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Review Article

ULTRASOUND GUIDED REGIONAL ANESTHESIA: WHAT WE KNOW, WHAT WE THINK WE KNOW, WHAT WE DON`T KNOW YET

(running title USGRA: overview about facts and questions)

An educational narrative review of literature

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Summary & Objectives

The introduction of ultrasound guidance over the last two decades brought progress, new blocks and new challenges to Regional Anesthesia. This narrative review addresses and discusses facts, frequent questions, beliefs, controversies, unsolved issues, open safety questions and existing knowledge gaps related to efficacy and safety of ultrasound guided regional anesthesia (USGRA), based on the available literature. We discuss evidence-based advantages and limitations of ultrasound guidance, as well as unresolved questions, with respect to successful anesthesia, undesired side effects and patient safety, like nerve injury and local anesthetic systemic toxicity (LAST). In an educational approach we also emphasize some practical aspects of our everyday experience as well as necessary structural requirements.

Key Words *Anesthesia; peripheral regional; Ultrasonography; Patient safety; Nerve injury; Adjuvants; Hygiene aspects; Coagulation disorders*

Introduction

From the end of the 90s, several advantages of Ultrasound Guided Regional Anesthesia (USGRA) compared to classical techniques have been described[1,2,3]. Up to this moment, peripheral nerves or groups of nerves (plexuses) have been located either by anatomical landmarks and provoking nerve paresthesia or by electric nerve stimulation, inducing a motoric or sensory response. This led to a high rate of unsuccessful blocks, insufficient analgesia and probably to a high rate of unnoticed intraneural injections. Historically described and used techniques like fascial "clicks" by using blunt needles, provoking paresthesia by nerve needle encounters, injecting „ice-cold" saline or the transarterial approach for axillary plexus, could cause discomfort or harm. The use of nerve stimulation to provoke a motoric nerve response had painful side effects when used in a fractured limb. The use of ultrasound for the first time allowed visualization of anatomy at the bedside. Technical improvements like smaller bedside ultrasound machines, higher frequency probes and better software solutions have led to a growing popularity of ultrasound guided nerve and fascial blocks worldwide. Further technical solutions, availability of affordable ultrasound machines all over the world and changes in clinical approach are necessary to improve patient safety[4].

Material and Methods

Literature research of PubMed/ MEDLINE, Google Scholar and NYSORA learning system (nysoralms.com). Key words / search terms: Ultrasound guided regional anesthesia, nerve blocks,

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fascial blocks, efficacy and success rate of ultrasound guided nerve blocks, education and training in ultrasound guided regional anesthesia, needle guidance, needle tip detection and technical solutions, in plane and out of plane needle insertion, equipment, ultrasound machines, nerve injury, incidence of nerve injuries related to regional anesthesia, local anesthetic systemic toxicity (LAST), dual guidance, nerve stimulation, injection pressure monitoring, triple guidance, hygiene in regional anesthesia, infection prevention in regional anesthesia, regional anesthesia and coagulation disorders, patient safety in regional anesthesia. We included scientific reviews and meta-analyses, randomized controlled trials, prospective cohort studies, retrospective cohort studies, animal studies, cadaver studies, textbook chapters, case series, case reports, editorials and pertinent correspondence in English language, German language and French language in our research, to identify and address controversies and open questions related to USGRA. We did not perform Jada or GRADE scoring of the references. We did not perform meta-analysis. Thus, effect size and risk differences for the questions raised are not numbered. Aiming at an educational compilation and presentation of the current knowledge, we focused on the last 15 years, but also included very pertinent or groundbreaking older references. We analyzed all sources for relevance for the questions asked. The characteristics, quality and limitations of references are mentioned and discussed in the text, where deemed necessary.

Indisputable advantages of direct imaging

Ultrasound offers the real time imaging of three important aspects[5]:

- Visualization of the anatomy. This includes the structures to block (plexus, bigger nerves of the upper and lower limb, fascial planes), but also surrounding tissue layers and structures to avoid like vessels or pleura. An important advantage is the fact, that ultrasound detects anatomical variations and abnormalities. For example, the relationship between nerves and vessels is very variable and with landmark techniques this may lead to failed blocks or to injuries.
- Visualization and guidance of the needle to avoid damage of anatomical structures on its pathway. This reduces the risk of needle trauma, though it can be challenging to visualize the needle tip at all times. This will be discussed later on.
- Ability to see the distribution and spread of local anesthetics in real time. If the applied volume doesn`t spread around the desired areas, the needle tip can and must be repositioned and adjusted. This was impossible with all the former techniques.

Sonoanatomy: Is it possible to get the whole picture?

The ultrasound image must show at the same time the anatomical target structure and the needle tip. It is important to keep in mind that the image is two- dimensional, while anatomy is not. So profound knowledge of anatomy is necessary („you see what you are looking for"), but also practical training and knowledge about the technical features of the ultrasound machine. These skills are necessary to provide equivalent success compared to general anesthesia[6]. Optimizing the image and understanding sonoanatomy requires knowledge of the underlying basic principles of physics like choosing the right probe, frequency selection, image depth, the use of time gain compensation, adjusting focus, using filters etc. Axial and lateral resolution of the image, as well as the depth of tissue penetration by the ultrasound beam, are influenced by frequency, pulse length and the position of the narrowest zone of the ultrasound beam, the so- called focus. In real time pictures of moving objects – like needles advancing in tissue layers – temporal resolution, i.e., the frame rate with which consecutive images can be generated, is also important. Modern ultrasound machines offer several presets, the use of which in turn requires profound anatomical knowledge of the structures one wants to see, block or avoid. Trainable skills include optimizing the angle of insonation by tilting, sliding, rotating, aligning the transducer to the anatomical target structures and varying the degree of pressure applied to the probe. The mnemonic "PART – pressure, alignment rotation, tilting"- is useful and recommended in the literature[5]. Providers should master the use of different Doppler-modi to identify vessels

and differentiate them from nerval structures. M-Mode are useful to identify moving structures like pleura sliding or bowel movement, when performing fascial plane blocks at the trunk.

Knowledge of important acoustic artifacts like mirror artifact, reverberation artifact, acoustic shadows (by bone or air), acoustic enhancement (by fluids), noise and twinkling artifacts, lateral cystic shadowing etc. is of the most importance, as those phenomena may fake or occult anatomical structures and lead to incorrect needle guidance[5,6,7]. The needle itself may be reflecting the ultrasound waves so extensively, that it creates reverberation and mirror artifacts. A summary of different artifacts, their physical origin and significance, as well as of challenges presented by patients' anatomy is presented at[8].

How can we optimize training and education?

Structured training and education in ultrasound guided regional anesthesia should be mandatory for residents. In any training program it seems important that teachers emphasize basic, but helpful details like an ergonomic position of the ultrasound machine. A mandatory minimum number of ultrasound- guided blocks during residency is part of the specialist training program in several countries and teaching curricula have been implemented[9] or fellowships suggested[10]. Remarkably, even very short training rotations of 4 weeks with structured instructions improved residents´ recognition of relevant sonoanatomy significantly[11]. Some authors argue that competency-based education with skilled and dedicated supervisors, quality assessment, educational feedback and a structured educational environment is at least as important as the numbers performed, especially when it comes to difficult cases[12]. The exact amount of training needed is scientifically unknown, although there is some data from cadaver studies[13,] and is variably dependent on the trainees` and trainers` personal and didactic skills[14]. There are several training programs including cadaver workshops[15,16] or meat models[17] without one method being defined as „gold standard" based on scientific data and further research needed[18,19]. A combination of different methods like simulation, using meat models, debriefing, supervision and feedback recommended[20]. Reviews confirm that simulation in regional anesthesia training is useful[21,22,23]. Structured expert feedback is superior to self- directed learning on simulation training[24]. ESAIC recently published a guideline (PERSEUS regional anesthesia) with a strong focus on education, training and certification. They define an "expert trainer in ultrasound-guided regional anesthesia" and suggest performance indicators. To follow these guidelines will require profound change of national training programs, as they mostly still focus on numbers only and USGRA fellowships need to be established[25]. Software programs integrating pictures of the „real", anatomy into the software of ultrasound machines may help to improve teaching and learning. Recent technical developments to guide needle placement close to the nerves without puncturing them, include passive magnetic ultrasound needle guidance technology, which improved accuracy of needle procedures in one study[26] but is not yet widely available. Other possible technical improvements for teaching in the future include ultrasound combined with pressure guidance, video visualization guidance, electromyography guidance, electromagnetic Guidance Positioning Systems (GPS), image fusion guidance and the combination of artificial intelligence (AI) with neural networks and pattern recognition with ultrasound[27]. AI significantly improves recognition of anatomical structures by non-experts[28] but its value in teaching and clinical setting is yet to be investigated[29]. Today there is no strong evidence of superiority for any of these to recommend them as a standard in teaching[30]. There is an ongoing debate how many different blocks the average anesthetist should master. Turbitt et al. raise the question if we really need more blocks or rather better practice and widespread implementation of some „basic blocks", also called „high value nerve blocks"[31]. As ultrasound allows the development of more and more different approaches, this is an important question for further educational programs with regard to competency in basic regional anesthesia for as many anesthesiologists as possible. It is unclear how many different blocks need to be implemented in the standard of care and multimodal analgesia programs and thus in the mandatory education of specialists. It seems more promising to focus on blocks that have been proved effective, efficient and easy to implement in any clinical setting[19,31,32,33].

Is an in plane needle insertion really safer than out of plane?

In the author`s personal experience it is crucial, that beginners understand the terms „short axis and long axis", which refer to the anatomic structure, and the terms „in plane and out of plane" that refer to the position of needle and probe. In plane signifies the needle parallel to, out of plane perpendicular to the long axis of the probe.

There is no data to establish a superiority of one of these methods with regard to patient safety. A topic of controversy is the approach to the interscalene block. Dorsal scapular and long thoracic nerves are often difficult to visualize inside the medial scalene muscle. They are prone to injury by an in plane needle path through the muscle[34]. A direct comparison of both techniques in an RCT on 84 patients with interscalene catheters did not find any difference in complications or success rate[35]. Literature on vascular access with ultrasound is contradictory about the best approach[36,37,38,39], while available trials on peripheral blocks are mostly inconclusive[40]. In a direct comparison with 24 students on an ultrasound phantom, Meiser et al. found a significant difference in success and time with and without needle navigation, but not between in plane and out of plane insertion[41]. Another trial found needle guidance helpful for an out of plane approach by inexperienced sonographers but did not compare it directly to in plane[42]. Other authors found no superiority of a needle tracking system for in plane insertion in a blinded cross-over RCT on 26 volunteers[43]. It is indeed challenging but crucial, to visualize the needle tip in any approach[44]. Using an in plane approach, which is often presented as „best practice"[34], the needle must be aligned perfectly parallel to the probe, but may in fact often be introduced slightly oblique. It is dangerous to misinterpret a part of the shaft for the needle tip, which is in fact some millimeters further, possibly causing damage. Furthermore, it is sometimes difficult to get the best picture of the needle and of the target structure at the same time, due to anisotropy of nerves. On the other hand, using an out of plane approach without being familiar with more complex techniques like the „walk down maneuver" and identifying the more hyperechoic small double signal of the needle tip, the needle tip can very easily be pushed behind the scanning plane[7]. In practice, many people prefer an in plane approach in teaching, but we do not have any satisfactory evidence about the best introduction technique, neither in general, nor for each single block. Furthermore, there may be differences between single blocks and catheter insertion[45]. Needle recognition software (electronic beam steering) and technical solutions like „harmonic imaging" (nonlinear propagation of the ultrasound waves through the tissue layers), "compound imaging" (multiple images of an object combined in one image) are available on most of the modern ultrasound machines, even if strong evidence of their efficacy is lacking. Furthermore, they show limitations in deep blocks. "Echogenic" needles with polymeric coating may be helpful in both insertion techniques, when puncture angles become steeper than 30-45 degrees to the probe, but they are not ubiquitously available[46]. In obese patients, where the ultrasound beam is attenuated and problems with axial, lateral and temporal resolution and reverberation become more pertinent, „hydrolocation" or „hydrodissection" with minimal amounts of saline is useful to identify the needle tip and increase safety[44,47,48] without deteriorating the quality of block[49]. Small amounts of fluid create a space to advance the needle further and serve as an acoustic window with dorsal enhancement. It is crucial not to have any air microbubbles in the syringe.

What are the evidence-based advantages of USGRA?

For more than 10 years there is an ongoing debate about the level of evidence on the advantages of ultrasound[50]. From the end of the 90s to the first decade of the 2000s, there have been multiple trials comparing USGRA and neurostimulation for different blocks. Major findings included[25,51,52]:

- Improved success of sensory blocks
- Decreased need for rescue analgesia
- Faster onset of the blocks / reduced time to achieve an effective block
- Speedier execution of the block
- Less procedural pain
- Less skin punctures
- Less vascular punctures

- Reduced amount and volume of local anesthetics needed
- Reduced incidence of Local Anesthetics Systemic toxicity (LAST)

The PERSEUS- RA guidelines by ESAIC emphasize the fact that there are only a few high-quality clinical trials and cohort studies and there is "remarkably little good evidence of this nature"[25]. Hopkins questioned the need for such comparative trials in a remarkable editorial 15 years ago, citing several obvious benefits of USGRA[53]. Considering the limitations of many trials, we decided to include the findings of previous systematic reviews. Liu et al. in an older systematic review, analyzing 14 RCTs and 2 case series with over 100 patients, reported a reduced number of attempts and shorter time to perform blocks with USGRA compared to neurostimulation. They reported improved block quality only in "some cases". The efficacy of ultrasound guidance was high but not significantly better than with neurostimulation. In 2009, despite several small studies stating the opposite, the authors of this review concluded that ultrasound was not inferior but did not significantly improve the success of regional anesthesia. There wasn't any data on nerve injuries, as no serious complications had been reported in the included studies[54]. In contrast, another meta-analysis and systematic review of RCTs by Abrahams et al., also in 2009, found faster onset, higher success rate, longer duration and a relative risk reduction of 84% for vascular punctures with USGRA compared to nerve stimulation, but data and sample size were not sufficient to show a reduction of nerve injuries and LAST[55]. Munirama and McLeod, in a meta-analysis of over 2000 patients, found significantly less vascular punctures, reduced periprocedural pain and less need for analgesic rescue with a significantly improved block success rate (91,8 vs.82,8%) when using ultrasound compared to nerve stimulation. In their review, combining ultrasound and neurostimulation did not show any further improvement[56]. Schnabel et al. in a meta-analysis of perineural catheter placement with ultrasound vs. nerve stimulation found similar pain scores postoperatively, but reduced rates of accidental vascular puncture, which is relevant for patient safety to prevent LAST[57]. More recently, Neal et al. investigated patient safety, i.e., local anesthetic systemic toxicity (LAST), nerve injury, and, in upper extremity blocks, pneumothorax and the incidence of hemidiaphragmatic paresis, focusing on data published since 2009 and on RCTs with more than 500 patients, Ultrasound reduced the incidence of LAST. Ultrasound reduced the incidence of pneumothorax in supraclavicular blocks. Hemidiaphragmatic paresis occurred more rarely but was still present. USGRA did not substantially reduce the incidence of regional anesthesia related nerve injury[58,59]. Other trials confirmed the finding, that ultrasound guidance reduces the incidence of LAST by reducing (but not excluding) the probability of intravascular injection[60]. Besides the reduced volume of local anesthetics needed, the most important safety improvement is the direct sight of LA distribution. If the spread is not detectable, the needle tip may be in a vessel. Injecting local anesthetics in small aliquots of 3 ml, and looking for correct distribution of the fluid around the target structure is the best possible prophylaxis against LAST and recommended in guidelines and textbooks[5,61]. A study by Zhang et al. in 2019 found higher rates of LAST using ultrasound alone, compared to nerve stimulation. The authors suggested the combined use of ultrasound and nerve stimulation to lower the risk. This trial investigated only deep blocks (lumbar plexus block combined with posterior transgluteal sciatic nerve block), where it can be difficult to determine the spread of LA[62]. Thus, even with ultrasound, written guidelines for the treatment of LAST must be available and every provider must know where the lipid solution is stored.

What is the value of „dual guidance"?

As discussed above, ultrasound is superior to locate nerves[63,64]. In superficial, easy to visualize targets on the upper limb, using additional nerve stimulation (dual guidance), doesn`t improve success rates and may cause discomfort[65,66]. This can be different in deeper blocks, where it is challenging to locate the nerve correctly and visibility is often bad due to the opposition between resolution and penetration depth (N. obturatorius, lumbar plexus block, transgluteal sciatic block)[67].

Some authors suggest dual guidance as a safety tool for education and teaching, as most USGRA

beginners tend to advance the needle without correctly visualizing the tip[68]. On the other hand, this is quite old data and sensible tissues like vessels or pleura can`t be detected by nerve stimulation. A recent review by Gadsden[69] summarizes the advantages of using nerve stimulation as a supplement to ultrasound. Gadsen, as well as Khurana et al. in an ASRA newsletter[70], argue that ultrasound and nerve stimulation are complementary to improve patient safety. "Protective nerve stimulation"[71] is an additional safety tool. Neurostimulation serves as a monitor against needle-nerve contact. A threshold as low as 0,2 mA accurately differentiates between extra- vs. intraneurals needle tip position, but a current up to 0,5 mA could not rule out an intraneural needle placement[72,73]. Protective nerve stimulation with 0,5 - 1,0 mA has been suggested to avoid nerves not reliably seen with ultrasound but anatomically in the path to the target[71,74]. The ASRA advisory panel suggests a motor response < 0,5 mA should be interpreted as intraneural needle position[75]. There are also some disadvantages of dual guidance. Analysis of retrospective data reports a higher incidence of multiple skin punctures but doesn`t provide data about an increased infection rate[76]. Author authors found significantly prolonged procedure times[77,78]. Furthermore, the safety of 0,5 mA to avoid nerve contact may be questioned, as there are older case reports and animal models with intraneural needle position and currents up to 1,7 mA, without any motor response[79,80]. This could be especially pertinent in patients with underlying conditions like diabetes mellitus and at risk for nerve injuries. Furthermore, although studies showed faster learning curves for ultrasound than for nerve stimulation[64], some authors advocate for the role of dual guidance in the education of novices[69].

What do we know about the incidence of nerve injuries and the role of ultrasound?

In general, nerve injuries associated to regional anesthesia are a rare event, but data is very heterogeneous. In children with blocks performed under general anesthesia the risk of transient neurological deficits was 1,6- 3,6: 10000 and the risk of permanent neurological deficit from 0 - 0,4: 10000 with no difference between neuroaxial and peripheral blocks[81]. In case series on persistent phrenic palsy after interscalene block, an incidence of 0,048% was reported[82], while a prospective observational study found an incidence of 1%[83]. An Australasian survey of more than 7000 blocks reported 0,4: 1000 block related nerve injuries with a 95% confidence interval ranging from 0,08- 1,1:1000[84]. The main problem of data on nerve injuries related to nerve blocks in general and to USGRA in particular is the fact that causality of regional anesthesia is often unclear as surgery, positioning, traction and tourniquet also cause peripheral nerve injury. Inflammation, vasoconstriction, hypothermia, electrolyte disorders, ischemia due to hypotension or pressure and preexisting conditions like Diabetes mellitus with neuropathy, alcohol or tobacco abuse, are common pathomechanisms. Patient, surgical and anesthetic factors contribute to nerve injuries, which are more common in upper than in lower limb blocks, while a higher incidence for proximal than for distal blocks is controversial and not supported by evidence. Nerve injuries related to peripheral nerve blocks are rarely permanent. The persistence of symptoms decreases from 3 to 6 months to one year[72,75]. According to older retrospective data over a 10 year period, the incidence of neurological complications seems to be more dependent on the type of surgery and the patient`s condition than on nerve blocks[85]. Nerve injuries are different from postoperative neurological symptoms (PONS), transient neurologic deficits lasting up to 2 weeks (mostly paresthesia), which can occur in 8%[86]. There is no evidence that the use of ultrasound reduces the incidence of nerve injuries or PONS. Though the hypothesis of pressure induced nerve ischemia by high volumes of local anesthetic and thus a potential benefit of ultrasound thanks to reduced injection volume has been raised[87], there isn`t any confirming evidence. Needle-nerve contact with damage to the nerve vasculature and micro-hematoma, but especially injection of local anesthetics into fascicles leads to direct damage, ischemia and inflammation, depending on volume and concentration[88,89]. Unfortunately, ultrasound is not accurate enough to differentiate reliably between intra- and extraneural needle position[90,91]. No single nerve localization technique shows superiority in reducing the risk of nerve injury yet. Thanks to technical innovation, this may be subject to further investigation in the future[92,93]. That`s why the use of nerve stimulation together with ultrasound as a safety feature

has been advocated for, as discussed above. Nevertheless, we could not find any comparative studies to state an outcome difference in block related nerve injuries between USGRA alone and ultrasound with nerve stimulation.

Can pressure control combined with ultrasound avoid nerve injuries?

Monitoring further variables like pain during injection- though unreliable, as shown by old data[94,95], looking for the spread of local anesthetic without nerve swelling[96,97] and injection pressure to avoid intraneural injection are recommendable[98]. Injection pressure monitoring and limiting the injection pressure to < 15 psi can minimize the risk of nerve injury. High injection pressure is possibly a sign of intraneural injection[99,100,101,102] and may lead to nerve damage[103]. The subjective pressure evaluation ("syringe feel") even of experienced anesthesiologists is unreliable and dependent on the needle type[104]. An injection with compressing an air column over a fluid is the traditional technique to control injection pressure, but now commercial solutions are available. The ASRA practice advisory[75] and the NYSORA group[105] recommend a multi- modal technique to avoid potential nerve injuries, combining all 3 techniques of ultrasound, nerve stimulation and pressure monitoring altogether („triple guidance, triple monitoring"). A pragmatical algorithm is available at[5]. The current evidence suggest that all methods are complementary and a single best practice to avoid nerve injury can`t be recommended[106,107]. A recent prospective observational investigating a multimodal approach is limited by the lack of randomization and blinding[108]. Much of the evidence for risk factors of nerve injury comes from cadaver models, animal models and case reports and clinical relevance remains uncertain[106,109].

Further ultrasound related approaches to avoid nerve injury

Abouzied and Wilson question some of the ultrasound related established "best practices" with regard to patient safety[34]. In fact**,** it has not been scientifically proved yet, that "circumferential" spread of local anesthetics around nerves is mandatory for a successful block. For some nerves like popliteal sciatic this may be advantageous according to a single center proof of concept trial on 64 adults[110]. On the other hand, more needle manipulations near the nerve lead to more possible needle-nerve contacts and possible injury. Especially in a femoral nerve block or sciatic nerve block for postoperative analgesia combined with general anesthesia, a single local anesthetic depot lateral to the nerve is sufficient and may avoid trauma[111]. Because of the previously explained difficulties to see the needle tip at any time, it seems reasonable to place the needle intentionally near, but not too close to the nerve, measuring opening pressure and looking at the local anesthetics spread, instead of aiming the needle directly at the nerve[112]. In a cadaver model there was a statistically significant lower incidence of intraneural injections with a tangential approach compared to a direct approach to the nerve[113,114]. Other authors suggest the use of ultrasound to stay farer away from the nerval borders altogether[115]. We know that all local anesthetics can be neurotoxic to different degrees[116,117,118]. As this is a dose dependent effect, reducing concentration and volume – a proved advantage of USGRA - may reduce the risk of nerve damage.

Using ultrasound, is the awake, conscious patient still mandatory?

Even with the use of ultrasound, current international guidelines recommend performing nerve blocks in an awake, conscious adult[72,75]. Nevertheless, paresthesia or injection pain does not reliably indicate peripheral nerve damage, but reversely if a conscious patient complains about such symptoms, this must prompt cessation of injection and needle repositioning[70]. However, in children or in patients at risk of movement during the procedure, performing the block under general anesthesia is not excluded or even recommended[119,120,121,122], if the benefit outweighs the risk. As shown in[81], it obviously does not provoke more permanent nerve injuries. To this date, the strongest argument to advocate for performing blocks in the conscious patient, is to minimize the risk for wrong- sided blocks (WSNB) as a part of the „stop before you

block“ campaign[123,124]. Furthermore, in conscious patients, neurological symptoms of LAST are easy to notice. Nevertheless, atypical presentations of LAST like cardiovascular symptoms without CNS symptoms or a delayed onset of symptoms after as long as 60 minutes are possible[61], as USGRA has reduced intravascular injections[60]. Furthermore, in clinical practice, it seems clear that geriatric patients with dementia may benefit from an opioid sparing multimodal pain therapy concept including USGRA[125]. Often, they do not fulfill the criteria of “consciousness” and tend to move a lot during the procedure.

Are adjuvants necessary, useful and safe in USGRA?

As many local anesthetics cause vasoconstriction to different degrees, the use of adrenaline can reinforce this effect and lead to ischemic nerve damage[75,126]. Thus, at least according to animal studies, adrenaline as an adjuvant is not a good choice, especially around poorly vascularized nerves like the sciatic nerve or in patients with risk factors for neuropathy and microangiopathy like diabetes[127]. Adrenaline increases the safe dose of local anesthetics with regard to LAST, but as discussed before, thanks to USGRA doses and volumes for most blocks have significantly decreased. Adrenaline as an adjuvant to local anesthetics can detect intravascular injection, but at least 15µg Adrenaline is necessary to detect a relevant increase in heart rate and blood pressure with limited reliability in pain, stress, with beta-blockage or in geriatric patients[61]. So slow injection and meticulous observation of LA spread in real time ultrasound may be safer and more useful than adding adrenaline, without the risk of ischemia. Other common adjuvants are dexamethasone, clonidine and dexmedetomidine, opioids, ketamine and anti-inflammatory drugs (NSAID). The aim is to enhance efficacy of the block, prolong the clinical duration and reduce the dose of local anesthetics[128,129]. Neither of them is per se neurotoxic but in vitro they showed different effects on the neurotoxicity of ropivacaine[130]. The clinical significance of these findings remains unclear[131]. All adjuvants have typical systemic side effects like hypotension and bradycardia and are off- label- drugs for perineural use[132]. Findings for clonidine are heterogenous while dexmedetomidine and dexamethasone prolong blocks significantly in clinical practice and dexmedetomidine didn`t show any neurotoxicity in animal models[133,134,135,136]. Neither the action nor the side effects of adjuvants can be altered using ultrasound. Adjuvants and USGRA may be complementary in reducing the dose and thus potential neurotoxicity of local anesthetics.

Are infections a problem specifically related to USGRA?

Permanent nerve injury and loss of function may happen through infectious complications. There are many more case reports of disastrous complications like meningitis or abscesses in neuroaxial anesthesia than in US- guided peripheral nerve blocks. Data on ultrasound guided neuroaxial anesthesia is rather recent and no infectious complications related to the use of ultrasound have been reported[137,138,139,140]. Most of the trials report lesser needle passes through the skin with ultrasound guidance. This could theoretically be an advantage. Nevertheless, the use of ultrasound equipment is a potential risk for infectious complications, so disinfection standards and barrier cautions are mandatory. In single shot peripheral nerve blockades, infectious complications are a very rare event[141]. Catheter techniques have a higher incidence and demand a higher standard of hygienic barriers, but all this data is retrospective, mostly older and none of it directly related to the use of ultrasound[142,143,144,145]. Most of the hygienic recommendations for USGRA are the same as for the insertion of central lines and the prevention of central line–associated bloodstream infections (CLABSI). The recommendations are conclusions by analogy from preventing bloodstream infections (BSI). Effectiveness of every single step is hard to assess, so a bundle approach is the method of choice. Bundles have provided evidence of infection prevention in different health care settings[146,147], so they should also be useful for USGRA. The German society of Anesthesiology and Intensive Care (DGAI) has published hygiene recommendations for regional anesthesia in 2006, updated in 2015 („10 commandments“) and recently re-published in an educational

overview[148]. Successful infection control is possible by following these recommendations[149]. Some of these rules directly rely to the use of ultrasound. There is no data that using ultrasound per se leads to more infections. Nevertheless, to maintain an aseptic field for catheter techniques, it is essential to cover the probe and the whole cable with a long sterile sheath to avoid contamination of the puncture site or the needle. In single shot technique, a short cover of the probe or inserting the needle 2 cm away from the probe after correct skin disinfection is sufficient. There is no data comparing those two techniques, at least in teaching of novices we recommend using a short cover at any time. Sterile saline is the best choice to improve the contact to the skin and the image as needling through disinfectants is not advisable[112]. Chlorhexidine with alcohol may be neurotoxic to an unknown extent[150,151]. Needling through sterile gel may cause nerval inflammation, if gel is spread into the tissue[152]. The results from different animal models are inconclusive[153,154]. If gel is used, it should be single-use and sterile, as non-sterile, multiuse gel is a recently identified source of infections and outbreaks with opportunistic bacteria[155,156,157]. After each patient, it is mandatory to clean and disinfect the ultrasound probe and the touchscreen/ keyboard of the ultrasound machine with disinfecting substances authorized by the manufacturer. An Australian trial performed microbial tests for contamination of ultrasound equipment in the ICU and emergency departments, not directly related to regional anesthesia. They found a high rate of contamination and thus a possible risk of transmission of infectious diseases by ultrasound probes and machines[158], prompting national guidelines for reprocessing probes[159]. Similar recommendations exist from the European Society of Radiology Ultrasound Working Group and the American College of Emergency Physicians[160,161].

Is USGRA safe(r) in coagulation disorders?

Hematoma is a long-known cause of nerve damage even in superficial peripheral blocks[162,163]. Mandatory safety rules for known coagulation disorders or antithrombotic medication exist for many years, but the focus was on neuroaxial anesthesia and the rules for ultrasound guided peripheral nerve blocks and fascial blocks were only conclusions by analogy. Pharmacokinetics of antithrombotic drugs and case series of complications formed the base of recommendations[164]. The incidence of neurological sequelae due to hematoma associated with neuraxial anesthesia varies from less than 1 in 150 000 for epidural anesthesia in labor and less than 1 in 220 000 for spinal anesthesia in obstetrics, to 1 in 3000 in elderly women undergoing orthopedic surgery[165]. There are no trials yet directly comparing the incidence of epidural hematoma in neuroaxial anesthesia with or without ultrasound. Former meta-analyses on ultrasound guided epidurals found a lower incidence of traumatic punctures, skin punctures, needle redirections, postprocedural back pain, headache and failed blocks, as well as a higher first pass success rate, but didn`t report differences in the incidence of epidural hematoma[166,167,168]. Even if real time imaging seems much safer than a „blind" puncture, the use of ultrasound does not exclude vascular punctures for sure and there is no data yet supporting the idea that the use of ultrasound can exclude the formation of hematoma after nerve blocks in patients with coagulation disorders. Thus, the very recent joint ESAIC/ ESRA guideline is the best available approach to assess the bleeding risk, based on the pharmacological principle of half- lives of drugs, renal function, the question of a „traumatic puncture" and the very useful and pragmatical distinction in „superficial" (compressible) and „deep" blocks. It clearly states that ultrasound guidance does not modify the recommended time intervals in deep blocks or neuroaxial anesthesia. In superficial blocks these restrictions do not apply, no matter if USGRA, nerve stimulation or dual- guidance is used[169].

Conclusion

The introduction of ultrasound massively increased the interest in peripheral regional anesthesia. Several advantages of ultrasound are evidence based, but for patient safety, especially to prevent nerve injuries, ultrasound alone is not a "magic bullet" and a combination of techniques and safety measures is essential[170]. Several questions remain open to investigation and the evidence is not very robust. New pathophysiological hypotheses on

nerve injury[171] and the ongoing technical progress of ultrasound machines and needle guidance tools, as well as the unresolved question, how many and which of the different blocks are really useful in clinical practice, will demand further research.

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Original Article

COMPARISON OF ADDITION OF FENTANYL OR CLONIDINE TO INTRATHECAL BUPIVACAINE VERSUS INTRATHECAL BUPIVACAINE ALONE FOR LOWER LIMB SURGERIES IN ELDERLY PATIENTS: A PROSPECTIVE, RANDOMISED STUDY

(Intrathecal Fentanyl/Clonidine ± Bupivacaine for surgery in elderly)

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Abstract

Introduction: *Orthopaedic long bone fracture surgeries in elderly patients have their own inherent risks during anaesthesia. We aimed to compare the effect of adding clonidine or fentanyl to low dose intrathecal bupivacaine as opposed to intrathecal bupivacaine alone.* ***Materials and methods:*** *A prospective, double-blind study was conducted in ninety elderly patients undergoing lower limb surgery under spinal anaesthesia. After randomly allocating the patients to three groups, Group BC [Bupivacaine + Clonidine]: 9 mg bupivacaine (0.5%) + clonidine 15 μg + saline, Group BF [Bupivacaine + Fentanyl] : 9 mg bupivacaine (0.5%) + fentanyl 20 μg, Group BS [Bupivacaine + Saline] : 9 mg bupivacaine (0.5%) + saline. The time for onset of sensory and motor block, highest sensory level achieved, time taken to achieve peak sensory and motor blockade, duration of analgesia and side-effects were compared between the three groups. The relevant statistical analyses were done.* ***Results:*** *The time taken for the sensory level and motor block to recede was the longest in group BC. The duration of analgesia was maximum in the group BC group and minimum in group BS. Incidence of hypotension and use of ephedrine was maximum in Group BC.* ***Conclusion:*** *Fentanyl or clonidine added to low dose intrathecal bupivacaine for lower limb surgery in the elderly significantly increases the duration of analgesia compared with intrathecal bupivacaine alone, clonidine more than fentanyl.*

Key words: *Intrathecal; fentanyl; clonidine; Bupivacaine; elderly patients; lower limb surgeries*

Introduction

Spinal anaesthesia is the most commonly used anaesthetic technique for surgeries of orthopaedic long bone fracture in elderly patients. The adjuvants used in spinal anaesthesia have gained popularity because they reduce the quantity of local anaesthetics (LA), increase the duration of action and enhance the quality of analgesia[1,2]. Opioids and local anaesthetics co-administered intrathecally have synergistic analgesic effect, increasing the sensory blockade while maintaining the haemodynamics[3]. Fentanyl is a synthetic lipophilic opioid with a fast onset of action, greater analgesic potency and unlike morphine has much less tendency to cause delayed respiratory depression[4]. Clonidine, a selective partial agonist for alpha-2 adrenoreceptors, is an attractive alternative to commonly used opioids and is known to prolong sensory and motor effects of LA[5,6]. Although both of these adjuvants have been individually studied, our research revealed limited literature comparing these spinal additives in the geriatric population for lower limb surgery.

Objective

Our study aimed at comparing the effects of combining clonidine or fentanyl to intrathecal bupivacaine versus bupivacaine alone in elderly patients posted for surgical repair of fracture neck

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femur or fracture hip. We aimed to compare the duration of analgesia, block characteristics and side-effects between the three groups.

Materials and Methods

A prospective, randomised double blind interventional clinical study was conducted in a tertiary care centre over a period of one year from January 2021 to December 2021 after approval of the hospital ethics committee. A total number of ninety patients of ASA class (American Society of Anaesthesiologists) I and II or III, were recruited for the study after obtaining informed consent. The inclusion criteria included patients between 65-80 years, scheduled for Richard's plate-screw internal fixation of femoral neck fractures and Austin–Moore hemiarthroplasty for subcapital fractures of the femoral neck.

Patients with impaired kidney or liver functions, patients with a history of spine surgery, infection at injection sites, coagulopathy, hypersensitivity to local anaesthetics or opioids, mental disturbance or neurological disease were excluded from the study. Also, cases were excluded if the sensory level was inadequate after 30 minutes of LA injection.

All patients were allocated into three groups (30 patients each) by simple randomization using sealed envelopes. All patients were given Tab. Alprazolam (0.25mg) and Tab. Ranitidine (150mg) the night before surgery.

Group BC (Bupivacaine - Clonidine group) was administered 9 mg (1.8 ml) 0.5% heavy bupivacaine + clonidine 15 μg (0.1ml) + saline (0.3 ml).

Group BF (Bupivacaine - Fentanyl group) was administered 9 mg (1.8 ml) 0.5% heavy bupivacaine + fentanyl 20 μg (0.4ml).

Group BS (Bupivacaine - Saline group) was administered 9 mg (1.8 ml) 0.5% heavy bupivacaine + saline (0.4ml).

Total volume in all the three groups was 2.2 ml.

An anaesthesiologist not included in any other aspect of the study prepared the test drug solution and another anaesthesiologist blinded to the test drug performed the subarachnoid block and recorded the observations.

After securing an 18-gauge intravenous access with Ringer lactate on flow, standard monitoring according to ASA guidelines was initiated. Spinal puncture was performed at L3–4 or L4–5 level using a 25 G Quincke needle with the patient in a seated position. After ensuring free flow of clear CSF, the drugs were administered in separate syringes. The additive or saline was injected via a 1ml syringe and bupivacaine via a 2 ml syringe. The injection of the local anaesthetic (1.8 ml) was made over 30 seconds, that is 0.06 ml/sec. The patients were then made supine with support for head and shoulders.

The time of completion of spinal injection was designated as time 0 and other time points were measured from this time. As a routine oxygen was administered via nasal prongs to all patients.

The level of sensory block, defined as the dermatomal segment with loss of temperature sense to cold on each side of the midthoracic line, was measured every 5 minutes, until it reached the peak level with four consecutive tests. The following parameters were recorded:

a) onset of sensory block
b) peak sensory block time that is from time 0 to peak block level
c) onset of motor blockade
d) time taken to achieve maximum degree of motor block

Motor block was scored using a modified Bromage scale

1: complete motor block
2: almost complete motor block: able only to move the feet
3: partial motor block: is able to move the knees
4: detectable weakness of hip flexion: able to raise the leg but is unable to keep it raised
5: no detectable weakness of hip flexion: able to keep the leg raised for 10 s at least
6: no weakness at all

e) time for sensory level to regress to level L1 from time 0
f) time of recovery from motor block to modified Bromage 0
g) use of supplemental analgesics perioperatively
h) time to the first analgesic request after operation

The pulse rate (PR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), respiratory rate (RR), sedation score (SS) were monitored, pre-operatively, every 5 minutes after the subarachnoid block for

45 minutes and then every 15 minutes till the end of surgery, every hour in the recovery room till the sensory level reached L1 and thereafter in the ward until the demand for rescue analgesic by staff who were also unaware of study group allocation. Any episode of hypotension after spinal anaesthesia was recorded. Hypotension was defined as a SBP less than 110 mmHg or mean arterial pressure of less than or equal to 65 mmHg and was managed with fluid bolus or 3 mg ephedrine intravenously. Clinically, relevant bradycardia was defined as heart rate less than 50 beats/min and was treated with atropine 0.6 mg intravenously.

Intraoperative sedation score was graded 0: Wide awake; 1: Sleeping comfortably but responding to verbal commands; 2: Deep sleep but arousable; 3: Not arousable[7]. Adverse effects such as pruritus, dryness of mouth, dizziness, nausea vomiting and hypoxemia (SpO2 ≤ 90%) were recorded during the surgery and recovery period and treated if required.

Any other intraoperative complication was recorded and managed appropriately. Post-operatively, time for demand of analgesic was recorded. The intensity of pain was assessed using a 10-point VAS. Duration of analgesia was defined as the duration between time 0 to VAS score of 4 or more. Slow intravenous tramadol 50 mg followed by 1 gram paracetamol infusion (if needed) were administered as a rescue analgesic.

SPSS 20.0 software was used for the statistical analysis. The sample size was calculated based on the assumption that a difference of 50 min in the duration of analgesia between the groups was significant. Minimum of 28 patients were required in each group to produce a significant difference assuming a type-1 error of 0.05 and power of 0.95.

Continuous data and frequency (percentage) was represented as mean ± standard deviation and nonparametric (categorical) data was written as median (range). The groups were compared using analysis of variance (ANOVA). Comparison between the groups was done using the post hoc Tukey test. Intra group comparisons were done using repeated measures ANOVA and post hoc Bonferroni's test. $P < 0.05$ was considered statistically significant. $P < 0.001$ was considered highly statistically significant.

Results

Among the 90 patients enrolled in the study, 89 patients completed the study and were included in the data analysis (Figure 1). The Group BF, Group BC and Group BS included 30, 29 and 30 patients respectively. These groups did not differ with respect to the demographic variables. The surgical time was also comparable between the three groups (Table 1).

Comparison of mean onset of sensory block showed no significant difference between the three groups. Group BC needed the longest time to reach peak sensory level 9.76 ± 2.97 min and Group BF needed at least 9.6 ±5.14 min. The highest sensory level attained was T4: 2,3 and 2 patients in BF, BC, BS groups respectively. Time taken for the onset of the motor block was longest in Group BS group 5.8 ± 1.38 min and fastest in Group BC, 5.17 ± 1.31 min. Peak motor block (min) was achieved slowest in Group BS 10.93 ± 2.59 min and fastest in Group BF 10.4 ± 3.32 min. 2 patients in group BS group, 1 in group BF and 1 in group BC had a modified Bromage score of 2, rest of the patients had complete motor blockade. Time taken for the sensory level to recede to L1 was the longest in the BC group and shortest in the BS group, 177.41 ± 32.83 min in the BC group, 147 ± 27.97 min in the BF group and 115.17 ± 43 in the BS group. The intergroup difference was statistically significant. Comparison of the mean motor block duration (min) between the three groups showed significant difference between the three groups. The highest mean values were seen in Group BC (127.28 ± 16.98) followed by Group BF (113.57 ± 16.84) and Group B (89.43 ± 28.5). The duration of effective analgesia was maximum in the BC group, 371.38 ± 91.21 min and minimum in BS group, 181.5 ± 61.58 min. This difference was statistically significant. Group BF had duration of analgesia for 306.33 ± 100.35 min, and this was significantly less compared to the BC group (Table 2).

There was a decrease in the pulse rate as compared to the baseline in all the three groups, but it was not significant and none of the patients needed atropine. Comparison of pulse rate between the three groups did not show any significant difference between the groups.

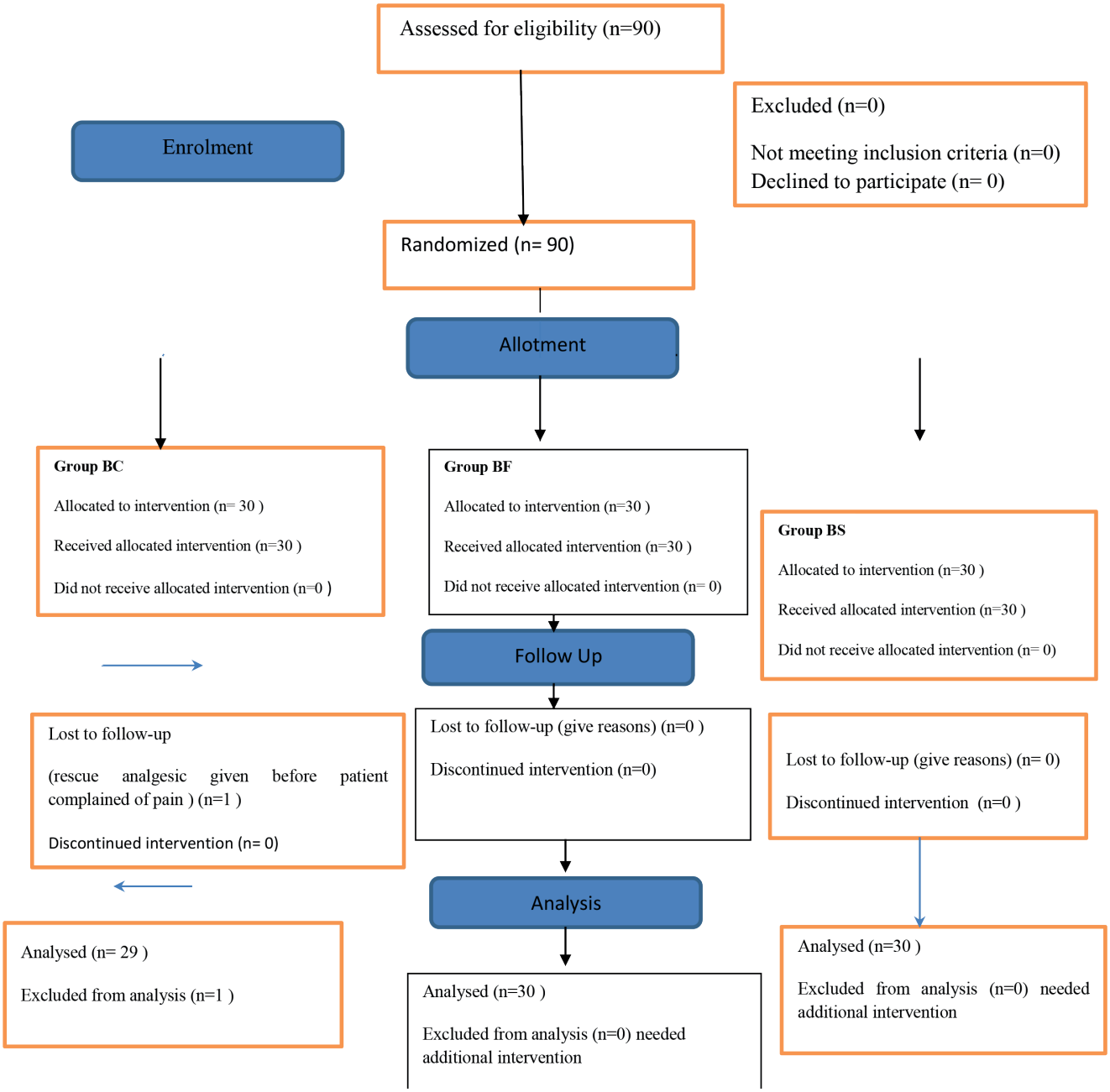

Figure 1: Consort Chart

Group BC (Bupivacaine-Clonidine group), Group BF(Bupivacaine – Fentanyl group), Group BS (Bupivacaine – Saline group)

Table 1: Demographic variables

	Group BF (n=30)	Group BC (n=29)	Group BS (n=30)	P VALUE
Age (years)	72.8±9.08	71.59±6.58	72.93±6.91	0.717
Weight (kg)	52.53±9.33	51±7.44	52.97±8.93	0.657
Height (cm)	151.9±7.41	149.45±5.49	153.43±8.64	0.114
Gender F/M	19/11	20/9	20/10	
ASA I/II/III	4/19/7	3/18/8	3/19/8	
Surgical time (min)	93.67±20.59	92.59±18.4	90±19.7	0.759

Table 2: Comparison of subarachnoid block characteristics

	Group BF (n=30)	Group BC (n=29)	Group BS (n=30)	P value	Group BF vs Group BC difference (P value)	Group BF vs Group BS difference (P value)	Group BC vs Group BS difference (P value)
Sensory onset (min)	4.77±1.61	4.34±1.7	5.1±1.27	0.173	0.42 (0.544)	-0.33 (0.679)	-0.76 (0.148)
Time for max sensory level (min)	9.6±5.14	9.76±2.97	9.73±2.41	0.989	-0.16 (0.985)	-0.13 (0.989)	0.03 (1)
Maximum sensory level	T10:4; T8:17; T6:7; T4:2	T10:3; T8:14; T6:9; T4:3	T10:3; T8:18; T6:7; T4:2				
Motor onset (min)	5.33±1.42	5.17±1.31	5.8±1.38	0.193	0.16 (0.894)	-0.47 (0.389)	-0.63 (0.19)
Time for peak motor block (min)	10.4±3.32	10.79±3.16	10.93±2.59	0.78	-0.39 (0.873)	-0.53 (0.775)	-0.14 (0.983)
Time taken for sensory level to recede to L1 (min)	147±27.97	177.41±32.83	115.17±43	**<0.001**	**-30.41 (0.004)**	**31.83 (0.002)**	**62.25 (<0.001)**
Motor block duration (min)	113.57 ± 16.84	127.28 ± 16.98	89.43 ± 28.5	**<0.001**	**-13.71 (0.043)**	**24.13 (<0.001)**	**37.84 (<0.001)**
Duration of analgesia (min)	306.33±100.35	371.38±91.21	181.5±61.58	**<0.001**	**-65.05 (0.013)**	**124.83 (<0.001)**	**189.88 (<0.001)**
Ephedrine use (mg)	4.1 ± 6.47	7.14 ± 6.18	4.4 ± 4	0.082	-3.04 (0.103)	-0.3 (0.977)	2.74 (0.157)

Intragroup analysis showed a significant decrease in SBP from 10 minutes till 180 minutes post SAB in all the groups. There was a significant difference in the systolic blood pressure between the three groups after 10 minutes of the subarachnoid block. The BF group had the highest mean systolic pressures until 180 minutes. After that the difference was insignificant. 21 patients in the BC group, 14 patients in BF and 15 patients in the BS group needed fluid boluses or ephedrine to maintain SBP >/= 110 mmHg or MAP >/= 65 mmHg . The mean arterial pressure in the BF group was significantly higher than the BC and BS group from 10 minutes after SAB (Figure 2). But the MAP in all the groups remained above 65 mmHg throughout the duration of the study.

Consumption of ephedrine use between the three groups showed no significant difference between the three groups (test value of 2.573 and p value of 0.082). The highest mean values were seen in Group BC (7.14 ± 6.18) followed by Group B (4.4 ± 4) and Group BF (4.1 ± 6.47) (Table 2).

The sedation score was significantly more in the BF and BC group compared to the BS group. The patients in the BF group were significantly more sedated compared to the BC group. But the above differences were seen only from 15 minutes to 1 hour of SAB

Pruritus was seen in 4 patients in the BF group. No other side effects were recorded in any of the groups.

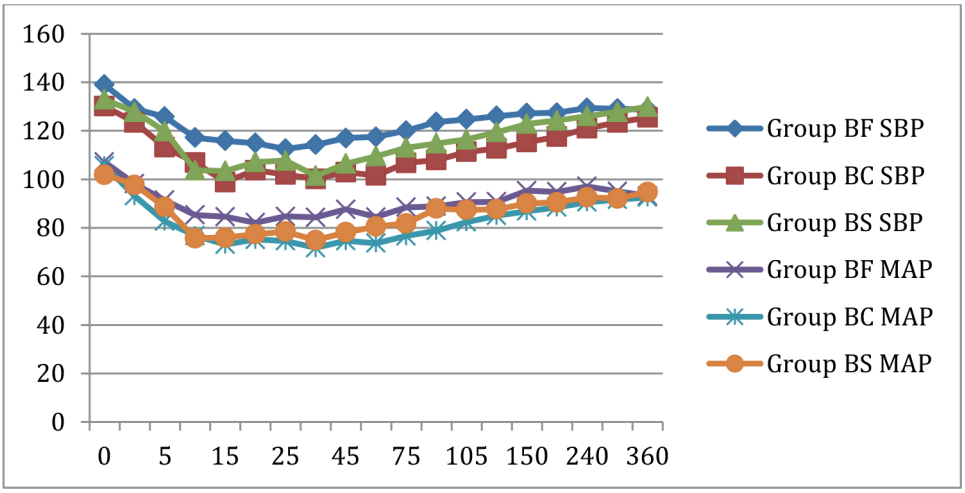

Figure 2: Comparison of Systolic Blood pressure (SBP) and Mean Arterial Pressure (MAP) between the three groups (Mean+/- SD)

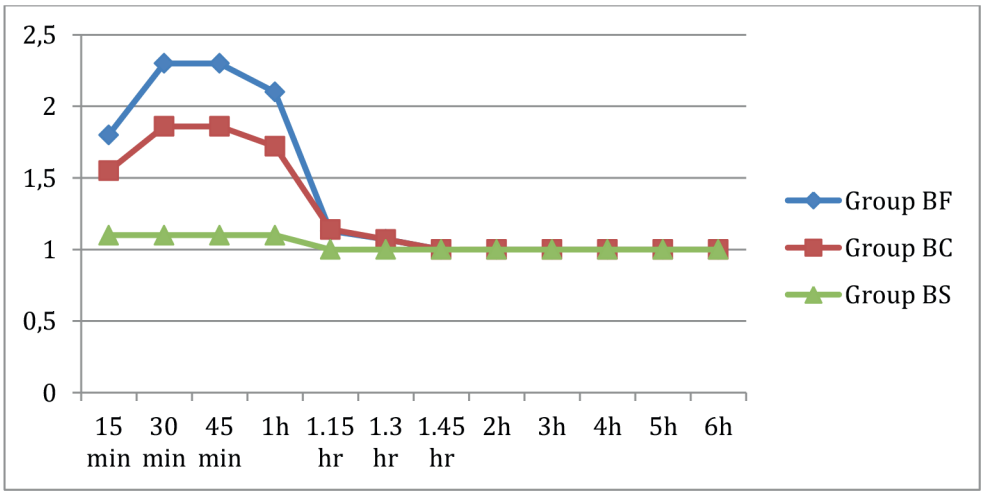

Figure 3: Comparison of Sedation Score between the three groups (Mean +/-SD)

Discussion

In the present study, the addition of clonidine or fentanyl to intrathecal bupivacaine in the elderly increased the duration of analgesia compared to placebo, clonidine significantly more effective than fentanyl.

With rising life expectancy worldwide, the number of elderly individuals is increasing and it is estimated that the incidence of hip fracture will rise from 1.66 million in 1990 to 6.26 million by 2050[8]. A higher mortality is seen in the elderly trauma patients as compared to young patients due to pre-existing comorbidities, decreased physiologic response after traumatic injury, poor response from the cardiovascular reserve, diminished cardiac output and poor functional capacity during periods of stress that impair their ability to tolerate injury[9]. With respect to the type of anaesthesia, no significant differences have been found in the postoperative complications or 30-day mortality of patients who received general anaesthesia versus spinal anaesthesia for the surgical repair of a hip fracture.[1] However spinal anaesthesia decreased early mortality, reduced the cases of deep vein thrombosis, acute postoperative confusion, myocardial infarction, pneumonia, fatal pulmonary embolism, postoperative hypoxia, hospital stay and also reduced the incidence of Postoperative Cognitive Dysfunction (POCD) in the first postoperative week[11,12,13].

Surgery for fracture femur or hip lasts for 75-90 minutes and can be managed with single shot spinal anaesthesia. But providing adequate anaesthesia and analgesia while maintaining stable haemodynamics with minimal side effects in the senior citizens remains a challenge. This can be overcome with addition of adjuvants to local anaesthetics. Alpha 2 agonists and opioids are arguably the most commonly used additives.

Haemodynamic stability is much better in patients who receive a low dose (5-10 mg) of intrathecal 0.5% bupivacaine in combination with opioids due to minimal potential effects on sympathetic pathways[14].

Fentanyl is the most often used intrathecal lipophilic opioid. Addition of fentanyl to local anaesthetics prolongs the duration of sensory block/ effective analgesia possibly due to the residual analgesic effect of the fentanyl that manifests after the sensory block due to the effect of the intrathecal local anaesthetic (0.5% hyperbaric bupivacaine) has been dissipated[15]. It has minimal cephalic spread thus reducing the risk of delayed respiratory depression and aiding in early ambulation[14].

Clonidine is also often used as an adjuvant because it has several advantages and is considered safe. It causes hyperpolarization of postsynaptic dorsal horn neurons and depression of the release of C-fiber transmitters. Binding of clonidine to motor neurons in the dorsal horn may prolong motor block[16]. Clonidine in small doses of 15 μg or 30 μg was seen to prolong duration of analgesia and potentiate sensory block levels produced by 9 mg hyperbaric bupivacaine in elderly patients[15,16].

It has been demonstrated that addition of fentanyl combined with minidose (4 mg) isobaric bupivacaine prolongs the sensory block with dramatically less hypotension as compared with conventional dose of isobaric bupivacaine[17]. But the use of minidose hyperbaric bupivacaine alone will not provide sufficient sensory or motor level[18].

As the study group involved single shot spinal anaesthesia, 0.5% hyperbaric bupivacaine 1.8 ml (9 mg) was used in order to ensure that the sensory and motor blockade was adequate in all the groups. Although earlier studies have compared various doses of clonidine or fentanyl added to intrathecal bupivacaine in young adults, there are only a few studies comparing clonidine or fentanyl added to bupivacaine in the elderly[7,16,19,20,21].

In the present study, onset of sensory block and maximum sensory level achieved did not differ between the three groups. This was similar to the study in which 25 mg fentanyl added to 10 mg 0.5% bupivacaine was compared with 10 mg bupivacaine alone[15].

Contrary to this, addition of fentanyl hastened the onset of the sensory block and the peak sensory level achieved when 12.5mg 0.5% bupivacaine was compared with 7.5 mg 0.5% bupivacaine with fentanyl[3].

Our study did not find any significant difference between onset and degree of motor blockade between the three groups. However, other studies differed in their findings. Desai D. et al found that the maximum Bromage score of motor block was lesser in group BF compared with bupivacaine alone because fentanyl has differential synergism with local anaesthetic agents and acts on only Aδ & C

fibres so it cannot add to motor blockade of local anaesthetic agent[3]. However, Lalita Gauri Mitra et al, C Olofsson et al, did not observe any difference in motor blockade with addition of Fentanyl[22,23]. Similar to present study, clonidine 15 μg or 30 μg added to 9 mg bupivacaine, did not affect the onset of surgical anaesthesia as compared with bupivacaine alone[16].

This study found that the time taken for sensory regression to L1 and recovery from motor blockade were longest in the BC group followed by the BF group; the sensory level receded earliest in the BS group. Agarwal D. had found that the addition of clonidine had prolonged the mean time for sensory regression to T_{12} level and motor block regression[16]. In another study, regression time to L1 level was longer in the BF group in comparison to group B[3].

Addition of fentanyl or clonidine significantly increased the duration of analgesia as compared with the group receiving bupivacaine alone, clonidine more than fentanyl. One patient in the BF group and 3 patients in the BS group undergoing dynamic hip screw insertion grew restless and complained of pain during the final skin sutures. They were given intravenous fentanyl in 20 mcg instalments. Once the awkward surgical position was corrected and patients were made supine, they were comfortable in the immediate post-operative period.

A systematic review reported a 31.3% incidence of hypotension in patients receiving clonidine 15-150 μg without evidence of dose responsiveness versus a 20% incidence in controls[24]. On the contrary, haemodynamic stability was well-maintained in elderly patients when clonidine or fentanyl was used as adjuvant to bupivacaine during the transurethral resection of bladder tumour or prostate[21,25]. In another study, the addition of 15 or 30 μg clonidine to 9 mg 0.5% bupivacaine did not cause an increase in the incidence of hypotension when compared with 9 mg bupivacaine alone[16]. But in the present study, incidence of hypotension and the use of ephedrine was more in the BC group compared with the other two groups.

Desai D. et al found that the incidence of hypotension in the bupivacaine group was higher than the bupivacaine-fentanyl group[3]. But they had used 12 mg bupivacaine in group B and 7.5 mg bupivacaine in group BF. We used the same dose of bupivacaine (9 mg) in all the groups. Among the changes relevant for geriatric trauma care is that the threshold for hypotension is suggested to be 110 mmHg, not 90 mmHg[9,26]. The increased incidence of hypotension in our study could be due to the higher threshold for hypotension; most of the previous studies have defined hypotension as SBP < 90 mmHg or 25% decrease from baseline.

Sedation score was comparable in all the three groups. Three patients in the BF group complained of pruritus. None of the patients in the BC or BS groups developed pruritus. No other side effect was recorded in any patient.

Limitations

The limitation of this study was the small sample size. Also the patients on different antihypertensives were not segregated and compared with regards to their hemodynamic characteristics.

Conclusion

Fentanyl or clonidine added to low dose intrathecal bupivacaine in the elderly for lower limb surgery significantly increase the duration of analgesia compared with intrathecal bupivacaine alone. The incidence of hypotension and use of ephedrine was highest in the clonidine group compared with the other two.

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Original Article

A PROSPECTIVE, RANDOMIZED, DOUBLE BLINDED COMPARATIVE STUDY BETWEEN 0.5% BUPIVACAINE AND 0.5% BUPIVACAINE WITH PENTAZOCINE AS AN ADJUVANT IN SUPRACLAVICULAR BRACHIAL PLEXUS BLOCK FOR POST OPERATIVE ANALGESIA IN UPPER LIMB SURGERY

(Pentazocine as adjuvant in brachial plexus block)

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Summary

Introduction: *In upper limb surgery supraclavicular brachial plexus (SCBP) block with 0.5% bupivacaine is commonly used for anesthesia. To increase the duration of sensory block opioids are used along with bupivacaine, but data on the effect of pentazocine as adjuvant with bupivacaine in SCBP block is still lacking. The study aimed to compare the duration of postoperative analgesia, sensory and motor block between 0.5% bupivacaine and 0.5% bupivacaine with pentazocine as an adjuvant in SCBP.* ***Methods:*** *The study was conducted on 60 consenting patients, posted for upper limb orthopedic surgery involving the forearm under SCBP block. Patients were randomly divided into two groups. Group B received 19 ml of 0.5 % bupivacaine with 1 ml of normal saline; Group BP received 19 ml of 0.5 % bupivacaine with 1 ml pentazocine (30 mg). Block characteristics, duration of postoperative analgesia, and side effects if any were recorded. Statistical analysis was done using the student t-test and Chi-square test for continuous and categorical variables respectively.* ***Results:*** *The onset of sensory (11.47 ± 1.57 vs. 16.8 ± 2.23 min) and motor (8.17 ± 1.14 vs. 13.9 ± 2.44 min) block was significantly faster in the BP group. Duration of sensory (392.33 ± 9.92 vs. 357.2 ± 8.76 min) and motor (379.27 ± 9.28 vs. 347.27 ± 9.13 min) block was also prolonged in group BP ($p < 0.0001$). Duration of postoperative analgesia was more ($p < 0.0001$) in the BP group (407.43 ± 10.46 vs 367.3 ± 8.74min).* ***Conclusion:*** *Pentazocine as an adjuvant with bupivacaine in SCBP block provides faster onset, prolonged duration of the block, and postoperative analgesia*

Key words: *Analgesia; brachial plexus block; bupivacaine; pentazocine*

Introduction

Both intra-operative and post-operative pain is a real concern in anesthesia. Intraoperative pain relief is mandatory for stable hemodynamic and smooth surgical procedure whereas postoperative pain relief accelerates early recovery of the patient. In upper limb surgery, supraclavicular brachial plexus (SCBP) block with a long-acting local anesthetic (bupivacaine, ropivacaine, and levobupivacaine) is a widely used method[1].

However, to increase the duration of the sensory blockade and postoperative analgesia, opioids (morphine, fentanyl, buprenorphine, tramadol), alpha 2 agonists (clonidine and dexmedetomidine), dexamethasone, magnesium, and epinephrine are used as an adjuvant with 0.5% bupivacaine, 0.5% levobupivacaine and 0.75% of ropivacaine[2]. The addition of an adjuvant to local anesthetic not only prolongs the duration but also reduces the dose of local anesthetic leading to less chance of systemic toxicity[3].

Pentazocine, a synthetic agonist-antagonist opioid, acts as a weak antagonist or a partial agonist at μ - opioid receptors. Analgesia is produced mainly through interaction with the kappa (k1) receptor[4]. Pentazocine has been used as sole anesthetic or adjuvant to 0.5% bupivacaine via the spinal and epidural route in the dose range of 0.8 mg to

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60 mg without any adverse effects and effectively produced sensory block, motor block, and analgesia[5-8]. In the present study we planned to use pentazocine as an adjuvant to 0.5% bupivacaine in the SCBP block.

An alternate hypothesis was accepted for the present study assuming that a significant difference would be observed by adding 30 mg pentazocine to 0.5% bupivacaine for SCBP block regarding the duration of block and postoperative analgesia depending on the observations made by the pilot study.

Objective

The primary objective of the study was to compare the duration of postoperative analgesia as well as the duration of sensory and motor block. Comparison of sedation and the onset of sensory and motor block were secondary objectives.

Methods

After obtaining institutional ethics committee clearance and successful registration in the clinical trials registry of India (CTRI/2020/07/026494 dated 10.07.2020), this prospective, randomized, double-blinded, analytical study was conducted in orthopedic operation theatre of a tertiary care hospital from August 2020. to July 2021. with 60 ASA I and II patients of either sex, aged between 18-60 years admitted for elective upper limb orthopedic surgery involving the forearm under supraclavicular brachial plexus (SCBP) block. All the patients were included in the study after written informed consent. Patients having any contraindications to regional anesthesia (coagulopathy, infection in the supraclavicular region or obese patient (body mass index >30 kg/m^2)) were excluded from the study. Patients who have a history of severe systemic disease, neuromuscular, psychological disorders, or allergy to the study drugs were also excluded from the study. Patients with a history of chronic drug, alcohol, or analgesic abuse and pregnant patients were not included in the present study. Patients who required supplementary analgesic or anesthetic intra-operatively or converted to general anesthesia were also excluded from the study.

As there is no previous study on pentazocine as an adjuvant to 0.5% bupivacaine in supraclavicular brachial plexus block, a pilot study was done by an anesthesiologist (not related to this study) on 30 patients (15 patients in each group)[9]. It was observed that 80% (12 patients) of the patients who received pentazocine as an adjuvant to 0.5% bupivacaine had effective pain relief for 6 hours, compared to 40% (6 patients) when normal saline was used as an adjuvant.

Accepting an alpha error of 5% (CI 95%), power of the study of 80%, and considering the effect to be one-tailed, we get a sample size of 48 patients to be divided into two groups (24 patients in each group) using OpenEpi version 3.01 software (2013 version). To compensate for losses and dropouts particularly due to the administration of intraoperative opioids or conversion to general anesthesia, 30 patients were included in each group.

Patients were randomly divided into two groups B (bupivacaine group) and BP (bupivacaine with preservative-free pentazocine group). Group B received 19 ml of 0.5 % bupivacaine with 1 ml of normal saline; Group BP received 19 ml of 0.5 % bupivacaine added with 1 ml of preservative-free pentazocine (30 mg/ml). SCBP blocks were performed with the help of a nerve locator.

After the patient was properly explained the technique, positioning was done and approximately 1–1.5 cm above the midpoint of the clavicle 2 ml of 2% Xylocaine was infiltrated and a mark was made. A 22-gauge 5 cm, insulated, Stimuplex® A needle with a stimulation frequency of 1 Hz was used. Output current was initially set at 2 mA and then gradually decreased to < 0.5 mA. With persistent motor response in the forearm and hand at 0.5 mA, the study drug was injected slowly after negative aspiration. The anesthesiologist who performed the SCBP block and maintained the record of different parameters was unaware of the group allocation. Randomization by computer-generated random number table and sealed envelope technique was used. Drug preparation was done by an anesthesiologist not involved in the study outside the OT, depending on the group to which the number in the envelope belongs.

The sensory block was evaluated using alcohol swabs every two min after administration of the study drug in the distribution of musculocutaneous (anterolateral forearm), median (lateral 2/3rd

of hand and the tips of digits 1-4), ulnar (palm and medial side of hand and digits 3-5), and radial (posterior aspect of the lateral forearm and wrist; posterior arm) nerve. Time for the onset of sensory block was defined as the time from completion of injection (Time 0) to the time when less sensation to cold swab began to be detected in the distribution of any one of the major nerves on the operating limb compared to the contralateral side.

The block was failed if the sensory block was found to be inadequate in any of the nerve distribution after 30 min of drug administration and such patients were then excluded from the study and considered for general anesthesia or supplemental intravenous analgesic or anesthetic. All the patients were given moist O_2 4L/min via nasal prong throughout the intra-operative period.

Motor block was assessed for four nerves (flexion of the elbow, thumb adduction, thumb abduction, and thumb opposition). Motor blockade was assessed on a 3-point scale: 0 = no block (full extension and flexion of elbow, wrist, and fingers); 1 = reduced motor power with the finger movements; and 2 = complete motor block with no finger movement[10]. Time from completion of drug administration to the development of motor block score ≥ 1 was noted as the onset of motor block and score 2 was recorded as the time for complete motor block.

Sensory and motor block were assessed every 15-minute interval after the end of surgery along with Visual Analogue Scale (VAS) score. Duration of sensory block was measured from the onset of sensory block to complete return of sensation to cold swab in the distribution of all four nerves in the operating limb. Duration of motor block was defined as the time of attaining score 1 before surgery to complete recovery of motor power of the hand and fingers, i.e., score 0 after surgery.

After the patient complained of a VAS score ≥ 4 (which was explained previously to the patients) in the postoperative ward, paracetamol 1g I.V. was given (not exceeding 3g/24h). If the patient still complained of pain a half hour after paracetamol administration, pentazocine 30 mg was administered intramuscularly. Duration of postoperative analgesia (time interval between the onset of sensory block to the time of administration of 1st analgesic) was also noted.

Heart rate, intraoperative systolic, diastolic, and mean arterial blood pressures at 5 minutes time intervals up to 2 hours (after drug administration). Electrocardiogram (ECG), respiratory rate (RR), and oxygen saturation (SpO_2) were continuously monitored throughout the period. Side effects such as hypotension, bradycardia, nausea, vomiting, pruritus, shivering, and respiratory depression (RR less than 8 per minute) were recorded till 6 hours postoperatively[11]. Sedation was assessed using Ramsay's sedation score every two hours postoperatively. (Score 1- Anxious, agitated, or restless, 2 - Cooperative, oriented, and tranquil, 3 - Responds to command, 4 - Asleep but has a brisk response to a light glabellar tap or loud auditory stimulus, 5 - Asleep and has a sluggish response to a light glabellar tap or loud auditory stimulus, 6 - Asleep no response)[12].

Continuous variables were expressed as mean ± standard deviation (SD) and categorical variables were expressed as percentages. Results were analyzed by Mann-Whitney U-test for nonparametric and unpaired Student's t-test for parametric data. For categorical data, the Chi-square test and Fischer's exact test were used as appropriate. A p-value < 0.05 was considered statistically significant. Data analysis was done by Statistical Package for the Social Science or SPSS® software released in 2015, (Version 23.0. Armonk, NY: IBM Corp.).

Results

74 patients were enrolled in the study. Six patients refused to participate in the study and eight patients did not meet the inclusion criteria so, 60 patients were finally allocated into two study groups by simple randomization (Figure 1).

Differences in age, gender, and weight in both groups B and BP were not significant in our study. The duration of surgery and the ASA physical status of the patients were also comparable between the groups (Table 1).

The onset of motor and sensory block was significantly faster in patients who received pentazocine in brachial plexus block ($p < 0.0001$). Duration of sensory and motor block was also significantly prolonged when pentazocine was administered with bupivacaine in the brachial plexus block ($p < 0.0001$). Total analgesia duration was found to be

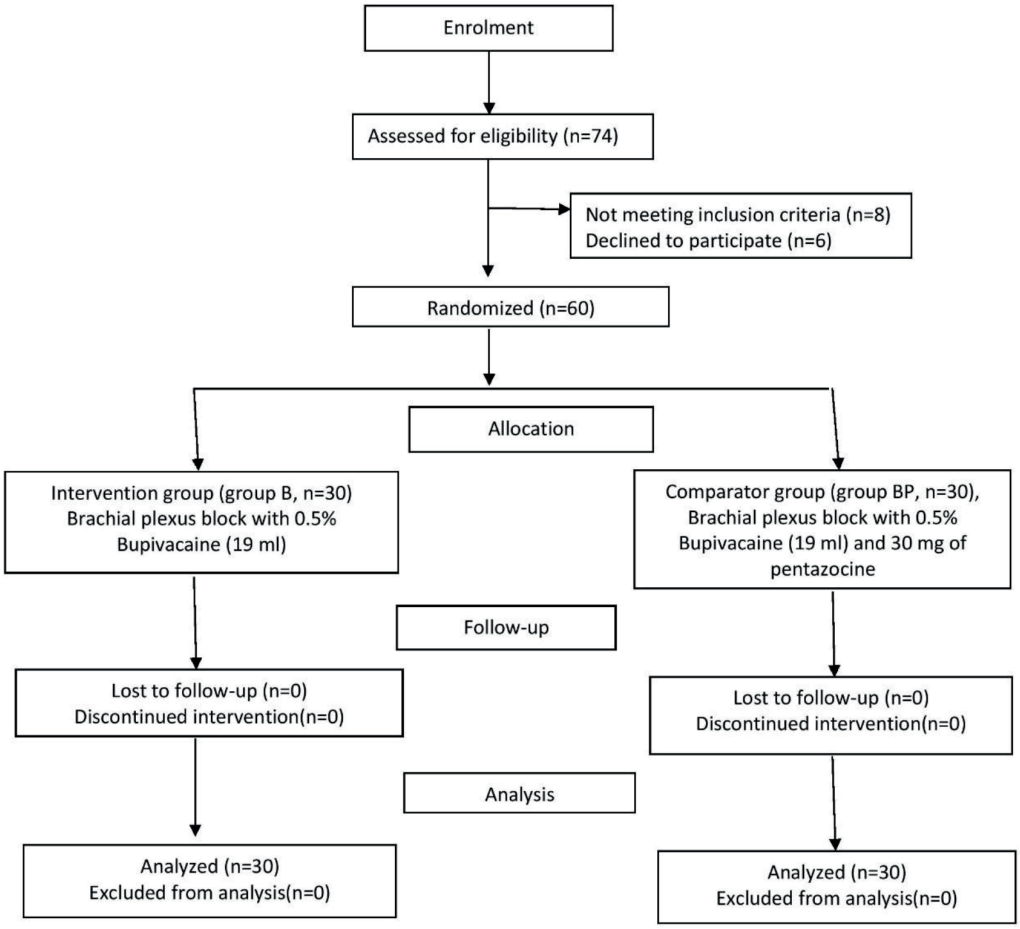

Figure 1: CONSORT 2010 STUDY FLOW CHART

Table 1: Demographic Profile

	Group B (n=30)	Group BP (n=30)	*P* value
Age (yrs)	39.37 ±11.35	39.17 ± 4.96	0.932 #
Sex (M/F)	17/13	16/14	1*
ASA status (I/II)	25/5	27/3	1*
Weight (kg)	64.2 ± 5.98	66.1 ± 6.38	0.300 #
Duration of surgery (min)	76.5 ± 10.66	76.87 ± 10.92	1#

ASA: American Society of Anesthesiologists, *Chi-Squared Test #Unpaired Student's t-test

Table 2: Block characteristics and analgesia

Duration in min	Group B (n=30)	Group BP (n=30)	*P* value
Onset of sensory block	16.8 ± 2.23	11.47± 1.57*	<0.0001#
Onset of motor block	13.9 ± 2.44	8.17 ± 1.14*	<0.0001#
Duration of sensory block	357.2 ± 8.76	392.33 ± 9.92*	<0.0001#
Duration of motor block	347.27 ± 9.13	379.27± 9.28*	<0.0001#
Total analgesia duration	367.3 ± 8.74	407.43 ±10.46*	<0.0001#

#Unpaired Student's t-test

significantly higher in group BP than in group B ($p < 0.0001$) (Table 2).

Hemodynamic parameters like heart rate, systolic blood pressure, diastolic blood pressure, and mean arterial blood pressure up to 2 hours (after drug administration) were compared in both groups intraoperatively. Intraoperative hemodynamic parameters were found not significant between the groups ($p > 0.060$ in all instances). Intraoperative oxygen saturation level was also found insignificant.

Intraoperative Ramsay sedation score was higher in patients who received pentazocine (4.5 ± 0.57) compared to those who did not (1.57 ± 0.57) ($p < 0.0001$)(Table 3).

Table 3: Highest Ramsay sedation score

	Group B (Mean±SD)	Group BP (Mean±SD)	P – value
Ramsay Sedation Score	1.57 ± 0.57	4.5 ± 0.57*	<0.0001@

@ Mann-Whitney U-test

In the current study, no patient had any significant adverse effects (pneumothorax, post-operative vomiting, oxygen saturation < 90% at any time point, bradycardia, signs of local anesthetic toxicity, neurological complication, etc.). But a total of 4 patients (2 patients in each group) complained about mild nausea at different time points which subsided without any medications.

Discussion

Though ropivacaine and levobupivacaine have lower cardiac toxicity, clinically no difference was observed in the previous studies regarding adverse effects of bupivacaine, levobupivacaine, and ropivacaine[13-15]. In the present study we have used bupivacaine as it is widely available and relatively cheaper compared to other long-acting local anesthetics.

Several pure agonist opioids like morphine, fentanyl, and sufentanil have been used as adjuvants to local anesthetics for brachial plexus block with varying degrees of success[3,16].

The mechanism of action of opioids in peripheral blocks is still undefined. Evidence of the existence of peripheral opioid receptors is present. When an opioid is used along with local anesthetic in peripheral nerve block, prolongation of analgesia is probably due to axonal diffusion (e.g. through the neuronal sheath of nerves) into epidural or subarachnoid space and binding with opioid receptors in the dorsal root of the spinal cord. It can also be due to systemic absorption of opioids[17].

Opioids belonging to mixed agonist-antagonists like butorphanol and nalbuphine have also been used as adjuvants to local anesthetics in several studies with favorable results[18-24]. Pentazocine belongs to a mixed agonist-antagonist opioid-like nalbuphine and butorphanol[4,25] but no study to date has used pentazocine as an adjuvant to local anesthetic in brachial plexus block.

In SCBP block, previous studies have used nalbuphine as adjuvant in the dose range of 5-10 mg[18-20], whereas butorphanol has been used in the dose range of 1-2 mg[22-24]. When used parenterally, 30 mg of pentazocine is equivalent to 10 mg of morphine which is again equivalent to 10 mg of nalbuphine[4,25] whereas 1 mg butorphanol is equivalent to 30 mg pentazocine[26]. In the present study, an equipotent dose of pentazocine compared to nalbuphine and butorphanol has been used.

Pentazocine has been used in neuraxial block (spinal and epidural) in higher doses (60 mg in one study and 1.5 mg/kg in another) without any incidence of neuropathy, so we consider it to be safe when used in peripheral nerve block[5,6].

Studies with morphine[27], fentanyl[28] and tramadol[29,30] as an adjuvant to local anesthetic have observed rapid onset of sensory and motor block similar to the present study. Duration of sensory and motor block was prolonged in the previous studies using pure opioid agonist as an adjuvant in different doses which also supports our observation. Duration of postoperative analgesia was also

increased with pure opioid agonist adjuvant similar to the present study.

In our study, the onset of motor block was much faster than the onset of sensory block which supports the 'core and mantle' concept of Winnie et al[31]. According to this concept, the sensory fibers are situated centrally, and motor fibers are placed peripherally in the brachial plexus. So, local anesthetics, when administered for brachial plexus block, are absorbed earlier by peripheral motor fibers than central sensory fibers causing the earlier onset of motor block.

In a previous study by Nazir et al[18] who used 10 mg of nalbuphine (equivalent to 30 mg pentazocine) with 30 ml of 0.375% bupivacaine in SCBP block observed mean duration of sensory and motor block of 373.17 and 313.92 min respectively, which is similar to our study. The mean duration of analgesia observed by them was 389.33 min which is also close to the present study, but the onset time for the sensory and motor block was faster in a previous study (4.89 and 8.83 min respectively). This may be due to a higher volume of local anesthetic used by the other study.

Another study using nalbuphine (10 mg) with 30 ml of 0.5% levobupivacaine in SCBP block has found a longer mean duration of sensory (519.11 min) and motor (484.54 min) block along with a longer duration of analgesia (531.45 min)[19]. This difference from our study may be due to the higher dose and volume of levobupivacaine used in their study compared to a lower dose of bupivacaine in the present study.

Study by Chiruvella et al[20] has also observed a longer duration of sensory block (708.67 min) and duration of analgesia (833.55 min) than the present study where they used 10 mg of nalbuphine with 29 ml of 0.375% levobupivacaine for brachial plexus block. The duration of the motor block (418.4 min) was close to our observation.

A study by Vengadessane et al[21] has observed a longer duration of block and postoperative analgesia with a lesser dose of the drug (nalbuphine 50 µg/kg with 20 ml of 0.5% bupivacaine). This may be attributable to the use of ultrasound in their study.

Study by Bharathi et al[22] has recorded mean sensory block (396.23 min), motor block (305.6 min) and duration of analgesia (511.73 min) with 1 mg nalbuphine (equipotent to 30 mg of pentazocine) in brachial plexus block which is similar to the present study.

Previous studies, where 2 mg of butorphanol was used with local anesthetic for SCBP block, have also recorded longer duration of block and analgesia[22,23].

In the present study, patients of pentazocine with bupivacaine group had a higher sedation score compared to patients who received only bupivacaine (Table 3). This sedation may be caused by the absorption of pentazocine by the blood vessels present in the tissue surrounding the brachial plexus. This absorbed pentazocine present in blood vessels crosses the blood-brain barrier and acts as an agonist on the kappa receptor which produces sedation[32]. This is similar to the study by Bhatia et al[23] with butorphanol with axillary brachial plexus block.

The present study is not without limitations. Ultrasound guidance for the brachial plexus block was not used as it was unavailable. There is a possibility that with the use of ultrasound a lesser amount of local anesthetic could have been used. Pediatric and geriatric patients have not been included and fixed dose and volume of drugs on every patient has been used. A dose-ranging study using various doses of pentazocine to find out the most suitable dose of pentazocine in SCBP block is required. Patient and surgeon satisfaction scores were also not assessed in the present study. We also did not evaluate the 24-hour rescue analgesic requirement.

Conclusion

From this study it can be concluded that the addition of pentazocine to bupivacaine in supraclavicular brachial plexus block resulted in a significantly early onset of sensory and motor block, prolonged duration of both sensory and motor block and prolonged duration of analgesia when compared with bupivacaine alone without any significant changes in hemodynamic and without any significant adverse effects.

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