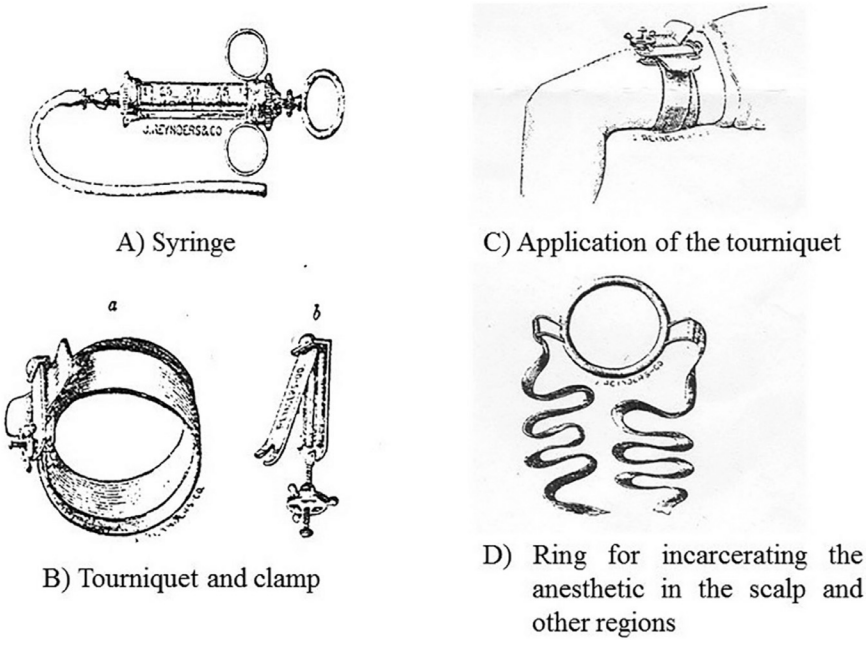
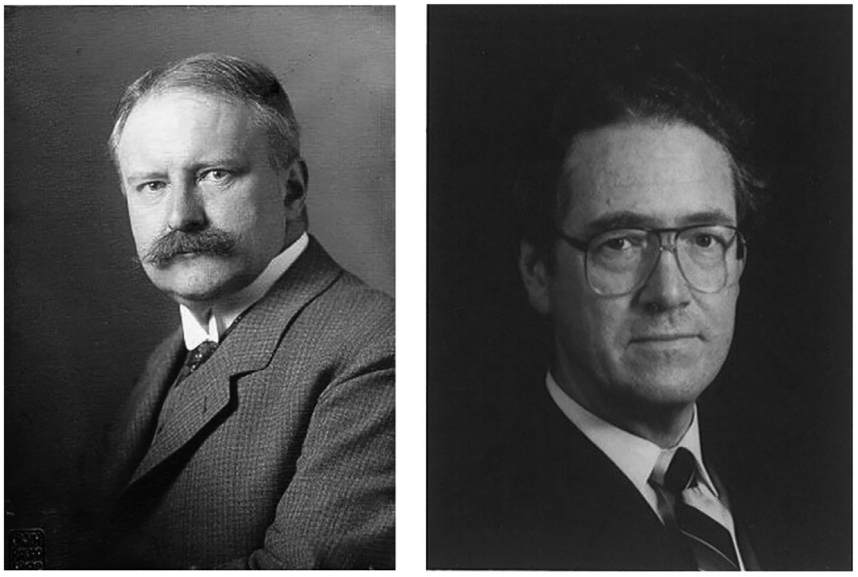


Fig. 1. A selection of items described by J. Leonard Corning to enable anesthesia with cocaine hydrochloride: After exsanguination by means of an Esmarch's bandage, a syringe (A) was applied to inject the anesthetic solution. For this anesthetic technique he designed a new type of tourniquet (B), which was secured around the limb by means of a clamp (B, C). For the incarceration of the anesthetic in special regions (eg head, face, neck, breast, and some regions of the back) Corning used rings of various sizes (D) (modified after[4]).



A) August Bier B) Charles McKinnon Holmes

Fig. 2. (A) The father of IVRA, the German surgeon August Bier, around 1920. (B) After IVRA fell into oblivion during the following decades, the New Zealand anesthesiologist Charles McKinnon Holmes re-pioneered it in the 1960s (pictures are taken from the private collection of Prof. Michael Goerig).

hand. He applied lidocaine (lignocaine) for IVRA which has potential advantages regarding the quality of tissue penetration, potency, effectivity and risk-benefit profile. These advantages may have contributed to the high success rate. These findings drew attention to IVRA and significantly contributed to its revival. In the same year, the Boston orthopedist H. Michael Bell and his colleagues repopularized IVRA. They stated: "It is simpler and more effective than supraclavicular or axillary brachial plexus blocks for upper extremity anesthesia. The same is true for femoral and sciatic blocks for lower extremity anesthesia."[14] Due to the potential systemic cardiovascular and neurotoxic side effects of the LA being used, other authors were more restrained and skeptical about IVRA.[15] In 1965, the Scottish orthopedist Brian R. Kennedy and his colleagues concluded in their article published in the British Medical Journal: "We do not feel justified in continuing to use this technique with lidocaine in view of the high incidence of toxic phenomena."[15]

It was probably due to the worldwide use of IVRA and the huge variability of observed side effects that opinions differed about IVRA, even within English-speaking countries: Kennedy et al,[15] authors from Cardiff in Wales, described not only neurological signs of LA toxicity, but also changes in blood pressure and ECG abnormalities (in one case even with asystole). Thus, IVRA was seen as a dangerous method. Interestingly, when patients were asked whether they would choose general anesthesia or IVRA if undergoing the same operation again, 64% of the patients preferred IVRA.[15]

IVRA is now popular in many countries because it can be used for numerous operations and procedures. Diverse modifications, new developments, supportive measures and adjuvants have been suggested and tested to further enhance the effect of IVRA.[16–18] IVRA has some important advantages: The fast onset of effect (5-10 min), high success rates, good muscle relaxation and fast return of sensation.[17] In some clinical constellations it might represent a preferable low-risk technique for multimorbid patients with a high-risk profile for general anesthesia (GA). IVRA is easily performed, cost-effective and relatively safe, making it suitable for outpatients undergoing hand surgery.[19,20] Later on, due to the improved methods of monitoring through continuously applied ECG, automated blood pressure measurement and, in the 1970s, pulse oximetry,[21,22] IVRA became safer. Moreover, it could also be safely applied bilaterally (eg, for carpal tunnel release), preferably in a sequential manner.[23]

IVRA has been applied for the management of the complex regional pain syndrome (CRPS), especially located in the upper limb.[24–26] However, due to a lack of evidence demonstrating a beneficial treatment effect of IVRA in patients with CRPS type 1, it cannot be routinely recommended for this indication.[27]

Technical Procedure

For IVRA—as initially introduced by August Bier—an elastic bandage for the limbs, an Esmarch's bandage for proximal garroting and a second bandage for the distal tourniquets were necessary. After using the proximal and, frequently, the mentioned distal tourniquet to keep the LA in place, August Bier injected up to 100 mL of a 0.5% solution[28] under high pressure after a "venae sectio" and the insertion of a specially designed venous cannula in the distal vein.[29] Shortly after applying the LA agent, the distal tourniquet was removed.

Since August Bier's historical "Venous Anesthesia",[1] the technique of IVRA has been substantially modified and simplified. However, protocols vary broadly between users depending on country, local or institutional standards and the extremity being operated on. Thus, regarding the technical aspects of the procedure, authors cannot emphasize a single standard technique based on existing evidence. Table 1 represents an example for an applicable technical approach for IVRA. The development of technically outstanding methods for garroting (eg, double-chambered, two-cuffed and electronically-controlled tourniquets with alarm function) improved the clinical practicability of IVRA.

Later, associations like The American Society of Regional Anesthesia and the Association of Anaesthetists of Great Britain and Ireland were founded, and they helped standardize procedures. Before that, a broad variation of technical aspects among different countries and institutions existed.

The extremity's exsanguination is a crucial step in preparing the patient for IVRA. Sufficient exsanguination is the major determinant for the quality of IVRA, especially if only small volumes of LA are to

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Aus der Königl. chirurgischen Universitätsklinik in Berlin.

Ueber Venenanästhesie.

Von

Prof. Dr. August Bier.

(Nach einem Vortrag, gehalten in der Berliner medizinischen Gesellschaft am 10. März 1909.)

Der grosse Nervenstamm ist vor dem Eindringen anästhesierender Mittel durch seine Bindegewebsscheide geschützt, das beweist unzweifelhaft die Rückenmarksanästhesie. Geringe Dosen der Anästhetika, die auf einen mittelgrossen peripheren Nerven gespritzt diesen in seiner Empfindungsleitung unverändert lassen, rufen, wenn sie im Rückenmarkssack die scheidenlosen Nerven treffen, Betäubungen von grossartiger Ausdehnung, ja unter Umständen des ganzen Körpers hervor. Der Weg für eine schnelle und erfolgreiche lokale Anästhesie ausgedehnter und tiefer Körperteile ist also vorgezeichnet: Es gilt die schützende Bindegewebsscheide der Nerven zu überwinden. Gelingt dies, so genügen überraschend geringe Mengen des betäubenden Giftes, um Schmerzleitung und Empfindung aufzuheben. Der Weg ist auch schon beschritten worden, um Anästhesien beim Menschen zu erzeugen; man hat, weil die perineurale Injektion bei grösseren Nerven versagte, durch sogenannte endoneurale Einspritzungen sogar den Nervus ischiadicus leitungsunfähig gemacht. Aber dies Verfahren ist praktisch unbrauchbar, denn es setzt Voroperationen voraus, die der beabsichtigten eigentlichen Operation an Grösse kaum nachstehen. Zudem würden sich diese Voroperationen kaum wirklich schmerzlos ausführen lassen.

Der einfachere und natürliche Weg, um der Nervensubstanz sowohl im Stamm als in dessen Ausbreitungen und Endigungen das Anästhetikum zuzuführen, ist die Blutbahn. Dieser Weg ist überall da gangbar, wo sich künstliche Blutleere anwenden lässt. Am vollkommensten würde sich vielleicht von der Arterie aus das Anästhetikum im Gliede verbreiten lassen. Dass dies geht, aber praktisch unbrauchbar ist, braucht wohl nicht näher erörtert zu werden. Es setzt, ganz abgesehen von der schwierigen Injektionstechnik, wieder eine viel zu grosse und umständliche, unter gewöhnlicher Lokalanästhesie auszuführende Voroperation voraus. (Als ich dies schon niedergeschrieben hatte, ersah ich aus einem Referat der Münchener med. Wochenschrift, 1909, No. 4, dass ein spanischer Arzt Goyanes diese Art der Gefässanästhesie auf Grund von Tierversuchen und 2 Operationen am Menschen empfiehlt [Acad. Medico-quirurg. Español. 16. November 1908]. Ich glaube nicht, dass er viel Glück damit haben wird.) So bleibt denn die überall leicht aufzufindende und mit einer kleinen und wenig eingreifenden Operation freizulegende Hautvene als Eingangspforte in das Gefässsystem übrig. Da das Kind nun einmal einen Namen haben muss, will ich diese Art der Anästhesie „Venenanästhesie“ nennen, obwohl ich mir bewusst bin, dass vom

„Venenanästhesie“

Fig. 3. Original article "Ueber Venenanästhesie" (1909) [On venous anesthesia] by the German surgeon August Bier, in which he precisely described his technique on IVRA.[1]

be applied.[33,34] Esmarch's bandage can be very painful or inapplicable, especially in patients with open wounds. Farbood and Shahbazi compared two methods of limb exsanguination: The Esmarch's bandage vs limb elevation to 90 degrees for 5 minutes. They concluded that (upper) limb elevation can be equally effective for exsanguination.[35]

After induction of IVRA, the following clinical signs indicate a successful anesthesia[30]:

- Sensation of heat
- Paresthesia (tingling)
- Pale skin patch
- Numbness and loss of sensitivity (after 3-5 minutes)
- Motor blockade
- Development of anesthesia from the fingertips upwards[36]

Contraindications and Indications for IVRA

Bier classified IVRA as a safe technique with a good safety margin. However, he was also aware of possible complications: after limb amputations he observed phlegmons at the amputation stump in patients with a preexisting phlegmon or (diabetic) gangrene. Therefore, he strongly advised against using IVRA in patients with diabetic gangrene or phlegmon recommended spinal anesthesia as the preferred anesthetic method in these cases. Nevertheless, further contraindications were postulated during the next decades and are listed in Table 2.[28] He also stated that IVRA should only be used in cases where other forms of local anesthesia were not appropriated, like extensive operations on the limbs (eg, amputations). Nevertheless, Bier also used this method to operate on patients with Dupuytren's contracture and, interestingly, he even preferred IVRA over spinal anesthesia.[28] IVRA

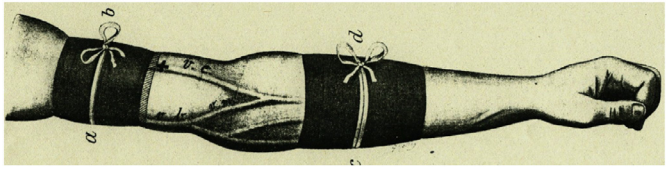

Fig. 4. Proximal and distal tourniquet, as described by August Bier in his article " Venenanästhesie" (1909) [On venous anesthesia]. They were used to keep the local anesthetic in place.[1]

can be applied for surgical procedures of the upper and lower limbs, which can be performed under Esmarch's method and do not exceed 120 min.[31] However, most authors consider IVRA best suited for operations lasting less than one hour. The involved personnel should be aware of potential side effects associated which the systemic wash-in of intravenous administered LA.[31,34]

Advantages of IVRA

For Bier, IVRA was a big step forward in the area of local anesthesia. Apart from phlegmons, he did not observe severe complications. He ascertained that IVRA was safer and better tolerated by patients as compared to spinal anesthesia.[28] Holmes declared that IVRA is "a safe simple method of producing analgesia of the limbs, which does not require special training or extensive experience".[39] He had the impression that "the danger of pneumothorax and other complications that may follow brachial-plexus block is avoided, and patients may safely be allowed to return home soon after the operation."[39] Furthermore, Holmes mentioned a good analgesia and relaxation during IVRA and that "the bloodless field is often appreciated by the surgeon".[39] "The method is particularly useful for simple injuries of the arm or leg, especially in patients who are ill-prepared for general anesthesia, or when the doctor is forced to work single-handed."[39]

Advantages for IVRA include:

- Suitable for selected high-risk patients with contraindications for GA[30]
- Cost effectiveness[30]
- Safe technique, low incidence of systemic toxicity[30–32]
- No risk for nerve lesions or pneumothorax like with plexus blockades[30]
- No complex anatomical knowledge needed[30]
- Quick response time (5-10 minutes)[30]
- Rapid post-operative recovery[30]
- Usually efficient muscular paralysis[30]
- High success rates (approximately 96%)[40]
- High acceptance among patients[30]

Table 1
Example for a technical approach for IVRA (modified after[17,30–32])

Technical Requirements and Prerequisites
• Same patient preparations as for GA (eg, fasting, premedication) • Monitoring and resuscitation facilities, anesthesia workstation and equipment should not differ from those required for GA; setting must allow the immediate conversion to GA • Two intravenous cannulas (eg, 20- or 22-gauge) are placed: The first one (systemic access) in a limb apart from the operation site, the second one (local access) as distal as possible on the limb to be operated on (with the cannula tip directed proximally). • A tourniquet (eg, double-chambered pneumatic tourniquet) is placed proximally around the arm or leg (ensure that the skin underneath the tourniquet is well padded). • Exsanguination by using an elastic band (Esmarch's bandage) should be performed as completely as possible. Elevation of the arm for up to 3 minutes with manual compression of the brachial artery before inflation of the tourniquet might also be useful. • Insufflation of the proximal chamber with continuous monitoring of the cuff pressure: Recommendations for the optimal insufflation-pressure are still inconsistent: ○ Maintain a tourniquet-pressure of 300 mmHg or at least 80-100 mmHg above systolic arterial blood pressure. • After the removal of the Esmarch's bandage the absence of pulses should be verified (radial or dorsalis pedis artery).
Onset of IVRA
• With the proximal chamber inflated a low concentrated, high-volume LA solution (see below, Table 3) may slowly be injected (eg, 20 mL/min). ○ Note that a fast injection with high injection pressures exceeding garroting pressure may lead to a systemic escape of LA and therefore must be avoided. Injection should occur over a minimum of 90 sec. • Dosages vary among authors. Brown et al[30] proposed 50 mL of a 0.5% lidocaine solution for the upper extremity and 150 mL of a 0.25% lidocaine solution for the lower extremity. • If analgesia is adequate, the distal chamber of a double-chambered tourniquet can be inflated. After verification of an adequate distal chamber-pressure, the proximal chamber can be deflated to minimize tourniquet pain. • The response time depends on the applied LA and adjuvants. The definite analgesic effect is often achieved after 5-10 min and is usually accompanied by muscular paralysis.
Offset of IVRA
• To minimize the risk of potentially toxic systemic LA release, the tourniquet must not be deflated within 15-20 minutes after injection (minimum injection-release time until the local anesthetic is "fixed to tissue"). • Tourniquet insufflation time should not exceed the maximal tourniquet time of 120 minutes. • After surgery is completed, the release of the local anesthetic in the circulation should be done gradually, multi-staged (eg, over a period of 10 minutes). • Once both chambers are fully released, a rapid regress of symptoms can be expected. • Postoperative monitoring for 30 minutes is mandatory.

Complications and Side-Effects of IVRA

In 1909, Bier reported that he did not observe any LA toxicity, even without following any precautions. However, he was aware of the possible side effects that may occur.[28] Therefore, he recommended releasing the proximal tourniquet intermittently and slowly at the end of the procedure to minimize possible hazardous effects. He also suggested using arterial pressure to wash out the local anesthetic through the open wound.[29]

Severe complications in IVRA are rare.[30] They can be classified as drug- or tourniquet-related complications.

Minor Adverse Events

Most of the observed minor side effects are associated with symptoms of the central nervous system (CNS): Dizziness, blurred vision, facial tingling, facial numbness, metallic taste, tinnitus, difficulty in speaking and dysphoria. Dunbar and Mazze described a probability of 2.1% for mild CNS reactions.[40]

Major Adverse Events

Seizures, myoclonia, cardiac depression and death (as it was reported for bupivacaine) have been reported in the context with IVRA.[41–43] Cardiac arrest occurred after the use of bupivacaine for IVRA.[43–45] In three of the five deaths resulting from IVRA with

Table 2
Absolute and relative contraindications for IVRA (modified after[17,31,34,37,38])

Absolute Contraindications	Relative Contraindications
• Open wounds, heavy injuries and infections of the limbs • Hypersensitivity or allergy to local anesthetics • Impaired perfusion of the limb (eg, Morbus Raynaud, scleroderma) • Deep vein thrombosis or thrombophlebitis • Uncontrolled arterial hypertension • Surgical procedures in which the limb cannot be completely exsanguination • Patient refusal	• Uncooperative patient • Obesity (due to the cuff's unreliability on obese arms) • Anatomical anomalies of the operated extremity • Neuropathies (eg, Diabetes mellitus) • Arrhythmias (especially bradycardia) • Surgical procedures taking longer than 120 minutes • Sickle cell disease • Paget's disease

bupivacaine, the cuff was not inflated properly when it still was necessary.[43]

In the 1980s, higher-concentrated solutions of bupivacaine and etidocaine were used for epidural anesthesia. After deadly incidents occurred, thus emphasizing the danger of bupivacaine once more, opioids and LA began to be used together, improving safety.[46]

Systemic Escape of LA

During Bier's time, methods of monitoring were very limited. Development of better monitoring, such as changes in heart rate and rhythm as detected by ECG, permitted LA toxicity, to be detected earlier. An intact tourniquet is mandatory to minimize the risk of a systemic spillover of the LA leading to potentially life-threatening systemic neuro- or cardiotoxic reactions. The risks are greatest during injection of the LA and the deflation of the tourniquet after surgery. The systemic escape of LA may be caused by a mismatch of tourniquet pressure and venous (injection)-pressure.[47,48] Fast injection and high volumes of LA solution might contribute to this mismatch. An unintended deflation of the tourniquet during the vulnerable period might lead to toxic LA plasma levels. A venous leakage under the tourniquet cuff (probably induced by high injection pressures or due to fracture manipulations) may permit the escape of LA into systemic circulation.[47] Be aware that a minimum injection-release time of 30 minutes does not definitively avoid hazardous intoxications.[48]

Precautions to Minimize the Risk of Tourniquet-Related Complications

August Bier had already realized that leakage under the tourniquet had to be avoided for preventing the systemic flush-in of LA. A sufficient tourniquet pressure had to be maintained, although this might lead to the patients' pain and discomfort.[28] In the 1960s, Holmes monitored the tourniquet pressure by maintaining the tourniquet pressure above the systolic blood pressure.[39] Later, new reliable tourniquet systems, eg, double-chambered cuffs, became available, thus facilitating tourniquet pressure control.

- Ensure the regular maintenance of the inflation pressure equipment
- Choose an adequate cuff width (optimal width: 20% wider than the diameter of the limb)[49]
- Maintain sufficient cuff pressure (300 mmHg) to avoid the escape of the LA[49]
- Avoid a high venous pressure, which depends on the injection-rate, -site and -volume and on the effectivity of exsanguination[49]:
  - A slow injection of the LA in a distal vein over at least 90 sec is mandatory

Tourniquet-Related Complications

According to Bier, the tourniquet was tolerated well by most of the patients. Only a few individuals complained about discomfort.[28] Bier's successor Holmes reported of 13 patients who felt discomfort due to the tightness of the tourniquet.[39]

Another striking disadvantage is the tourniquet pain (temporary ischemic or tourniquet pressure-related nerve injuries with an incidence of 1:8.000), which is mainly caused by pressure and ischemia.[34] Therefore, most patients need a supplementary analgesic treatment.[16] Other minor, tourniquet-related complications include widespread petechiae, skin discoloration, thrombophlebitis and urticaria.[48]

Local Anesthetics

Originally, IVRA was performed with 0.5% procaine (trade name Novocaine) solution of 80 mL (up to 100 mL).[28] In comparison, Holmes mainly used 0.5% lidocaine solution of 40 mL for the upper extremity and up to 100 mL for lower extremtities.[39] Interestingly, Bell and coauthors already chose dosages adapted to a patient's body weight.[14]

In today's literature, dosages of LA for IVRA are not consistent. According to some authors, it is common to inject a volume of 1 mL/kg body weight for the upper extremity and 1.5 mL/kg for the lower extremity.[50] Others recommend applying a volume of 40-50 mL for the upper extremity[17] and 60-80 mL for the lower extremity[30] without adding vasoconstrictors to the LA agent.[17] Furthermore, it is evident that higher concentrations of LA correlate with a faster onset of anesthesia and an improved motor block.[50]

An "ideal" anesthetic agent does not exist. This "ideal" drug would allow applying high dosages while bearing no toxic adverse effects. Moreover, it would have a short response time without promoting large hemodynamic changes,[30] while offering a minimal tourniquet pain and a long-lasting post-deflation analgesia.[51] Table 3 presents an overview of different LA.

Prilocaine

Prilocaine is regarded as the LA of choice due its favorable ratio between potency and toxicity.[30,52,53] It belongs to the amide group and is metabolized by the liver while bearing only a few side effects (eg, methemoglobinemia) when given in usual doses.[30] In case of carefully checked equipment and an experienced anesthesiologist, a concentration of 0.75% prilocaine might be appropriate to assure an adequate IVRA. Otherwise, a concentration of 0.5% is recommended.[54]

Due to the risk of causing methemoglobinemia, which was described the first time in 1964, prilocaine is not available in North America.[55] However, neither serious adverse events nor deaths were reported in 45,000 IVRAs, making prilocaine an extremely safe LA.[56]

Lidocaine

The incidence and severity of adverse events during IVRA with lidocaine appears to be comparably low if administered in appropriate dosages (Table 3). Lidocaine has been widely used in combination with various adjuvants. It offers a fast onset of analgesia (4.5 ± 0.3 minutes) and offset of analgesic effects within 5.8 ± 0.5 minutes after tourniquet deflation.[31,57] The metabolization rate of lidocaine is 8-10 minutes (alpha phase) and 108 minutes (beta phase), respectively.[30] Being an antiarrhythmic agent, lidocaine is known for its cardiovascular safety.[58] The Fellowship of the British Royal College of Anaesthetists (FRCA) recommended a dose of 40 mL of a 0.5% lidocaine solution (without epinephrine).[59]

Prilocaine vs Lidocaine—Commentary

While lidocaine is regarded as the first-choice LA for IVRA in North America,[41] prilocaine is primarily used in Europe.[60] Although IVRA with prilocaine is considered as exceptionally safe, it was withdrawn from the market in the USA due to the risk of causing methemoglobinemia. Bartholomew and Sloan found neither serious adverse complications nor deaths in 45,000 cases of IVRA with prilocaine.[56] Interestingly, opposing conclusions were made by Davidson et al[53] in 2002. These authors compared the analgesic effect of prilocaine and lidocaine in forearm fractures in children and concluded that lidocaine offers a "superior analgesia". However, prilocaine was praised for its lower toxicity. Due to its fast tissue redistribution and rapid hepatic metabolism, prilocaine has an enhanced disappearance rate from blood.[61] Moreover, it is believed to be taken up by peripheral tissues and to be released at a slow rate after tourniquet deflation.[61] Obviously, prilocaine should be used with caution in patients with impaired cardiovascular or lung function because a miscarriage of oxygen due to methemoglobinemia might become clinically relevant. However, this side effect is very unlikely to occur, when prilocaine is

applied in usual dosages (see Table 3). Prilocaine can therefore be regarded as a safe drug for IVRA.

Bupivacaine

Bupivacaine is a very lipophilic and long-acting LA and offers a longer postoperative analgesic effect than lidocaine.[57,62] For IVRA, bupivacaine has been administered in a dose of 1.5 mg/kg (at a 0.2% bupivacaine solution).[61] Due to the risk of cardiac arrest,[43–45] bupivacaine is not recommended for IVRA.[17,30] Interestingly, in three of five deaths resulting from IVRA with bupivacaine, the cuff was not inflated properly at a point where it still was necessary.[43] The plasma concentration levels of bupivacaine vary broadly. The toxic plasma level of unbound bupivacaine lies between 0.13 and 0.51 mg/l (mean free arterial plasma concentration 0.3 mg/l).[63] In vivo, two binding proteins for bupivacaine exist: "α1-acid glycoprotein, the influence of which is predominant at low concentrations, and albumin, which plays the major role at high concentrations."[64] Due to the inflated cuffs and the resulting lack of perfusion, lactic acid accumulates in the blood. Lactic acid alters bupivacaine's protein binding, resulting in an increase in free bupivacaine concentration.[64] Therefore, it seems to be possible to reduce the amount of bupivacaine in plasma by the application of lipid solutions, thus lowering bupivacaine's systemic toxicity.[65]

Ropivacaine

Ropivacaine is a pure S(-)enantiomer, which is a racemate developed to reduce potential neuro- and cardiotoxicity.[63] Chan et al[66] compared the anesthetic effect of two concentrations of ropivacaine (1.2 and 1.8 mg/kg, maximum dose of 180 mg) and that of lidocaine (3 mg/kg). They demonstrated that the time of anesthetic onset of lidocaine and ropivacaine was similar. However, in contrast to lidocaine, higher concentrations of ropivacaine (1.8 mg/kg) were able to maintain a longer residual sensory block. Asik et al[67] compared 0.2% and 0.25% ropivacaine with 0.5% lidocaine for IVRA. They observed a prolonged tourniquet tolerance time and a better postoperative analgesia when using ropivacaine, especially at higher concentrations. Therefore, ropivacaine is effective for IVRA and is a recommended alternative to lidocaine. Nevertheless, it is not part of the daily clinical routine in IVRA.[30,67] Table 3 shows the dosages of the most common LA in IVRA. All doses are referred to a volume of 40-50 mL.[17,30]

Lipid Resuscitation

In 2003, Weinberg et al reported about the successful resuscitation of dogs in which toxic levels of bupivacaine were produced. All "treated" dogs received a lipid emulsion and were rescued. The control group consisted of 6 "untreated" dogs, which could not be resuscitated.[70] Shortly after, Rosenblatt and colleagues published a remarkable case-report about a 58-year-old patient who developed a tonic-clonic seizure and then a cardiac arrest after an interscalene block with bupivacaine and mepivacaine. It was presumed that the cardiac arrest was bupivacaine-related and they decided to try resuscitation with a lipid emulsion. Subsequently, a sinus-rhythm was restored and the patient did not suffer any neurological deficit.[71] "A once feared complication of regional anesthesia may have just become slightly less fearsome".[72]

The American Society of Regional Anesthesia and the Association of Anaesthetists of Great Britain and Ireland provide guidelines for lipid emulsion resuscitation in cases of LA toxicity. Although descriptions may vary, the priority of every intervention starts with the establishment of an adequate airway management, followed by seizure suppression (by means of benzodiazepines) and by the infusion of a lipid emulsion, when clinically indicated. Also, measurements for basic life support including chest compressions may be necessary to ensure tissue perfusion as well as the circulation of the resuscitating agent.[73]

It is recommended to use a large bolus injection of a 20% lipid solution (1.5 mL/kg), followed by a continuous infusion (0.25-0.5 mL/kg/min) for 10 min. Note that the initial bolus injection is critical for fast resolution of symptoms.[73]

Local Anesthetics—Conclusions

- Prilocaine and lidocaine both are effective for IVRA and are routinely applied in daily practice.
- Prilocaine seems to be safe if applied in adequate dosages.
- Bupivacaine should not be used for IVRA.
- Ropivacaine is a promising long-acting alternative for IVRA but more trials are needed.
- Institutions performing IVRA should immediately be able to apply lipid resuscitation in cases of intoxication with LA.[73]
  - Initially: Bolus injection of a 20% lipid solution (1.5 mL/kg)
  - Maintain continuous infusion of 0.25-0.5 mL/kg/min over 10 minutes

Adjuvant Drugs

In the 1990s, several publications discussed adjuvant drugs for IVRA.[74] It was a logical step to evaluate the effects of adjuvant drugs for IVRA as it had become a daily practice to combine differently acting drugs in general anesthesia. For IVRA, the adjuvants were intended to reduce post-deflation pain and to achieve a better quality and longer duration of analgesia.[51] However, with a few exceptions, adjuvants have not shown uniform and reproducible effects in IVRA. An overview of adjuvants is given in Table 4.

Table 3
LA options in IVRA. Bupivacaine is not listed because it is not recommended for IVRA (cardiac arrest).[a,17,30,44] All doses refer to a volume of 40-50 mL.[17,30]

Local Anesthetic Agent	Concentration [%]	Dose [mg/kg body weight]	Specific Adverse Effects
Ester			
Chloroprocaine[30]	0.25-2	8	Thrombophlebitis
Amides			
Prilocaine[b17,54,55,61]	0.5 (0.75 [a])	3-4	Methemolobinemia: Very unlikely when administered in appropriate dosages; occurs within 4-8 h after application
Lidocaine[17,31]	0.5	1.5-3	Mild bradycardia, dizziness or tinnitus
Articaine[68,69]	0.5		Erythematous rash at the site of injection
Levobupivacaine[30]	0.125	2	
Ropivacaine[c,30]	0.2-0.375	1.2-1.8	
Mepivacaine[17]	0.5	1.5-3	

[a] Due to the risk of cardiac arrest,[44] bupivacaine is not recommended anymore.[17,30]
[b] Prilocaine is unavailable in the USA. Use 0.75% prilocaine solution only in combination with a carefully maintained equipment and an experienced anesthesiologist.[54]
[c] For ropivacaine more clinical trials are needed.[30]

Opioids

Opioid receptors exist in both the central nervous system and the peripheral tissues. Nevertheless, except for meperidine (also known as pethidine), other opioids were not proven to have a significant clinical benefit as adjuvants for IVRA.[51] Although meperidine showed some benefits (like enhancement of IVRA due to better postoperative analgesia),[75] side effects like light-headedness and nausea were also present.[73]

Muscle Relaxants

Atracurium (2 mg) in adult upper limb surgery was beneficial in terms of muscle relaxation because poor muscle relaxation might compromise the quality of the surgical procedure.[76] Atracurium, which follows the rules of Hofmann elimination, is considered as the neuromuscular blocking agent of choice.[68]

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

Although many NSAIDs have been extensively studied, only ketorolac (20 mg),[51,77,78] tenoxicam (20 mg)[51,79] and acetylsalicylate (90 mg)[51] were found to improve postoperative analgesia and to reduce tourniquet pain. Dose-determination studies demonstrated no further advantages of ketorolac doses above 20 mg.[80]

Benzodiazepines

Benzodiazepine receptors can be found in all mammalian peripheral tissues.[81] Supplementation with midazolam of an IVRA based on lidocaine may improve the quality of anesthesia and perioperative analgesia with a faster onset of the motor and sensory block.[82]

Clonidine

Clonidine is a central alpha-2-adrenoreceptor agonist. Clonidine (1 μg/kg) in a combination with 0.5% lidocaine may improve postoperative analgesia.[83] Although these findings have not consistently been shown by other authors,[84,85] Gentili et al described reduced tourniquet pain after the addition of 150 μg clonidine to lidocaine.[86]

NMDA-Antagonist: Ketamine

Although ketamine appeared to provide some alleviation of pain, patients exhibited hallucinations (ie, typical systemic ketamine effects) after tourniquet deflation, when it was used together with prilocaine or lidocaine.[87,88] Compared to its systemic administration, there is no beneficial effect when using ketamine as an adjuvant for IVRA.[88] Nevertheless, the combination of ketamine and LA can effectively delay tourniquet pain, reduce the patients' analgesic requirements and the block's time of onset.[89] For ketamine's use in IVRA, the recommended dosages are controversial.[87–89] Gorgias et al[89] recommended a dose of 0.1 μg/kg.

Further Agents

Table 4 lists other possible adjuvants, which have been studied to improve IVRA. Although some studies demonstrated their effectivity, the evidence of these findings remains questionable. Interestingly, Zhou et al[90] even reported on the use of emulsified isoflurane in synergistic action with lidocaine in rats.

Table 4
Overview of possible adjuvants for IVRA. Clinically relevant adjuvants are marked in bold.

Category	Adjuvant	Dose
Opioids	**Meperidine / Pethidine**[51,75,91]	**10-100 mg**
	Fentanyl[17]	0.1-0.2 mg
	Sufentanil[51]	25 μg
	Morphine[17]	1-6 mg
	Tramadol[74]	50-100 mg
Muscle relaxants	**Atracurium**[76]	**2 mg**
	Pancuronium[92]	0.5 mg
	Mivacurium[93]	0.6 mg
Benzodiazepines	Midazolam[82]	50 μg/kg[a]
Non-steroidal anti-inflammatory drugs (NSAIDs)	**Ketorolac**[94]	**20 mg**
	Tenoxicam[79]	**20 mg**
	Acetylsalicylate[51]	**90 mg**
	Dexketoprofen[95]	50 mg
	Lornoxicam[96]	8 mg
	Paracetamol / Acetaminophen[97]	300 mg
NMDA-antagonist	**Ketamine**[17]	**0.1 mg/kg**[a]
Steroids	Dexamethasone[78]	8 mg
Central alpha-2-adrenoreceptor agonist	Clonidine[17]	1 μg/kg[a]
Anticonvulsants	Gabapentin[98]	1.2 g
Inorganic salts	Magnesium sulphate[99]	1 g
Hormones	Melatonin[100]	10 mg
Nitrates	Nitroglycerin[101,102]	200-400 μg
Acetylcholinesterase inhibitor	Neostigmine[103]	0.5 mg
Serotonin 5-HT_3 receptor antagonist	Ondansetrone[104]	4 mg

[a] kg of body weight

IVRA in the Treatment of Complex Regional Pain Syndrome (CRPS)

Complex regional pain syndrome (CRPS) is a chronic pain condition with 2 types: Type 1 most commonly occurs postoperatively or after a forceful trauma, and type 2 (formerly known as causalgia) follows a nerve injury. Although different therapeutic options are available (drugs, nerve blocks, physical therapy, sympathectomy) the treatment of CRPS remains difficult and challenging. This is why it was a logical step to use IVRA as another treatment option.[24]

Between 2000 and 2012, Cossins et al[105] reviewed randomized controlled trials dealing with the treatment of CRPS. They stated that IVRA—as a treatment option for CRPS—remains a matter of controversial debate. This is consistent with the actual practical, diagnostic and treatment guidelines on CRPS.[106] These guidelines name several drugs for which the quality of evidence is low: bretylium, phentolamine, clonidine, lidocaine, and ketorolac (alone and/or in combination). The superiority of guanethidine over lidocaine could not consistently be proven.

In summary, it can be said that although multidisciplinary guidelines on the treatment of CRPS type I state that IVRA may provide beneficial effects,[27] IVRA does not belong to the first-line treatment methods for CRPS. More prospective data are needed, especially in pediatric patients.[107]

Conclusions

IVRA ("Bier's Block") is an established simple and safe anesthetic technique with a history of more than one hundred years. It can be applied for short surgical procedures of the upper and lower extremities and offers a favorable risk-benefit profile, cost-effectiveness and a fast on- and offset. Although major adverse events are rare during IVRA, systemic neuro- and cardiotoxic side effects may be linked to an uncontrolled systemic flush-in of LA; thus improper garroting, high venous injection pressure or premature recirculation must be avoided. Since newer methods for monitoring, specialized personnel and improved emergency equipment have developed since Bier's

time, IVRA has become a much safer technique. Most often the local anesthetics prilocaine or lidocaine are administered and some adjuvant drugs may be beneficial as a supplement to IVRA. Today, IVRA is still popular in many countries and is suitable for a wide selection of operations especially in the emergency room, for outpatients and for high-risk patients with contraindications for GA. Moreover, IVRA may be applied to achieve pain reduction in CRPS, although it does not belong to the first-line treatment methods for CRPS.

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