

Investigation of Verpamil Effect as Adjuvant Anaesthetic Drug

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Abstract

Many drugs have been studied as adjuvant to local anaesthetic solution for peripheral nerve blocks in order to increase the quality of block and to increase the duration of analgesia. This study used verapamil, a calcium channel blocking drug as adjuvant for supraclavicular block. To evaluate the effect of verapamil as an adjuvant to local anaesthetic solution in supraclavicular block. In this randomised prospective double blind control trial study we divided 60 ASA grade I,II patients undergoing elective upper limb surgery into two equal groups of 30 (n=30) each. Group A received brachial block with 2% lignocaine 10cc and 20 cc 0.5% bupivacaine with added NS .9% 1cc. Group B received 10 cc of 1.5% lignocaine and 20 cc of 0.5% bupivacaine with 1 cc verapamil (2.5 mg). Observations made regarding onset of sensory block and motor block, duration of sensory and motor block and duration of analgesia. Also haemodynamic parameters monitored to see any difference. Results are calculated using statcal software SPSS version 17, unpaired't' test and chi square test are used to compare numerical and categorical variables respectively. There was no difference in both the groups regarding onset of sensory, motor block, duration of motor block and duration of analgesia ($p>0.05$). Duration of sensory block is found to be significantly greater in group B(191+ 45) than in group A (163+ 4) this difference is statistically significant ($p=0.01$). Addition of verapamil as an adjuvant to local anaesthetic for supraclavicular block results in prolonged duration of sensory block without any effect on it.

Keywords: Adjuvants; analgesia; verapamil; supraclavicular block;

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1. Introduction

Since 1884 when Halsted performed first brachial plexus block[1], and in 1911 Hirshell [2] described its percutaneous technique, this type of regional anaesthesia being widely used for upper limb procedures with or without general anaesthesia and of many approaches supraclavicular approach has distinct advantage of dense, complete, reliable anaesthesia [3,4,5]. As it is performed at trunks level where plexus is compactly arranged over first rib. Use of ultrasound for giving peripheral blocks has increased its use and outcome due to precise location of administering the drug near to nerve. While catheter based techniques allows for sustained pain relief it comes with its own disadvantages and complications like catheter displacement , infection overall skill and cost [6].So adding adjuvant to enhance peripheral nerve block

efficacy and duration of analgesia still remains sought for option. Use of adjuvants for its synergistic action allows us to use lower concentrations of local anaesthetics and thereby reducing its systemic (cardiac and central nervous system) toxicity as well as local neural toxicity, it reduces postoperative opioid requirements and side effects associated with it. Various groups of drugs have been tried so far to find the ideal adjuvant. Use of vasoconstrictor like epinephrine has raised query for its potential neurotoxicity and its role is now limited to give test dose to rule out intravascular injection [7,8,9]. Wide range of opioids like morphine, fentanyl, tramadol ,buprenorphine have been tried with variable results [10,11,12,13,14,15,16,17] main concern using opioids is their side effects like nausea, vomiting, sedation, pruritus and potentiation of lignocaine mediated nerve

toxicity. Clonidine α_2 adrenoceptor antagonist has shown to prolong the duration of analgesia but associated with haemodynamic effects like hypotension, bradycardia in postoperative period and warns its use in high concentration and in high risk patients [18,19,20]. Use of dexmedetomidine is good choice [21] but requires post-operative monitoring for bradycardia and still further studies are required to make its use routine. Dexamethasone a potent anti-inflammatory agent has been tried as an adjuvant though there is increased duration of analgesia further well powered studies are required to establish its safety in terms of neurological complications [22]. Other As we know calcium ions have an important role in analgesia mediated by local anaesthetics. Calcium permeability is reduced by local anaesthetics. In addition calcium ion play an important role in opioid -receptor mediated analgesia. Various studies have shown that verapamil a calcium channel blocking drug can potentiate analgesic effect of local anaesthetic solution in epidurals or in regional blocks [27,28,29]. With this background we decided to investigate the effect of verapamil as an adjuvant to local anaesthetic in brachial plexus nerve. Using Hollmens scale 1.-normal sensation to pin prick, 2.- weak sensations but prick felt, 3.- prick felt as blunt touch, 4.- no sensation. Motor block assessed by conventional muscle power grading from 0- complete paralysis to 1- reduced mobility 2- no force but mobility present, 3- pronounced reduction in force, 4- slightly reduced muscular force and 5 - normal muscle power. We checked Thumb abduction for radial nerve, thumb adduction for ulnar nerve, thumb opposition for median nerve and elbow flexion by

Objectives: To see the effect of verapamil as an adjuvant on onset of sensory and motor block, duration of sensory and motor block and duration of analgesia.

2. Materials and Methods

This was randomised double blind prospective controlled trial study conducted in Dr D.Y. Patil Medical College, Kolhapur; from may 2011 to may 2013. After institutional ethical committee approved the project 60 patient of ASA grade I, II of either sex, aged between 18-60 yrs and weighing 50-100 kgs, to be undergoing upper limb elective surgery mainly orthopaedic, plastic and reconstructive surgery requiring >30 min time for procedure were enrolled in study. Patients who refused permission for study, were on oral verapamil, with history of peripheral neuropathy, with cardiac conduction abnormality, with deranged coagulative profile were excluded from study. All patients were clinically thoroughly evaluated and appropriately investigated on

previous day of surgery in preanaesthetic checkup clinic and written informed consent obtained for surgery and study, patients were given tab. Diazepam 10 mg at night and were kept nil by mouth overnight. Patients were randomly divided in two groups of 30 each by computer generated random number method i.e. Group A and Group B. All drug solutions required for block were prepared by anaesthesiologist colleague who was not involved in study or in giving anaesthesia.

Group A: Received brachial block with 10 ml of lignocaine 2% and 20 ml of .5% bupivacaine with normal saline 1ml added to it. This was control group.

Group B: Received brachial block with 10 ml of 2% lignocaine and 20 ml of .5% bupivacaine with 1ml inj verapamil (2.5mg) added to it. This was study group.

On arrival to operation theatre multipara monitor attached and iv line secured with 20 g IV cannula on opposite dorsum of hand and RL started. Baseline parameters like pulse rate, SBP, DBP, MBP, SPO2 recorded as preop values. After giving proper position to the patient brachial block by supraclavicular approach (2 cm above the midpoint of clavicle, lateral to subclavian artery pulsations on first rib) with 22g, 5 cm stimuplex needle was given under all aseptic precautions using PNS, taking fingers flexion to 0.3 mv as end point response. And total 30 cc volume of drugs given as mentioned above. Time of injection is noted. After the block following observations are made every 3 min interval about sensory and motor block till surgery is started, to note the onset of block and at every 30 min interval once surgery is over to note the duration of block. Sensory block assessed with pin prick on injection of drug and sensory block to scale 2. 2.-onset time for motor block: it was taken as time interval between injection of drug and motor block of grade 3. 3-duration of sensory block defined as time interval between complete block and return of normal sensation i.e. pinprick. 4.- duration of motor block was defined as time interval between complete paralysis to complete recovery of motor function to grade 5. 5- duration of analgesia is assessed by evaluating pain post operatively every 30 min when VAS score is >4 it is taken as need to provide supplementary analgesia and is provided with 100 mg of tramadol intramuscularly and time is noted. Time between onset of block and supplementary analgesia given was taken as duration of block. We monitored pulse, SBP, DBP, MBP, Spo2 every 5 min interval during surgery and every 30 min interval postoperatively. We sedated patients with inj pentazocine 0.3 mg/ kg iv and inj midazolam 0.04 mg /kg. We observed no untoward reactions, complications or failed block.

2.1 Statistical analysis

The data was statistically analysed using statcal softwareSPSS version 17.0. The various mentioned parameters and patients characteristics were compared using students unpaired 't' test and chi-square test . With $p < 0.05$ was taken as significant difference and $p < 0.01$ wa taken as highly significant difference. Numerical data variables were presented as mean and standard deviation while categorical variables were presented as frequency and percentage. As regards to numerical variables unpaired students 't' test was used while for categorical variables chi-square test was used. For analysis of demographic data for gender distribution chi- square test was applied along with calculation of degree of freedom (df) whereas for age and weight distribution unpaired students 't' test was applied.

3. Results and Discussion

Table 1. Age wise distribution of patients.

Group	N	Mean Age(yrs)	SD ±	Min	Max	t value	P value#	Significance
Group A	30	33.70	11.49	18	60	0.67	0.25	Not significant
Group B	30	31.76	10.64	18	60			

Unpaired t test

Table 1 showed Mean age of both the groups were comparable and showed no statistical difference ($p > 0.05$)

Table 2. Sexwise distribution of patients in two groups.

Group	Sex		Total
	Male	Female	
Group A	23	07	30
	76.67%	23.33%	100%
Group B	22	08	30
	73.33%	26.67%	100%
Total	45	15	60
	75%	25%	100%

Chi-square test	df	P value
0.089	1	0.76

Table 2 Showed overall there was no significant difference in both the groups as per sex distribution of patients.

Table 3. Group wise weight distribution of patients.

Group	N	Mean wt(kg)	SD±	t value	P value#	Significance
A	30	64	8	0.095	0.46	Not significant
B	30	64.2	8.01			

Unpaired 't' test

It was very clear from Table 3 that mean weight of the patients in both the groups was statistically comparable.

Table 4. Onset of sensory blockade in min in two groups

Group	Onset of block in min		t value	P value #	Significance
	Mean	SD+			
Group A	23.6	3.91	0.51	0.60	Not significant
Group B	23.1	3.53			

Unpaired 't' test

Table 4 compared the time taken for onset of sensory blockade in the two groups, though onset of blockade was little early in Group B it was ststistically not significant.

Table 5. Onset of motor blockade in both the groups

Group	Onset of motor blockade in min		t value (unpaired 't' test)	P value	Significance
	Mean	SD+			
Group A	26.8	3.43	0.72	0.4	Not significant
Group B	26.2	2.94			

Table 5 showed time taken for onset of motor block and was comparable without statistical significant difference.

Table 6 Duration of sensory block in both the groups in mins.

Group	Duration of sensory block (min)		t value	P value #	Significance
	Mean	SD+			
Group A	163	45.72	2.37	0.01*	Significant*
Group B	191	45.59			

Unpaired 't' test * Statistically significant

When duration of sensory blockade compared as seen in table

6 we found significantly longer duration of action in group B (P=0.01 statistically significant)

Table 7. Duration of motor block in both the groups.

Group	Duration of motor block (min)		't' value	P value #	Significance
	Mean	SD+			
Group A	151	43.5	0.35	0.72	Not Significant
Group B	155	43.9			

Unpaired 't' test

Table 7 compared the duration of motor blockade in both the groups and it was not found to be significantly different statistically.

Table 8. Duration of analgesia in both the groups in mins.

Group	Duration of analgesia (min)		t value	P value #	Significance
	Mean	SD+			
Group A	307	63.8	0.8	0.41	Not significant
Group B	321	69.1			

#Unpaired 't' test

When we compared duration of analgesia in both the groups above Table 8 showed the difference is statistically not significant, though there was little longer duration of analgesia in group B.

Also we recorded and observed any significant difference in between the groups regarding systolic, diastolic and mean blood pressure as well as pulse rate and oxygen saturation for every 5 min interval during procedure and every half an hr post operatively till 6 hrs. We did not note any significant difference. Neither any untoward reaction or side effect was not noted in any of the groups.

A variety of receptor mediate nociception on peripheral sensory axons, and peripheral

administration of appropriate drugs (adjuvants along with local anaesthetics) may have analgesic benefits and reduced systemic adverse effects. In an attempt to improve perioperative analgesia, variety of adjuvants such as opioids, clonidine, neostigmine have been administered concomitantly with local anaesthetic into the brachial plexus sheath but none proved ideal. The aim of this study was to evaluate whether additional anaesthetic and analgesic effect could be derived from administration of verapamil, a calcium channel blocker when used as adjuvant to local anaesthetic solution into brachial plexus sheath. Verapamil is a synthetic papaverine derivative, a L type of calcium channel blocker. It also inhibits fast sodium channel and has shown to have similar effect like local anaesthetic [30]. There are three different types of voltage gated calcium channels namely L,T and N . L and N type has significant role in regulation of release of neurotransmitter from neurons [31]. Amongst all N type are most potent antinociceptives but because of their neurotoxicity they are not suitable for clinical use. Pirec et al had shown its application with morphine in invitro experiments in rats where it attenuated a-delta and C fibres mediated nociception [32]. Somatic and visceral pain may be attenuated in dose dependant manner with L type of calcium channel blockers was the conclusion of Hara et al [33]. Omoto when used verapamil intrathecally found that by itself it doesn't have and sensory or motor blockade but when combined with lignocaine it significantly prolongs analgesia [34]. Laurito found no difference when verapamil is injected subcutaneously with local anaesthetic [35]. We conducted double blind study using verapamil as adjuvant to local anaesthetic for supraclavicular brachial plexus block and our results demonstrated significant prolongation of duration of sensory block but onset of sensory and motor block as well as duration of analgesia were not significantly affected. Our results are similar to results of Lall et al, where verapamil was used as adjuvant for brachial block.[29] Similarly Tabaeizavareh et al when used verapamil as adjuvant in epidural analgesia failed to find any difference in sensory and motor block characteristics[28]. Two different dose (2.5 and 5 mg) of verapamil as an adjuvant have been tried by Mosaffa who found that though onset of sensory and motor block was hastened in verapamil group dose wise there was no difference.[27] Kim and Choe also found decreased requirement of analgesics in postoperative period when verapamil used as adjuvant epidurally. [36,37]. Ruben found no effect on postop analgesic requirement when verapamil used as adjuvant in brachial plexus block. [38] Multiple other studies by Miranda, Carta, Hasegava favours use of verapamil as adjuvant as they found increased analgesic effects [39,40,41] Our results suggest that analgesic

effect of verapamil may have been short lived due to overdilution of drug or may have been masked by long acting bupivacaine. Verapamil epidurally gives better results may be due to action on spinal cord by attenuating neurotransmitters release. There is recent concept of 'multimodal perineural analgesia' where multiple agents with different mechanisms of action used with goal of providing perineural analgesia while avoiding exposure to high and potentially toxic levels of individual agents. There is still scope for further studies by using different calcium channel blocker or different dose of verapamil or may be verapamil with opioids as a part of multimodal perineural analgesia.

4. Conclusion

Addition of verapamil to lignocaine bupivacaine solution for brachial plexus block can modify the action of local anaesthetic by increasing duration of sensory block. Although dose used in our study failed to demonstrate any difference in onset of block or analgesia duration. So it does suggest that there is further scope for studies using different dose or different calcium channel blocker or verapamil with other opioid as a part of multimodal perineural analgesia

References

1. Crile H. Great moments in the history of anaesthesiology in A practice of anaesthesia 7th ed. London, UK: Liod -Luke;2003 .p-8
2. Buttner J. Axillary and midhumeral approach for brachial plexus block. *Curr Opin Anaesthesiology* 1998; 11:499-502
3. Jeon DG, Kim W. Case series:ultrasound guided supraclavicular block in 105 patients. *Korean Jr Anaesthesiology* 2010 Mar;58(3);267-271
4. Singh A, Gupta R, Vashisht M, Singh S, Kumari A, Aujala K S. Comparison of effectiveness of brachial plexus block by supraclavicular and axillary approaches alone or in combination. *Jr of Anaesth and clin pharmacol* 2010; 26(1): 31-34
5. Yang CM, Kwon HU, Cho CK et al. A comparison of infraclavicular and supraclavicular approaches block using nerve stimulation. *Korean Jr. Anaest.*2010 Mar; 58(3):260-266
6. Ilfeld BM. Continuous peripheral nerve blocks; a review of the published evidence. *Anaest. Analges.*2011;113(4):904-925. Pmid: 21821511 view article .pubmed/NCBI. Google scholar
7. Neal JM. Effect of epinephrine in local anaesthetics on the central and peripheral nervous system: Neurotoxicity and neural blood flow. *Reg Anaesth Pain Med.*2003;28:124-134 [Pubmed]
8. Myers RR, Heckman HM. Effects of local anaesthesia on nerve blood flow: studies using lignocaine with or without epinephrine. *Anaesthesiology* 1989; 71:757-762[Pubmed]

9. Welch MB, Brummett CM, Welch TD, Tremper KK, Shanks AM, Guglani P, Mashour GA. Perioperative peripheral nerve injuries: a retrospective study of 380,680 cases during a 10 yr period at a single institution. *Anaesthesiology* 2009;111:490-497 [Pubmed]
10. Bazin JE, Massoni C, Bruelle P, Fenies V, Groslier D, Schoeffler P. The addition of opioids to local anaesthetics in brachial plexus block: the comparative effect of morphine, buprenorphine and sufentanyl
Anaesthesia 1997;52:858-862[Pubmed]
11. Murphy DB, McCartney CJ, Chan VW. Novel analgesic adjuvants for brachial plexus block: a systematic review *Anaesthesia* 2009;90:1122-1128[Pubmed]
12. Fanelli G, Casati A, Magistris L, Berti M, Alebertin A, Scarioni M, Torri G, Fentanyl does not improve the nerve block characteristics of axillary brachial plexus anaesthesia performed with ropivacaine. *Acta Anaesthesiol. Scand.* 2001;45:590-594[Pubmed]
13. Moharari R, Sadeghi J, Khajavi M, Davari M, Mojtahedzadeh M. Fentanyl supplement expedites the onset time of sensory and motor blocking in interscalene lidocaine anaesthesia. *Daru* 2010;18:298-302[PMC free article][Pubmed]
14. Nashikawa K, Kanaya N, Nakayama M, Igarashi M, Tsunoda K, Namiki A. Fentanyl improves analgesia but prolongs the onset of axillary brachial plexus block by peripheral mechanism. *Anaesthesia Analg.* 2000;91: 384-387.[Pubmed]
15. Candido KD, Franco CD, Khan MA, Winni AP, Raja DS. Buprenorphine added to local anaesthetic for brachial plexus block to provide postoperative analgesia in outpatients. *Reg Anaesth. Pain Med.* 2001;26(4):352-356.pmid 9349066
16. Mannion S, O'Callaghan S, Murphy DB, Shorten GD. Tramadol as adjunct to psoas compartment block with levobupivacaine 0.5% : A randomised double blind study. *Br. J. Anaesth.* 2005;94:352-356[Pubmed]
17. William BA, Hough KA, Tsui BY, Ibinson JW, Gold MS, Gebhart GF. Neurotoxicity of adjuvants used in peripheral anaesthesia and analgesia in comparison with ropivacaine. *Reg. Anaesth., Pain Med.* 2011;36(3):225-230 pmid:21519308
18. Popping DM, Elia N, Marret E, Wenk M, Tramer MR. Clonidine as an adjuvant to local anaesthetic for peripheral nerves and plexus block: a meta-analysis of randomised trials. *Anaesthesiology* 2009;111:406-415 [Pubmed]
19. McCartney CJ, Duggan E, Apatu E, Should we add clonidine to local anaesthetic for peripheral nerve blockade? A qualitative systematic review of a literature. *Reg. Anaesth. Pain Med.* 2007;32:330-338[Pubmed]
20. Fournier R, Faust A, Chassot O, Gamulin Z. Perineural clonidine does not prolong levobupivacaine 0.5% after sciatic nerve block using the labat approach in foot and ankle surgery. *Reg. Anaesth. Pain Med.* 2012;37:521-524[Pubmed]
21. Abdallah FW, Brull R. Facilitatory effects of perineural dexmedetomidine on neuroaxial and peripheral nerve block :A systematic review and metaanalysis. *Br. J Anaesth.* 2013;110:915-925[Pubmed]
22. Biradar PA, Khiarnar P, Gopalkrishnn K. Effect of dexamethasone added to lignocaine in supraclavicular brachial plexus block: A prospective, randomised, double blind study. *Indian J Anaesth.* 2013;57:180-184[PMC free article][Pubmed]
23. Kirksey MA, Haskins SC, Cheng J, Liu SS. Local anaesthetic peripheral nerve block adjuvants for prolongation of analgesia :A systematic qualitative review. *Plos One* 2015;10:e0137312
24. Bouaziz H, Paqueron X, Bur ML, Merle M, Laxenaire MC, Benhamou D. No enhancement of sensory and motor blockade by neostigmine added to mepivacaine in axillary plexus block. *Anaesthesiology* 1999;91:78-83[Pubmed]
25. Lee IO, Kim WK, Kong MH, Lee MK, Kim NS, Choi YS, Lim SH. No enhancement of sensory and motor blockade by ketamine added to ropivacaine interscalene brachial plexus block. *Acta. Anaest. Scand.* 2002;46:821-826[Pubmed]
26. Abdelfatah AM, Elshaer AN. The effect of adding magnesium sulphate to lignocaine in an interscalene plexus block for shoulder arthroscopy. *Ain Shams J Anaesthesiol.* 2014;7:59-64
27. Mosaffa F, Salimi AR, Lahiji F, Mirkeshti. Evaluation of analgesic effect of 2 doses of verapamil with bupivacaine compared to bupivacaine alone in supraclavicular brachial plexus block. *Med. Jr. Islam. Repb. Iran* 2007;21(2):87-90
28. Tabaeizavareh MH, Omranifard M, Moalemi A. The effect of verapamil as an adjuvant agent with local anaesthetic on sensory block level, haemodynamic and post-operative pain. *Pak. Jr. Med. Sci.* 2012;28(2): 259-262
29. Lalla RK, Anant S, Nanda HS. Verapamil as an adjuvant to local anaesthetic for brachial plexus block. *Med. Jr Armed Force India* 2010;66:22-24[PMC free article][Pubmed]
30. Reves JG, Kissin I, Lell WA, Toasn S. Calcium entry blockers: Uses and implications for anaesthesiologists. *Anaesthesiology* 1982;57:504-518[Pubmed]
31. Pirec V, Laurito CE, Lu Y, Yeomans DC. The combined effect of N type of calcium channel blocker and morphine on A delta versus C fibre

- mediated nociception. *Anaest. Analges.* 2001;92:239-43 [Pubmed]
32. Hara K, Saito Y, Kirihara Y, Sakura S, Kosaka Y. Antinociceptive effects of intrathecal L-type calcium channel blocker on visceral and somatic stimuli in the rat. *Anaest. Analgesia.* 1998;87: 382-7 [Pubmed]
33. Ometo K, Iwasaki H, Kawamata M, Satao O, Namiki A. Effects of verapamil on spinal anaesthesia. *Anaesthe. Analges.* 1995;80:444-8 [Pubmed]
34. Laurito CE, Cohn SJ, Becker GL. Effects of subcutaneous verapamil on duration of local anaesthetic blockade. *Jr. Clin. Anaest.* 1994;6:414-418 [Pubmed]
35. Kim JS, Park JH, Kang SG, Choe H, Han YJ. Analgesic effect with epidural bupivacaine and verapamil in lower abdominal surgeries. *Korean Jr. Anaest.* 1996;32:239-45
36. Choe H, Kim JS, Ko SH, Kim DC, Han YJ, Song HS. Epidural verapamil reduces analgesic consumption after lower abdominal surgery. *Anath. Analges.* 1998;86:786-90 [Pubmed]
37. Reuben SS, Reuben JP. Brachial plexus anaesthesia with verapamil and or morphine. *Anath. Analges.* 2000;91:379-83 [Pubmed]
38. Hasegawa AE, Zacny JP. The influence of three types of calcium channel blockers on morphine effects on healthy volunteers. *Anaest. Analges.* 1997;85:663-8 [Pubmed]
39. Miranda HF, Bustamante D, Kramer V, Pelissier T, Saavedra H, Paeile C et al. Antinociceptive effects of calcium channel blockers. *Europ. Jr. Pharmaco.* 1992;217:137-41 [Pubmed]
40. Carta F, Bianchi M, Argenton S, Cervi D, Marolla G, Tamburini M, et al. Effect of nifedipin on morphine induced analgesia. *Anaesth. Analges.* 1990;70:493-8 [Pubmed]