International Journal of
Regional Anaesthesia

Technological and Pharmacological Advancements in Regional Anaesthesia and Acute Postoperative Pain

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The last two decades have seen immense popularity and interest for using ultrasound (US) in the practice of regional anaesthesia (RA) for performing regional nerve blocks, fascial plane blocks, and even for central neuraxial blocks [1-3]. Use of US in RA not only increase the success rate; it also reduced the complications and also facilitated several new blocks especially the fascial plane blocks in recent years. Probably this was just a beginning because, in recent years, many technological advances have been made to popularize RA, to make it safe, and to provide long-lasting analgesia to the patient [4, 5]. This editorial describes the technological and pharmacological advances made in the last decade related to RA and acute pain medicine.

Advanced Gadgets and Technology for RA:

Conventionally, the US machine used in routine RA practice is 2D or 2-dimensional, and the same is used in teaching institutes and workshops. The present US machines are light-weight, portable, have advanced features like touch-screen, high-resolution images, better needle visibility, taking snapshots or recording videos, and many more. Few papers have described the use of 3D US in RA. However, the issues with 3D-US in RA are a slow refresh rate than 2D and difficulty in real-time needle visualization and tracking [6, 7]. Few RA enthusiasts have demonstrated successful use of 4D-US in RA. By using the 4D US, the performer can simultaneously visualize multiple planes like longitudinal, cross-sectional, and coronal adjusting the probe. 4D also provided a spatial relationship between anatomical structures of interest compared to standard imaging, which could prevent undesirable complications. With 4D US accurate volume measurements of LA can be made with visualization of the spread of LA at the site of interest. However, the issues are 4D US needs a different machine and probe which might not be feasible for someone who already has the 2D US [8].

Portability has reached the next level with the introduction of the Lumify probe by Philips, USA. This probe can be connected to a smartphone or a tablet [9]. A Philips Lumify Ultrasound App is available for download on both Android and Apple phones for free. However, in India, the RA enthusiast needs to comply with the Pre-Conception and Pre-Natal Diagnostic Techniques (PC-PNDT) act before planning to buy and use it [10].

Robotics in US-guided RA:

In the medical field, the principles of robotics have been applied successfully in robotic-assisted surgeries, rehabilitation, medical transportation, sanitation of hospitals, and drug dispensing. In 2002, Cleary et al used a robotic system developed by URobotics (Urology Robotics) Laboratory to perform nerve and facet blocks at the lumbar region of embalmed cadavers successfully thus opening a new avenue for performing RA techniques using advanced technology [11]. Later Tighe et al performed US-guided nerve blocks in phantom using the da Vinci surgical robotic system (Intuitive Surgical, Sunnyvale, CA) [12]. This system is also used for robotic-assisted surgeries. The authors demonstrated successful single injections and perineural catheters using the robotic system. This led to the development of a task-specific robotic device for RA. Magellan system is a robotic system exclusively

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DOI: 10.13107/ijra.2022.v03i01.046 | www.ijrajournal.com |

developed for US-guided regional anaesthesia [13]. The Magellan system comprises a joystick, a robotic arm, and a software control system.

Hemmerling et al described the first robotic US-guided nerve blocks in humans using the Magellan system which is a robotic system for US-guided RA [14]. The authors employed the sciatic nerve block in 13 patients all of which were successful and required 3-4 minutes to perform. Morse et al conducted a study in which they compared success rates, learning curves, and inter-subject performance variability of robot-assisted and manual US-guided nerve block needle guidance in simulation [15]. A Magellan robotic nerve block system was used for this study. The authors concluded that robot-assisted nerve blocks lead to faster learning of needle guidance over manual positioning and reduce inter-subject performance variability. Currently, the Magellan system is not FDA-approved, is costly, has not been validated by comparative, randomized studies.

Injection Pressure Monitoring:

In the current practice of RA, monitoring injecting pressure while injecting LA for a peripheral nerve block or a fascial plane block is considered the gold standard. A high injection pressure i.e., more than 20 pounds per square inch (PSI) has been associated with intraneural or intrafascicular injection leading to unwanted neurological consequences postoperatively [16, 17]. At present there are three monitors available in the market with different pros and cons.

B-SmartTM (B. Braun Medical, Bethlehem, Pennsylvania, USA) was the first disposable, injection pressure monitor released in the market. It uses membrane sensing technology to monitor real-time injection pressure while injecting LA [18]. When the injection pressure crosses 15 psi, the piston-color changes from white to yellow, and after reaching a pressure of more than 20 psi, there is a change in piston color from yellow to orange [19]. NerveGuard® (Pajunk Medical Systems, Geisingen, Germany) is another gadget available for a similar purpose but with different technology. It detects high pressure while injecting (more than 20 psi) and automatically stops the injection of LA while performing a block. This is due to the presence of a Luer lock mechanism between the syringe and the extension tubing of the nerve block needle [20, 21]. Recently, Medovate, a company in the United Kingdom introduced the SAFIRA (SAFer Injection in Regional Anaesthesia) pump which gives a combined benefit of injection pressure monitoring and controlled injection of LA [22]. The SAFIRA system consists of three components; a sterile single-use syringe, a driver, and a foot pedal. The foot pedal has two parts, a green and a yellow. On pressing the green part of the foot pedal, the syringe loaded with LA will infuse the LA at the site of interest. On pressing the yellow part of the foot pedal, the loaded LA is aspirated before injection. There are three driver indicator lights. When the green is on, it means LA is infusing. A yellow light indicated aspiration, and red light is suggestive of either a low battery or an empty syringe. The company mentions that the driver and foot pedal can be used for up to 200 peripheral nerve blocks comfortably [23]. The pump is currently available in the UK, USA, Australia, Israel, and a few European countries.

Needle Visualization on the US:

The SonixGPS® system (Ultrasonix Medical Corp, Richmond, BC, Canada) is an electromagnetic needle tracking system developed for US-guided needle interventions. This needs specially designated needles for planned interventions. Niazi et al used this system in 20 patients for performing spinal anaesthesia and concluded that with its use, the procedure is simplified especially with an out-of-plane approach [24]. The experience of Brinkmann et al with 20 patients in whom they performed spinal anaesthesia was similar. They concluded that US-guided subarachnoid block was easy to perform, with a low rate of failure and complications [25].

Long-Acting, Sustained-Release Local Anaesthetics:

Liposomal bupivacaine, marketed as Exparel (Pacira Pharmaceuticals, Inc., Parsippany, NJ, USA) is an extended-release formulation of bupivacaine which was approved by US-FDA for a single-shot infiltration of the surgical site in 2011 [26]. In a review article published by Hamilton et al in Cochrane Database Systematic Review, it was concluded that the use of Exparel did appear to reduce postoperative pain when compared to a placebo [27].

Exparel consists of encapsulated multivesicular liposomes (DepoFoam formulation Multivesicular spherical lipid particles in a honeycomb formation). This unique liposomal-based structure confers stability and extended-release properties to the formulation. The median diameter of the liposome particles ranges from 24 to 31 μm [28]. Although Exparel was approved for use only for infiltration at the surgical site, researchers published their experiences of off-label use of Exparel in various peripheral nerve blocks of upper and lower extremities. To date, papers have been published with the use of Exparel in popliteal, ankle, femoral, intercostal, penile, pectoral nerve block, and transversus abdominis plane block with variable results [29-32]. With the introduction of liposome-based LA and analgesics and after the success depicted in case series and certain comparative studies, in the last few years there were

several pharmacological agents which were launched in the market.

SABER Bupivacaine:

Durect Pharmaceuticals, California, USA developed an experimental drug with a working name: SABER bupivacaine (POSIMIR®). It is available as a thick, translucent solution and consists of bupivacaine, biodegradable depot composition (sucrose acetate isobutyrate), and benzyl alcohol thereby causing extended-release of bupivacaine after infiltration at the surgical site. In a 5 ml solution, there is 132 mg per ml of bupivacaine base which is equivalent to 743 mg of bupivacaine hydrochloride in the 5 ml solution. Studies have shown that the analgesic efficacy after infiltration peaks at 13-17 hours and fades by 72 hrs.

Hadj et al randomized patients undergoing open hernia repair to receive 2.5 ml (330 mg), 5 ml (660 mg) of SABER-bupivacaine with placebo. In both the groups which received the experimental drug, the analgesic efficacy was better than the placebo with no interference in wound healing and devoid of any adverse events [33]. BESST (Bupivacaine Effectiveness and Safety in SABER Trial) is registered with clinicaltrials.gov and has 3 cohorts: 1-laparotomy, 2- laparoscopic cholecystectomy, 3-laparoscopic-assisted colectomy. The results of this trial have not been published yet [34]. As of now, SABER-bupivacaine still awaits US-FDA approval.

HTX-011:

HTX-011, now marketed as ZYNRELEF™ by Heron Therapeutics, Inc. is a novel formulation comprising extended-release, fixed-ratio of bupivacaine as the main drug with low-dose meloxicam to enhance the effectiveness of infiltrated bupivacaine [35]. This combination is integrated into a bioerodible polymer (Biochronomer®). On injection at the surgical site, there is controlled hydrolysis of the polymer which leads to sustained release of both bupivacaine and meloxicam for 3 days.

In the EPOCH-2 study, which is a phase 3, randomized, double-blind, active-controlled multicenter study; Viscusi et al enrolled 18 patients into 3 groups. In one group the patients received HTX-011, in second bupivacaine infiltration, and the third group received placebo. On analysis, the authors concluded that there was a significant improvement in postoperative pain control and a significant reduction in opioid consumption when compared to bupivacaine [36]. In another phase 2b, double-blind, placebo-controlled, and active-controlled trial by Lachiewicz et al, authors enrolled 232 patients undergoing unilateral total knee arthroplasty into 4 groups [37]. The first group received HTX-011 400 mg bupivacaine/12 mg meloxicam, applied without a needle into the surgical site. In the second group, patients received the same dose of HTX-011 with an additional 50 mg ropivacaine injection into the posterior capsule. The patients in the third and fourth group received bupivacaine 125 mg injection, and saline placebo injection respectively. On analysis, the authors concluded patients in the first two groups which received HTX-011 had better pain scores when compared to bupivacaine alone and placebo. ZYNRELEFTM is now US-FDA approved for treating acute postoperative pain by infiltration at the surgical site [38].

Neosaxitoxin:

Neosaxitoxin is a phycotoxin derived from the shellfish and has demonstrated a reversible block of voltage-gated sodium channels at the neuronal level. Neosaxitoxin shows more affinity to sodium channels in peripheral nerves when compared to that in the myocardium. This favorable property paved way for research in using it for prolonging the analgesic effect of LA.

Rodriguez-Navarro et al conducted a randomized, double-blind, placebo-controlled trial by recruiting 10 healthy volunteers who received subcutaneous injections in the middle posterior skin of the calf. One leg received 50 μg neosaxitoxin, and the contra-lateral leg received a placebo. The authors concluded that neosaxitoxin is an effective LA when injected into a subcutaneous plane [39]. In 2011, Rodriguez-Navarro et al conducted a randomized, double-blind trial comparing neosaxitoxin with bupivacaine via port infiltration for postoperative analgesia following laparoscopic cholecystectomy [40]. On analysis, the authors concluded that neosaxitoxin is safe, prolonged postoperative analgesia when compared to the control group. Later, Lobo et al investigated the safety and efficacy of neosaxitoxin alone and in combination with 0.2% bupivacaine with and without epinephrine in a double-blind, randomized, controlled trial involving 84 healthy male volunteers aged 18 to 35 years [41]. The authors concluded that neosaxitoxin combination did prolong LA and had a tolerable side effect profile. As of now, neosaxitoxin continues to be an experimental medication with no formal US-FDA approval and also lacks studies involving off-label use in clinical situations.

Percutaneous Peripheral Nerve Stimulation:

Percutaneous nerve stimulation (PNS) is a neuromodulation technique that has been used successfully in managing acute postoperative pain and chronic pain of

varying causes.[42] The stimulating electrode of PNS is placed under US guidance in or around the muscle/nerve, usually 1–3 cm from the target. Initially, the electrodes are tested by placing them at the desired site using a Tuohy needle. Once convinced, the electrodes are connected to an external battery source (implanted) to generate current for stimulation. This modality is not only opioid-free but does not even need LA. It can be kept in situ for up to 60 days. [43] The product is US-FDA approved for chronic pain, post-traumatic, and postoperative pain. The stimulator is marketed by SPRINT® PNS System. [44]

In summary, the popularity of RA amongst all anaesthesiologists resulted in extensive research in developing newer and safer technologies that can be applied in RA. The newer pharmacological agents which are either approved or under investigation can be useful in providing cost-effective and opioid-sparing analgesia in the postoperative period. In other words, the future of RA and acute pain medicine looks bright.

Conflict of interest: Nil **Source of support:** None

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Last accessed on: 8th January 2022.

How to cite this article: Nair AS, Diwan S | Technological and Pharmacological Advancements in Regional Anaesthesia and Acute Postoperative Pain | International Journal of Regional Anaesthesia | January-June 2022; 3(1): 03-07.