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Research Article

A Randomized, Double-Blind Trial Comparing Epinephrine versus Phenylephrine as a Vasoconstrictor in Regional Anesthesia for Upper Extremity Surgery

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Abstract: Regional blocks are often preferred to general anesthesia as they do not affect the body systemically and have the added benefit of providing extended pain relief with decreased use of analgesics. Vasoconstrictors are often added to local anesthetic (LA) solutions to prolong the block by reducing the clearance of the LA. This may help in reducing LA toxicity. Epinephrine has traditionally been the vasoconstrictor of choice. However, with both alpha and beta agonist properties, it may be problematic in patients taking beta-blockers. Phenylephrine, a pure alpha agonist, may be a better choice in these patients but has never been studied as an additive to las for upper extremity blocks. The primary objective of this study was to compare the efficacy (i.e., onset and duration of block) of epinephrine and two different concentrations of phenylephrine. The secondary objective was to study the side effects, if any, in each group.75 ASA I & II patients, above the age of 18, scheduled for elective operative shoulder arthroscopy under interscalene block with intravenous sedation were included in the study. These patients were randomly allocated to one of 3 groups. Group 1 received a standard LA mixture with 2.5 mcg/ml epinephrine. Group 2 received a standard LA mixture with 0.625 mcg/ml phenylephrine. Group 3 received a standard LA mixture with 1.25 mcg/ml. Phenylephrine. Onset and duration of block were recorded and analyzed. Recovery from the Block was assessed postoperatively in the PACU and via a phone call to the patient at home as Needed. Heart rates and blood pressures prior to block and for the first 30 minutes after the Initiation of the block was analyzed and compared. The median time to onset of block was 2, 2 and3 minutes for arms 1, 2, and 3 respectively. The median time to recovery from the block was 600, 542, and 593 minutes for Arms 1, 2, and 3 respectively. The differences in time to onset and recovery between the three groups were not statistically Significant. Changes in blood pressure and heart rate recorded at five-minute intervals over a Period of 30 minutes from the onset of the block were also not clinically significant between Groups. The replacement of a conservative dose of epinephrine (i.e., 2.5 mcg/ml) with Either 0.625 mcg/ml or 1.25 mcg/ml phenylephrine in local anesthetic solutions for upper Extremity block gives equivalent onset and duration of block without different effects on Heart rate and blood pressure.
Keywords: Local anesthetic, epinephrine, arthroscopy.

INTRODUCTION

Vasoconstrictors such as epinephrine are often added to local anesthetics to prolong the duration of neuraxial and peripheral nerve blocks. Vasoconstrictors prolong the exposure of the neurons to the local anesthetics by limiting diffusion of the anesthetic molecules into the bloodstream [1]. This has additional benefits of reducing peak plasma local anesthetic concentrations and of facilitating the detection of an intravascular injection, thus potentially reducing systemic local anesthetic toxicity. Adjunctive epinephrine prolongs anesthetic duration in a dose-dependent manner [2]. In peripheral nerve blocks, the concentration of epinephrine is typically up to a 1:200,000 dilution. Higher concentrations are associated with hemodynamic side effects such as increased heart rate and cardiac output. However, in patients at risk for cardiac ischemia or nerve injury as a consequence of decreased blood flow from chemotherapy, diabetes, or atherosclerotic disease, it may be safer to use weaker concentrations (1:400,000) or to avoid epinephrine altogether [3]. In these patients, phenylephephrine, a pure alpha agonist, may be a better choice of vasoconstrictor, because it does not increase the heart rate, cardiac output, or myocardial oxygen requirements. These advantages are particularly important in the case of accidental intravascular injection. However phenylephrine has never been studied as an additive to local anesthetics for upper extremity blocks. Studies comparing the prolongation of lidocaine spinal anesthesia by epinephrine and phenylephrine have given conflicting results [4]. Various other additives to local anesthetic solutions for peripheral blocks, such as clonidine, ketamine, and opioids, have also been studied, also with mixed results [3]. The primary objective of this study was to compare the effect on onset and duration of block of epinephrine and two different strengths of phenylephrine when added to lidocaine and bupivacaine for an interscalene block. The secondary objective was to study the side effects, if any, in each group.

METHODS

The New York Methodist Hospital Institutional Review Board approved the study. Seventy-five patients aged 18 and above with ASA physical status 1 and 2 scheduled for elective shoulder arthroscopy gave written informed consent and were included in the study. These patients were randomly allocated to one of the three groups using a computer generated randomization table. Exclusion criteria were history of allergy to local anesthetics, local infection at the site of block, and neurological deficits in the upper extremity. All groups received two syringes with a mixture of local anesthetic solution plus a vasoconstrictor (i.e., 18 ml 2% lidocaine + 2 ml 8.4% sodium bicarbonate + vasoconstrictor followed by 20 ml 0.5% bupivacaine + vasoconstrictor). In Groups 1, 2, and 3, the vasoconstrictors were 50 micrograms of epinephrine, 12.5 micrograms of phenylephrine, and 25 micrograms of phenylephrine, respectively. The solutions were all prepared from pharmaceuticals for clinical use, obtained from ordinary commercial sources (Bedford Laboratories, Bedford, Ohio; Hospira, Lake Forest, Ill; Braun, Irvine, Calif). The solutions were prepared in separate 20 ml syringes and were not mixed together before or during administration. An anesthesiologist not directly involved in the administration of the medications or evaluation of the block, enabling the administration and evaluation to be blinded, prepared the solutions. In order to reduce confounding variables, only the interscalene approach for the brachial plexus was used. All the anesthetics were for operative shoulder arthroscopy. The same clinician performed all the nerve blocks.

PROCEDURE

The blocks were facilitated using mild sedation with IV midazolam with or without fentanyl. A single injection interscalene block using the Winnie method was performed on all patients. To identify the brachial plexus, a 22 gauge, 2 inch insulated needle was used. The roots or trunks of the brachial plexus are located in the neck between the anterior and middle scalene muscles at the level of cricoid level or C6 level. The procedure was first well described by Alon Winnie in 1970. An acceptable motor response would be one involving the deltoid muscle or any muscle in the arm or hand .If deltoid muscle motor response was present at 0.3 mA, the placement of the needle was considered adequate for the block. The two syringes of local anesthetic solution for each study subjects, prepared prior to the block, were connected via a three-way stopcock to the extension tubing of the insulated needle. After adequate placement of the block needle and a negative aspiration, the lidocaine was injected in increments of 5cc with aspiration after each injection. Then, the bupivacaine was injected in the same manner. The injection of local anesthetic was completed within ninety seconds. Onset of block was assessed every 30 seconds after withdrawal of the needle. Onset of block was considered complete when the patient was unable to lift his or her arm against gravity. Motor block was preferred as it is more objective way as compared to sensory block, the heart rate and blood pressure was measured every five minutes for a period of 30 minutes after the initiation of the block. The study subjects were followed up via a phone call the day after surgery, since all the patients were discharged home the same day. The person making phone calls was blinded about the groups. The study subjects were asked about the first occurrence of discomfort after surgery. The duration of block was defined as the time until the first occurrence of discomfort.

STATISTICAL ANALYSIS

RESULTS

From Anesthesia charts' review conducted in the hospital for patients who used epinephrine in addition to lidocaine and bupivacaine, we found that the mean time to recover from the block (SEM) is 580 (10) minutes. Using Stata 13 statistical software, we found that we need a sample size of 25 patients in each group to prove equivalence of phenylephrine (either dose) to epinephrine. The study will have a power of 80% considering a p value of 0.05 or less to be significant. Time to event was used for statistical analysis, chi square for comparison of categorical data and ANOVA, or student T-test for numerical data where applicable. There were no significant demographic differences among the three study groups (Table1).

Table-1:

Age in years, mean (SEM)	49.2 (3.6)	54.2 (2.6)	50.1 (3.2)	0.6	ANOVA
Gender (M_F)	11_14	12_13	11_14	0.948	Chi Square
ASA (1_2)	11_14	8_17	6_19	0.32	Chi Square
Age in years, mean (SEM)	49.2 (3.6)	54.2 (2.6)	50.1 (3.2)	0.6	ANOVA
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Gender (M_F)	11_14	12_13	11_14	0.948	Chi Square
ASA (1_2)	11_14	8_17	6_19	0.32	Chi Square

All patients included in the study had a complete sensory and motor block throughout the surgery and through discharge from the PACU. All patients had adequate block for surgery; none required general anesthesia for failed block. None of the patients required admission to the hospital for overnight observation. The median time to onset of block was 2, 2 and3 minutes for arms 1, 2, and 3 respectively. The median time to recovery from the block was 600, 542, and 593 minutes for arms 1, 2, and 3 respectively (Table 2).

Table-2

	Arm 1	Arm 2	Arm 3	P value	Test used
Time to onset of block [median (Range)] in minutes	2 (1-27)	2 (1-8)	3 (1-15)	0.3836	Log-rank test
Time to recovery from the block [median (Range)] in minutes	600 (132-1024)	542 (119-1248)	593(187-1096)	0.9082	Log-rank test

The three groups did not differ significantly in terms of onset or duration of block. Changes in blood pressure and heart rate were recorded at five minute intervals over a period of 30 minutes from the onset of the block .Tables 3 and 4 represent the mean blood pressure and mean heart rate at every five minutes with standard error of mean. The results were also not clinically significant with $P > 0.05$ when comparing arms 2 and 3 with arm 1. The test used was Test used: ANOVA, with Bonferroni correction Figure 1 and figure 2 illustarte the changes in mean Blood Pressure and heart rate in all the three arms. Please note that the BP and the HR were measured every 5 minutes for 30 minutes (which is referred to as 1, 2 …etc.)

Table 3: Showing ANOVA

Mean BP for each arm (SEM)	**Arm 1**	**Arm 2**	**Arm 3**	**P value**
Mean BP Time 1 (after 5 minutes) (SEM)	90.125 (2.626)	91.106 (2.723)	90.093 (2.42)	0.9515
Mean BP Time 2 (after 10 minutes) (SEM)	89.055 (2.297)	88.586 (2.794)	88.267 (2.244)	0.9746
Mean BP Time 3 (after 15 minutes) (SEM)	86.777 (2.092)	87.92 (2.355)	88.346 (2.744)	0.8952
Mean BP Time 4 (after 20 minutes) (SEM)	85.777 (2.331)	88.933 (2.212)	87.426 (2.49)	0.6406
Mean BP Time 5 (after 25 minutes) (SEM)	85.861 (1.8)	89.013 (2.615)	88.053 (2.784)	0.6531
Mean BP Time 6 (after 30 minutes) (SEM)	85.277 (1.803)	87.8 (2.489)	92.613 (6.003)	0.4135
Mean BP Max (SEM)	94.18 (2.208)	95.36 (2.682)	98.293 (5.957)	0.4642
Mean BP Min (SEM)	81.833 (1.943)	83.44 (2.422)	83.28 (2.295)	0.4068

Table 4: Showing ANOVA

Mean HR for each arm (SEM)	**Arm 1**	**Arm 2**	**Arm 3**	**P value**
Mean HR Time 1 (after 5 minutes) (SEM)	71.9 (2.25)	72.6 (2.49)	70.72 (1.89)	0.8304
Mean HR Time 2 (after 10 minutes) (SEM)	71.38 (2.39)	73.32 (2.38)	69.96 (1.9)	0.5635
Mean HR Time 3 (after 15 minutes) (SEM)	71.17 (2.57)	73 (2.46)	69.72 (1.84)	0.6016
Mean HR Time 4 (after 20 minutes) (SEM)	71.63 (2.5)	74.28 (2.57)	70.36 (1.62)	0.4589
Mean HR Time 5 (after 25 minutes) (SEM)	73.5 (2.1)	73.44 (2.13)	71.4 (1.66)	0.693
Mean HR Time 6 (after 30 minutes) (SEM)	72.79 (2.33)	72.88 (1.88)	70.48(1.529)	0.6082
Mean HR Max (SEM)	76.75 (2.15)	77.4 (2.66)	73.84 (1.62)	0.4721
Mean HR Min (SEM)	67.88 (2.42)	69.56 (2.06)	66.56(1.712)	0.5899

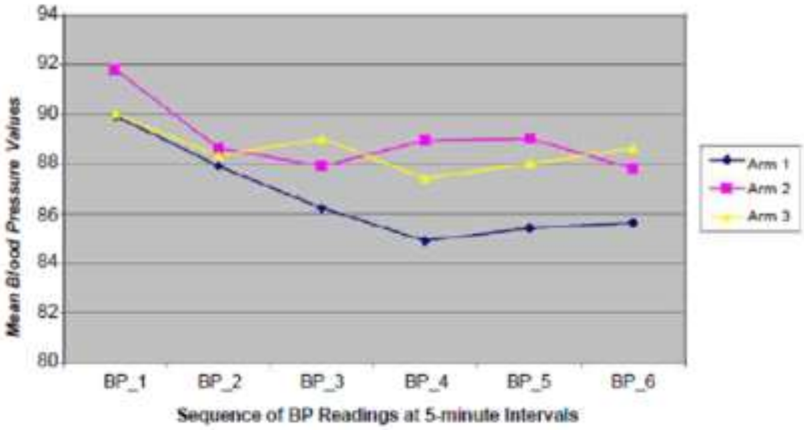

Fig-1: Showing the mean blood pressure within 30minutes

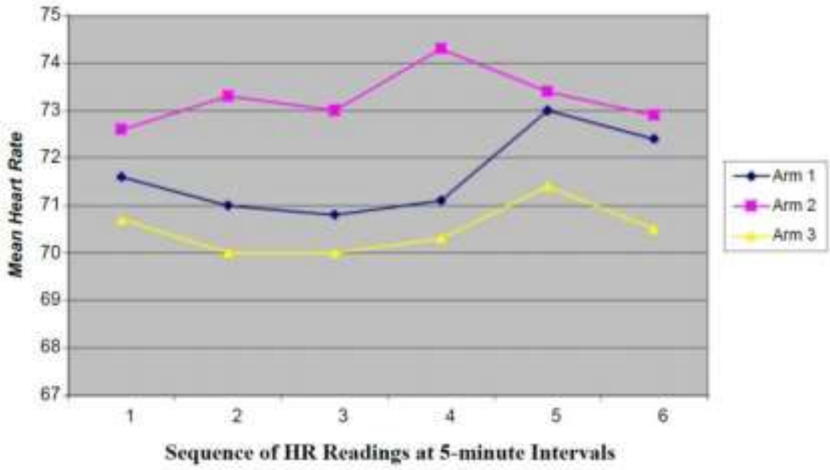

Fig-2: Showing the mean heart rates showing within 30minutes

Side Effects

None of the patients experienced short-term complications, such as intravascular injection, local anesthetic toxicity, or spinal block. There were no long-term complications reported by the surgeons.

DISCUSSION

Many anesthesiologists prefer regional blocks to general anesthesia as there are fewer systemic effects and the period of analgesia extends well beyond the intraoperative period, thus decreasing the need for analgesics. Sequentially administered local anesthetics with additives have been used with success in the past [5]. However, although there are studies which have investigated epinephrine and phenylephrine as additives to neuraxial anesthetics, no randomize d, double-blind investigations assessed the effects of epinephrine and phenylephrine in peripheral nerve blocks of upper extremity. One would presume that the pure alpha agonist of phenylephrine would be preferred to the mixed alpha and beta agonist of epinephrine in situations in which tachycardia would be detrimental. Our study demonstrated that the addition of phenylephrine vs. epinephrine to a local anesthetic solution for interscalene block did not produce statistically significant differences in duration or time to onset of an interscalene block. Epinephrine dose range is 2.5 – 10 mcg/ml. The dose selected for our study is 2.5 mcg/ml due to minimal compromise in nerve blood flow. Thus, while phenylephrine can be successfully used as an alternative to epinephrine in peripheral blocks of the upper extremity, there are no obvious advantages. Additionally, there are circumstances in which the anesthetic is injected in an area with greater vascularity. In these situations, such as an epidural injection, epinephrine also functions as an indicator of intravascular injection [6]. In this case, epinephrine would be superior to phenylephrine, so long as the transient effects of the epinephrine would not cause significant harm to the patient.

Study Limitations

The study was done in patients of ASA physical status 1 and 2 only. The difference between phenylephrine and epinephrine could not be fully evaluated in patients who are on chronic antihypertensive or beta blocker medications.

Also, the results may not be applicable in the more common neuraxial blocks. In assessing the time of onset of the nerve bloconly motor block was assessed; sensory block was not assessed. Assessing the duration of block by telephone in outpatients introduces the risk of error due to incorrect recollection.

CONCLUSION

The replacement of a conservative dose of epinephrine (i.e. 2.5 mcg/ml) with either 0.625 mcg/ml or 1.25 mcg/ml phenylephrine in local anesthetic solutions for upper extremity block gives equivalent onset and duration of block without adverse effects on heart rate and blood pressure

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