Comparative Study Between Dexmedetomidine and Dexamethasone as Adjuvants to Bupivacaine in Supraclavicular Brachial Plexus Block

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ABSTRACT

Background The supraclavicular brachial plexus block exhibits a good anesthetic and analgesic effect to the upper extremity below the shoulder (mid and lower shaft of humerus, elbow, forearm, hand and fingers) and reduces the need for opioid consumption. Among many medications, dexamethasone and dexmedetomidine had been used as effective adjuvants to the local anesthetics in brachial plexus block.

Aim: To compare the block characteristics with dexamethasone versus dexmedetomidine as adjuvant to bupivacaine hydrochloride in SCBPB.

Patient and methods: 75 patients' average weight were allocated and divided into three equal groups. Combined ultrasound and nerve stimulation – guided SCBPB had been done. Control group received 0.5% bupivacaine alone. Dexmedetomidine group, received 0.5% bupivacaine with dexmedetomidine. In dexamethasone group, patient received 0.5% BPV plus dexamethasone. The sensory block was tested by Hollmen scale, while Motor block was monitored by a modified Bromage Scale, Pain was monitored and evaluated by using the visual analogue score.

Results: A prolonged effect of both sensory and motor block were observed in both dexamethasone group and dexmedtomidine group(more significant in D) than group C. Total dose of analgesic (tramadol in mgs in 24 hours) was obviously reduced in dexamethasone and dexmedetomidine groups than group C.

Conclusion

Dexmedetomidine and dexamethasone both are good adjuvants in peripheral nerve blocks, but Dexamethasone had better effects on sensory and motor block duration in comparison with dexmedetomidine. Time of first analgesic request in dexamethasone group was longer than dexmedetomidine group.

INTRODUCTION

Supraclavicular block Provides a rapid onset of dense anesthesia of the arm with a single injection, the supraclavicular block is ideal for operations involving the arm and forearm, from the lower humerus down to the hand. The brachial plexus is most compact at the level of the trunks formed by the C5–T1 nerve roots, so nerve block at this level has the greatest likelihood of blocking all of the branches of the brachial plexus. This results in rapid onset times and, ultimately, high success rates for surgery and analgesia of the upper extremity, excluding the shoulder [1-4]

Palpation or ultrasound visualization of the subclavian artery just above the clavicle provides a useful anatomic landmark for locating the brachial plexus, which is lateral to the artery at this level.^[4] Proximity to the brachial plexus can be determined using by elicitation of a paresthesia, use of a peripheral nerve stimulator, or ultrasound guidance[5]

Bupivacaine is a local anesthetics that binds to the intracellular portion of voltage-gated sodium channels and blocks sodium influx into nerve cells, which prevents depolarization and hence, prevents nerve conduction. It typically begins working within 15 minutes and lasts for 2 to 8 hours.[5]

Adjuvants that are frequently added to local anesthetics to prolong analgesia include epinephrine, opioids,

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tramadol, ketamine, midazolam, magnesium, clonidine, dexmedetomidine and dexamethasone.[6-8]

Dexmedetomidine is an alpha 2 adrenergic receptor agonists, even ten times more selective than clonidine. It is a very versatile drug in anaesthesia practice, finding place in increasing number of clinical scenarios and is no more limited to intensive care unit (ICU) sedation. It is analgesic, has anaesthetic sparing effect, sympatholytic property, useful in other procedural sedation and has cardiovascular stabilizing property. It reduces delirium and preserves respiratory function which adds benefits to its uses. It prolongs the duration of both sensory and motor blockade induced by local anesthetics irrespective of the route of administration (e.g., epidural, caudal, or spinal) [9]. It enhances both central and peripheral neural blockade by local anesthetics[10]. Dexamethasone is type а of corticosteroid medication. Dexamethasone has antiinflammatory and immunosuppressant effects. [11, 12]. It is used in the treatment of many conditions, including enhancement of analgesic effect of local anesthetics.

Aim of this study is to compare the block characteristics with dexamethasone versus dexmedetomidine as adjuvant to bupivacaine hydrochloride in SCBPB. Comparative Study Between Dexmedetomidine and Dexamethasone as Adjuvants to

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PATIENTS AND METHODS

Comparative study was done at Al-Hussain teaching hospital /Samawa city/Iraq, 75 adult patients, aged 18-50 years, ASA I and II (average weight) are scheduled for various upper limb surgical procedures and involved for this study.

Exclusion criteria from this study include: Patients with ASA physical status > II, patients receiving analgesics, allergy to local anesthetics, refusal of the patient, history of bleeding tendency, neuropathies, pregnant women, infection at the site of injection, drugs allergy and immune compromised patients.

Informed written consent had been taken from these patients. I.V. access was applied in the other nonoperative hand and intravenous infusion of Hartmann's solution was started. Patient lying supine with head tilt to the contralateral side. IV midazolam 0.04 mg/kg was given. Expose the area of plexus block from the neck to the shoulder, sterilization of the area and probe with povidone iodine, used sterile gel, place the probe (linear type) above the clavicle, visualization of subclavian artery and firs rib or pleura, the brachial plexus is located lateral and superficial to the artery or sometime between artery and first rib. Introduce of 10 cm 22 gauge needle (which is connected to the nerve stimulator) lateral to the probe, visualize the tip of the needle to avoid any injury to the arteries or pleura, Doppler U/S used to visualize the vessels. The correct position of needle confirmed by combined ultrasound and nerve stimulation. When the correct position confirmed, aspirate then inject the drugs (to avoid intra vascular injection and should be no resistance during injection to avoid intraneural injection). Injection in two sites to cover all the area of brachial plexus.

Nerve stimulator type NYSORA was used, set to delivered (0.8 - 1.0 mA), injection of the drugs carried out when there is twitching of fingers at 0.5 mA.

Patient were allocated in three groups, 25 patients in each group. In control group (C), patient given 30 ml of 0.5% BPV with 2 ml of normal saline. Dexmedetomidine group (DEX), patient given 30 ml of 0.5% BPV with 2 ml of 100mcg of dexmedetomidine. In dexamethasone group (D), patient given 30 ml of 0.5% BPV with 2 ml of 8 mg dexamethasone. Pain during injection may indicates an intraneural placement of the needle and further injection should be avoided. Cases with partial block were dropped from this study. Basic monitoring was recorded

preoperatively, intraoperatively every 10 min until the end of surgery then at 2nd, 6th and 12th postoperative hours. Following administration of the drugs, the sensory block was tested by Hollmen scale [13] as:

Grade 1: Full sensation of pinprick. Grade 2: Weak sensation.

Grade 3: Recognized as touch. Grade 4: No sensation

Time of onset of the sensory block represented as the time passed from the giving of the L.A to the grade 2, while the time for the complete sensory block is extended to the grade 4. The total duration of the sensory block is the time that extended from grade 4 till the time when the Hollmen score less than 4 was reached. Motor block was monitored by a modified Bromage Scale[14].

Grade 0-normal motor function. Patient can raise his extended arm completely.

Grade 1- Patient flexes his elbow and move his fingers but cannot raise his extended arm

Grade 2- Can move his fingers only. Grade 3- Complete block.

Time of onset of motor blockade represented as the time passed to reach Grade-1 while the time to reach its peak effect extended from injection of the drugs to the Grade-3 motor blockade. The total duration represented as the time extended between giving of the drug to the return of the normal motor function (Grade-0). Pain was monitored and evaluated by using the visual analogue score (VAS) [15] in which a score of 0 indicates no pain and a score of 10 worst pain. The VAS measurements were obtained every three hours for the first 24 hours postoperatively. Rescue analgesic in the form of slow IV bolus of 50 mg of tramadol was administered at the VAS score of 4. Time of first request for painkiller and the total analgesic during the first 24 hours post-operative period were recorded.

Statistical analysis: Statistic with the SPSS program, version 24. The qualitative data had been analyzed by using of Chi - square. The quantitative data had been analyzed by using student's paired t-test was used. VAS was analyzed by the Friedman test.

RESULTS

Demographic parameters (age and sex) revealed that there was a predominance of males upon females in all group, this is of no clinically relevant effect on this study (Table 1). The mean duration of surgery was 79.13±20.58 minutes in Group C, 110.13±38.33 minutes in Group D and 95.25±30.22 minutes in Group DE.

TABLE 1: EXPERIMENTAL GROUPS AGE, SEX AND DURATION OF SURGERY

Parameters	Group (C)	Group (D)	Group (DEX)	P- value
Age (year)	37.45±10.80	34.05±10.01	35.90±10.77	0.348
Male / Female	18/7	17/8	15/10	0.646
Duration surgery of (minutes)	79.13±20.58	110.13±38.33	95.25±30.60	p<0.001

Sensory block:

Regarding the onset of sensory block, it was shorter in Group C (8.650 ± 0.90 minutes) as compared to Group D (9.60 ± 0.80 minutes) and group DEX (9.3 ± 0.9 minutes). This is of no clinically relevant effect though statistically significant. There was no significant effect in the time of

peak sensory block in all the groups as group C was (16.3 minutes), group D (16.62 minutes), group DEX (16.4 minutes). Regarding the total duration of sensory block, p- value was highly Significant between groups C (350.7 minutes), D (800.25 minutes) and DEX (630.3 minutes) as show in (Table 2, Fig 1)

TABLE 2: COMPARISON OF SENSORY BLOCK CHARACTERISTICS. SD: STANDARD DEVIATION, GROUP C (CONTROL), GROUP D(DEXAMETHASONE), GROUP DEX (DEXMEDETOMIDINE). +++ P<0.001 -HIGHLY SIGNIFICANT, ++ P<0.01 -VERY SIGNIFICANT, +</td>P<0.05 (0.02- 0.05)-SIGNIFICANT, (NS) P>0.05-NOT SIGNIFICANT

Parameters	Group (C)	Group (D)	Group (DEX)	P- value	P- value
	Mean ± SD	Mean ± SD	Mean ± SD		between groups
Sensory block onset (minutes)	8.650 ±0.90	9.60 ±0.80	9.3 ±0.9	p<0.001+++	Group C and D-0.000+++
					Group C and DEX-0.000+++
					Group D and DEX-0.265 (NS)
Peak of sensory block (minutes)	16.3 ±1.7	16.62 ±1.4	16.4 ±1.65	p>0.05	NS
Total duration of sensory block (minutes)	350.75 ±41.35	800.25 ±72.74	630.30 ±74.77	p<0.001+++	Group C and D-0.000+++
					Group C and DEX-0.000+++
					Group D and DEX-0.000+++

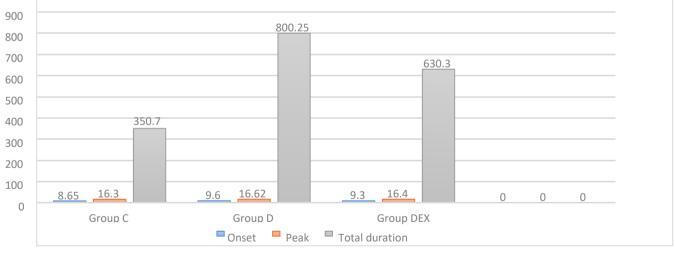


Figure3: Sensory block characteristics

Motor block

Regarding the onset of motor inhibition, it was shorter in Group C (9.6 \pm 0.8 minutes) as compared to Group D (10.30 \pm 0.72 minutes) and group DEX (10.0 \pm 0.92 minutes). This is of no clinically relevant effect though statistically significant. There was no significant variation

in the time of peak motor block in C (23 minutes), D (23.98 minutes) and DEX (23.31 minutes). Regarding the total duration of motor block, p-value was highly significant between groups C (240 minutes), D (482 minutes) and DEX (386 minutes) as shown in (Table 3, Fig 2).

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TABLE 3. COMPARISON OF MOTOR BLOCK CHARACTERISTICS. SD: STANDARD DEVIATION, GROUP C (CONTROL), GROUP D(DEXAMETHASONE), GROUP DEX (DEXMEDETOMIDINE). +++ P<0.001 -HIGHLY SIGNIFICANT, ++ P<0.01 -VERY SIGNIFICANT, +</td>P<0.05 (0.02- 0.05)-SIGNIFICANT, (NS) P>0.05-NOT SIGNIFICANT

Parameters	Group (C)	Group (D)	Group (DEX)	P- value	P- value between groups
	Mean ± SD	Mean ± SD	Mean ± SD		
Motor block onset (minutes)	9.6 ±0.8	10.30 ±0.72	10.0 ±0.92	p<0.001+++	Group C and D-0.000+++
					Group C and DEX-0.000+++
					Group D and DEX-0.068 (NS)
Peak of motor block (minutes)	23.00 ±2.11	23.98 ±1.41	23.31 ±1.5	p>0.05	NS
Total duration of motor block (minutes)	240.7 ±38.68	482.00 ±52.71	386.00 ±60.07	p<0.001+++	Group C and D-0.000+++
					Group C and DEX-0.000+++
					Group D and DEX-0.000+++

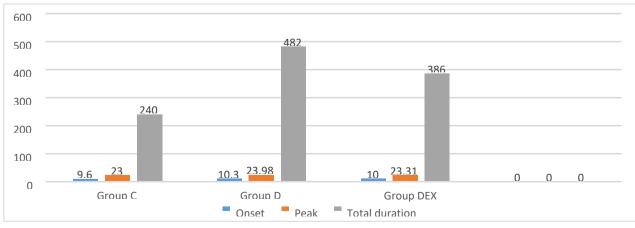


FIGURE 3. MOTOR BLOCK CHARACTERISTICS. C: CONTROL, D: DEXAMETHASONE, DEX: DEXMEDETOMIDINE

Regarding the onset of pain, was much earlier in Group C, mean of VAS was higher in group C >group DEX > group D. The maximum mean of VAS score occurs at 9th, 12th and

Onset of pain

GROUP

15th postoperative hours in group C, DEX and D respectively (table 4, Fig 3).

Time to maximum

unoor	onset of pum		VAS	mum
С	3 hr.	4±0.3	9	
DEX	6 hr.	3.7±0.4	12	
D	9 hr.	2.5±0.4	15	
4.5 4 3.5 3 2.5 2 1.5 1 0.5 0				
	nrs 6 hrs 9 hrs	5 12 hrs 15 hrs Axis Title	18 hrs 21 hrs	24 hrs
	Group C	Group D Gr	roup DEX DE	

TABLE 3. VAS AMONG C, D, DEX GROUP

Maximum VAS± SD

FIGURE 3: PAIN SCORES IN THE THREE GROUPS

Total dose of analgesic (tramadol in mgs in 24 hours) was significantly lower in group D and group DEX than group C. (Table 5).

 TABLE 5: TIME TO RESCUE ANALGESIC AND THE TOTAL DOSE REQUIRED. SD: STANDARD DEVIATION, GROUP C (CONTROL), GROUP D

 (DEXAMETHASONE), GROUP DEX (DEXMEDETOMIDINE). +++ P<0.001 -HIGHLY SIGNIFICANT, ++ P<0.01 -VERY SIGNIFICANT, +</td>

 P<0.05 (0.02- 0.05)-SIGNIFICANT, (NS) P>0.05-NOT SIGNIFICANT

Parameters	Group (C)	Group (D)	Group (DEX)	P- value	P-value between groups	
	Mean ± SD	Mean ± SD	Mean ± SD			
Time to rescue analgesic tramadol (minutes)	530.00 ±190.37	1030.0 ±182.95	814.61 ±188.	p<0.001+++	Group C and D-0.000+++ Group C and DEX-0.000+++	
					Group D and DEX-0.000+++	
Total dose of analgesic (tramadol) in mgs in 24 hours.	96.72 ±20.1	20.2 ±20.1	60.19 ±21.88	p<0.001+++	Group C and D-0.000+++ Group C and DEX-0.000+++ Group D and DEX- 0.000+++	

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DISCUSSION

In this study, a prolonged effect of both sensory and motor block was observed in both group DEX and group D (more significant in D) than group C.

Many studies use DEX as adjuvant to LA in peripheral nerve block and found that DEX is an excellent choice to improve block characteristics. [16]

Choi et al and Brummett et al. mention in their study of DEX as adjuvant LA in peripheral nerve block that the mechanism of action of DEX was multifactorial [17,18].while Masuki et al., Yoshitomi et al. and Talke et al. explained the effect of DEX as induce vasoconstriction through its action on α^2 adrenoceptors or produces analgesia peripherally by increasing the potassium conduction and decreasing norepinephrine release in C and A-delta neurons which is responsible for passage of pain stimulus, while it produce analgesia centrally through its action on the level of dorsal root ganglia and locus ceruleus by inhibit the release of substance p in the nociceptive pathway.[19-21]

Adding of steroid to LA in peripheral nerve blocks will effectively increase the duration of block, as it is potent anti-inflammatory and immunosuppressant agent, dexamethasone is preferred because of its highly antiinflammatory potency about (25_30) time than hydrocortisone. [22]

In this study Addition of 100mcg DEX to thirty ml of 0.5% BPV in peripheral nerve blocks significantly prolong sensory and motor block as well as prolong duration of analgesia, this result met with Marhofer et al, Swain et al, which had the same result in their studies [23-24].

On the other hand, use of 8 mg of D to thirty ml of 0.5% BPV in peripheral nerve blocks also significantly prolong sensory and motor block as well as prolong duration of analgesia, this result met with Swain et al. and Liu et al. [25]

As a result, both DEX & D are excellent adjuvant to LA in peripheral nerve blocks but duration of sensory and motor blocks was longer in Dexamethasone group as a compare to dexmeditomidine group, this result met with A. Naveen Kumar that had the same result in his studies. [26]

Korean J Pain et al. found in his study that dexmeditomidine and dexamethasone are both equal in prolongation of sensory and motor blocks and had the same onset, this discrepancy could be due to taken a smaller group (17) patient, with ropivacaine instead of bupivacaine hydrochloride (BPV) in deferent blocks (axillary brachial plexus block). [27]

On the other hand, Mohamed Hussien Hamada et al. mentions that dexmeditomedine as adjuvant to LA in peripheral nerve blocks produced relatively longer sensory and motor duration than dexamethasone [28]. This discrepancy could be due to using of small dose of dexamethasone [4mg] only and this is not enough to give the perfect action of dexamethasone as adjuvant to LA in peripheral nerve blocks.

Regarding the onset of sensory and motor blocks there are no clinically relevant effect, which met with the result of but on other side Vieira et al. [29]

Demographic parameters (age and sex) revealed that there was a predominance of males upon females in all group, this is of no clinically relevant effect on this study.

Regarding the onset of pain, was much earlier in group C, mean of VAS was higher in group C >group DE > group D. The maximum mean of VAS score occurs at 9th, 12th and 15th postoperative hours in group C, DE and D respectively. In group D only five patients received rescue analgesic and only after 15 hours post-operatively. Total dose of analgesic (tramadol in mgs in 24 hours) was significantly lower in group D and group DE than group C; this met with the result of A. Naveen Kumar et al. [76]. None of the patient required airway assistance due to sedation and this met with Mangal et al. and Abdelnaim et al. [30-31]

CONCLUSION

Dexmedetomidine and dexamethasone, both are good as adjuvants in peripheral nerve blocks, but dexamethasone had better effects on sensory and motor block duration in comparison with dexmedetomidine. The first time to analgesic request in dexamethasone group was longer than dexmedetomidine group.

RECOMMENDATION

This study recommended that dexamethasone is a preferable adjuvant to LA in SCBPB than dexmeditomidine with less VAS score.

REFERENCES

- 1. Wouden, J. and K.W. Miller, General Anesthetic Pharmacology. Principles of Pharmacology: The Pathophysiologic Basis of Drug Therapy, 2011: p. 240.
- 2. Buckenmaier, C., Military advanced regional anesthesia and analgesia handbook. 2009: Government Printing Office.
- 3. Sri Vikram Prabu, S., Prospective, Randomized Comparison of Modified Raj and Coracoid Approach for Infra Clavicular Block using Nerve Locator in Randomly Selected Adult Surgical Patients. 2010, Madras Medical College, Chennai.
- 4. Brown, D.L., Atlas of regional anesthesia. 2010: Elsevier Health Sciences.
- 5. Frey, U., Y. Huang, and E. Kandel, Effects of cAMP simulate a late stage of LTP in hippocampal CA1 neurons. Science, 1993. **260**(5114): p. 1661-1664.
- 6. Thankachan, S., Spinal anesthesia, Bupivacaine, Clonidine, Complete, effective and postoperative analgesia. A COMPARATIVE STUDY OF BUPIVACAINE AND BUPIVACAINE WITH CLONIDINE UNDER SPINAL ANESTHESIA IN PATIENT FOR TOTAL ABDOMINAL HYSTERECTOMY, 2015(6880).
- 7. Manuraj, V., et al., A comparative study of bupivacaine and bupivacaine with clonidine under spinal anesthesia in patient for total abdominal hysterectomy. Journal of Evolution of Medical and Dental Sciences, 2015. **4**(15): p. 2447-2459.
- 8. Eldor, J., Continuous intraperitoneal infusions of Bupivacaine, Bicarbonate and Steroids (BBS): A new modality for postoperative analgesia in laparoscopic operations?
- 9. Naaz, S. and E. Ozair, Dexmedetomidine in current anaesthesia practice-a review. Journal of clinical and diagnostic research: JCDR, 2014. **8**(10): p. GE01.
- 10. Yoshitomi, T., et al., Dexmedetomidine enhances the local anesthetic action of lidocaine via an α -2A adrenoceptor. Anesthesia & Analgesia, 2008. **107**(1): p. 96-101.
- 11. Liu, D., et al., A practical guide to the monitoring and management of the complications of systemic corticosteroid therapy. Allergy, Asthma & Clinical Immunology, 2013. **9**(1): p. 30.

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- Schäcke, H., W.-D. Döcke, and K. Asadullah, Mechanisms involved in the side effects of glucocorticoids. Pharmacology & therapeutics, 2002. 96(1): p. 23-43.
- 13. Luyssaert, S., et al., Evaluation of forest nutrition based on large-scale foliar surveys: are nutrition profiles the way of the future? Journal of Environmental Monitoring, 2004. **6**(2): p. 160-167.
- 14. Zaric, D., et al., Sensory and motor blockade during epidural analgesia with 1%, 0.75%, and 0.5% ropivacaine--a double-blind study. Anesthesia and analgesia, 1991. **72**(4): p. 509-515.
- Kelly, A., The minimum clinically significant difference in visual analogue scale pain score does not differ with severity of pain. Emergency Medicine Journal, 2001. 18(3): p. 205-207.
- Brown, D.L., Brachial plexus anesthesia: an analysis of options. The Yale journal of biology and medicine, 1993. 66(5): p. 415.
- 17. Chelly, J.E., Peripheral nerve blocks: a color atlas. 2009: Lippincott Williams & Wilkins.
- Neal, J.M., et al., Quantitative analysis of respiratory, motor, and sensory function after supraclavicular block. Anesthesia & Analgesia, 1998. 86(6): p. 1239-1244.
- Pingleton, S.K., Complications of acute respiratory failure. Am Rev Respir Dis, 1988. 137(6): p. 1463-1493.
- 20. Vanden Hoek, T.L., et al., Part 12: cardiac arrest in special situations: 2010 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. Circulation, 2010. 122(18_suppl_3): p. S829-S861.
- 21. Souron, V., Y. Reiland, and L. Delaunay, Pleural effusion and chest pain after continuous interscalene brachial plexus block. Reg Anesth Pain Med, 2003. 28(6): p. 535-538.
- Urmey, W.F., Pulmonary complications. Complications in Regional Anesthesia & Pain Medicine, 2007: p. 147-56.
- Bruce, B.G., et al., Brachial plexus blocks for upper extremity orthopaedic surgery. JAAOS-Journal of the American Academy of Orthopaedic Surgeons, 2012.
 20(1): p. 38-47.
- 24. Yang, C.W., et al., A comparison of infraclavicular and supraclavicular approaches to the brachial plexus using neurostimulation. Korean journal of anesthesiology, 2010. **58**(3): p. 260.
- 25. Jandard, C., et al., Infraclavicular block with lateral approach and nerve stimulation: extent of anesthesia and adverse effects. Regional anesthesia and pain medicine, 2002. **27**(1): p. 37-42.
- 26. Mian, A., et al., Brachial plexus anesthesia: a review of the relevant anatomy, complications, and anatomical variations. Clinical Anatomy, 2014. 27(2): p. 210-221.
- Hodgson, P.S., et al., The neurotoxicity of drugs given intrathecally (spinal). Anesthesia & Analgesia, 1999.
 88(4): p. 797-809.
- 28. Bagshaw, K.R., et al., Pain management via local anesthetics and responsive hydrogels. Therapeutic delivery, 2015. 6(2): p. 165-176.
- 29. Covino, B.G., Recent advances in local anaesthesia. Canadian
- 30. Richard, B.M., et al., Safety evaluation of EXPAREL (DepoFoam bupivacaine) administered by repeated subcutaneous injection in rabbits and dogs: species comparison. Journal of drug delivery, 2011. 2011.

31. Hahn, I.-H., R.S. Hoffman, and L.S. Nelson, EMLA®induced methemoglobinemia and systemic topical anesthetic toxicity. The Journal of emergency medicine, 2004. 26(1): p. 85-88.