Comparison of efficacy of intrathecal preformed hyperbaric levobupivacaine and bupivacaine with buprenorphine in infraumbilical surgeries - A prospective, randomised, clinical study.

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Abstract

Introduction: Baricity determines the spread of local anaesthetic agent in the cerebrospinal fluid. Hyperbaric bupivacaine was widely used for sub-arachnoid blockade. Levobupivacaine is S-enantiomer of racemic bupivacaine. There are studies where isobaric levobupivacaine is converted to hyperbaric form by adding dextrose solution. Recently there is availability of preformed hyperbaric levobupivacaine with 8% glucose.

Aims and objectives: We have done this study with primary objective to compare the sensory and motor blockade characteristics of preformed hyperbaric levobupivacaine with hyperbaric bupivacaine, after subarachnoid block, among the patients posted for infraumblical surgeries. Secondary objective is to compare the haemodynamic stability and post-operative analgesia duration.

Methods and methodology: This is a prospective, randomized, controlled, double blinded clinical trial. 200 patients posted for infraumblical surgeries were randomly allocated in two groups. Group-B and Group-L received preformed HB and HB respectively with 0.2 ml buprenorphine. Sensory and motor blockade characteristics, analgesia duration and patients with hypotension were noted down.

Result: There was no statistical significant difference in the sensory and motor blockade characteristics between HB and HL like sensory onset time (HB-111.9± 49.75 s; HL-111.9± 49.75 s; P=0.789); motor onset time (HB-128.87± 78.13 s; HL 123.76± 87.83 s; P=0.664); maximum sensory level attained (HB-7.04± 1.59 and HL-7.16± 1.58; P=0.594); time taken for maximum sensory block (HB-365.6± 108.6 s; HL- 361.95±97.86 s; P=0.803) and maximum motor blockade (HB-451±133.7 s; HL-450.95± 121.86 s; P=0.997). Post-operative analgesia duration (HB-249.55±70.7 min; HL-270.7±92.9 min, P=0.072) and patients with hypotension were HB-19% and HL-17% was also not statistically significant (P=0.713).

Conclusion: Preformed HL with buprenorphine is also a safe and better choice for spinal anaesthesia in infraumblical surgeries like HB because of its similar sensory blockade, motor blockade and haemodynamic effects as with preformed HB with buprenorphine.

Keywords: Anaesthetics local, analgesia, bupivacaine, hypotension, levobupivacaine, subarachnoid space

Introduction

Baricity is a ratio obtained by density of two substances. Density is mass per unit volume of substance. With respect to the local anaesthetic (LA) agents, baricity is the relative density of LA solution when compared to cerebro spinal fluid (CSF) at temperature of 37^0C[1].

Baricity of LA agent indicates its spread in the CSF. Addition of glucose to the LA solution proportionately increases its baricity. Hyperbaric bupivacaine (HB) is widely used LA. Studies with both, bupivacaine and levobupivacaine shows the superiority of hyperbaric solution over isobaric form because the onset of sensory blockade and peak sensory blockade time were faster with hyperbaric solutions in association with predictable sensory block distribution [2,3,4].

Levobupivacaine is an amide LA which is S-enantiomer of racemic bupivacaine[5]. Recent studies have shown it to be more cardio and neuro protective compared

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to bupivacaine for SAB[5,6,7]. Earlier levobupivacaine was available as only isobaric solution. Studies to show the impact of hyperbaric levobupivacaine (HL) was done by converting isobaric levobupivacaine to hyperbaric by adding dextrose solution by the anaesthesiologist[4,7]. These preparations might not be accurate and can affect the aseptic precaution taken for SAB. Also their effectiveness was compared with preformed hyperbaric bupivacaine. Thus comparing hyperbaric LA solution prepared at two different environments (levobupivacaine prepared beside the operating table manually and bupivacaine prepared in laboratory using computerised system) can affect the outcome of study.

Recently there is availability of preformed HL. Both levobupivacaine and bupivacaine has dextrose concentration of 80mg dl^{-1} to increase its density compared to CSF and eventually the baricity[8].

In the present study, we compared, preformed HB with preformed HL for SAB with a larger sample size of 200 patients. We had a hypothesis that HB had better sensory and motor blockade characteristics compared to HL and HL maintained more haemodynamic stability compared to HB. There are limited studies with preformed HL.

Primary objective of the study is to compare the sensory and motor blockade characteristics between HB and HL. Secondary objective is to compare the haemodynamic stability and post-operative analgesia duration.

Material and Methods

This is a prospective, randomized; double blinded study, done among 200 patients posted for infraumblical surgeries at this tertiary hospital, between the periods from September 2022 to April 2023.

In Casati et al. study, where complete regression of spinal anesthesia was at 210 ± 63 min with HL and 190 ± 51 min with HB[8]. Considering alpha error <0.05 and power (1- beta) >0.85 we obtained a sample size of 88 in each group. Including the ten percent of dropouts from the study we approximated our sample size to 100 in each group.

Institutional ethical clearance was obtained [ECR/134/Inst/KA/2013/RR-13]. Informed consent was taken from the patients. This randomized, controlled, clinical trial reporting recommendations were according to Consolidated Standards of Reporting Trials (CONSORT). Randomization was via computer generated number sequence and allocation concealment was maintained with sealed opaque envelope distributed by an anaesthesiologist not involved with the further study

Two hundred (n=200) patients aged between 18 to 60 years; belonging to American Society of Anaesthesiologist (ASA) class I and II; posted for infraumblical surgeries were included in the study.

Exclusion criteria were pregnant patients, ASA grade more than II, signs of raised intracranial pressure, infection to back or history of allergy to study drugs. Fifty four patients were excluded based on these criteria from the study.

After routine pre-anaesthetic evaluation, on the previous night, patients were pre-medicated with tablet alprazolam 0.5mg and were kept fasting till next day morning. On the day of surgery, patient's vital parameters were recorded like pulse rate (PR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), oxygen saturation (SPO_2) and electrocardiogram (ECG). Monitoring was done using multi-parameter monitor. Intravenous (IV) crystalloid was started at 10ml/kg.

Patients were grouped into 2 groups: Group B: received intrathecal 0.5% HB (Anawin HeavyNeon Laboratories Limited, Palghar, Maharashtra, India) 3ml with buprenorphine 0.2ml and Group L: received intrathecal preformed 0.5% HL (LevoAnawin Heavy Neon Laboratories Limited, Palghar, Maharashtra, India) 3 ml with buprenorphine 0.2ml. The study drug was loaded by an anaesthesiologist not involved with randomization. Another blinded anaesthesiologist blinded about the study drug gave SAB in sitting position under aseptic precautions between lumbar L3-L4 interspace, midline approach, using 25 gauge Quincke spinal needle (Becton, Dickinson, Madrid, Spain) after local infiltration of 2% lignocaine. Study drug was injected after obtaining free and clear flow of CSF, at the rate 0.1ml/sec This point of time was taken as 'starting time'. Patients were made to lie supine immediately. Study parameters were then recorded.

Sensory was assessed with the loss of pin prick sensation with 20-gauge hypodermic needle, whereas motor blockade was evaluated using a modified Bromage scale (MBS) (0 -no motor block; 1 -hip blocked; 2- hip and knee blocked; 3- hip, knee and ankle blocked). Sensory and motor blockade were assessed once in every 5- 10 seconds. Time of sensory and motor onset was from 'starting time' to sensory blockade level of first lumbar dermatome (L1) and MBS of 1 respectively. Maximum sensory and motor blockade was from 'starting time' to maximum sensory blockade and MBS of 3 respectively.

Pain intensity was assessed with visual analogue score (VAS) intraoperatively and postoperatively once in every two hours. VAS had 10 markings on a paper strip. Left extreme had '0' marking with no pain and

right extreme had '10' marking with worst pain. IV diclofenac 75mg was given as rescue analgesic if VAS was more than 3. Time duration from 'starting time' to rescue analgesia was considered as post-operative analgesia duration.

Fall in SBP more than 30% from basaline value was considered as hypotension and treated with 300 ml crystalloid rush and if still uncontrolled, IV ephedrine 6mg bolus was given and repeated. Total number of ephedrine doses given and total number of patients developed hypotension in both the groups was noted down. Bradycardia was considered if heart rate falls less than 60 beats per minute which was treated with 0.01mg/kg of atropine.

Statistical analysis was done by using statistical package for social sciences (SPSS) software version 20 (SPSS Inc, Chicago, IL). Quantitative data like most of the demographics, sensory and motor characteristics were expressed as mean and standard deviation. Comparison was done using independent sample-t test. Categorical data like ASA grade, sex, type of surgery, number of patients developing intra-operative hypotension and number of doses of ephedrine needed were expressed as frequency and percentage. For this Fisher's test and Chi-square test were used to compare.

Result:

Table-1: Demographic and baseline vitals characteristics along with type of surgery in both the groups

Sl. no	Parameters		Group- B	Group-L	Test	**p
1.	Age (mean ± *SD)		42.47±13.85	40.8±13.06	Sample-t test	0.382
2.	Sex	Males (%)	77 (77%)	74 (74%)	Fisher's test	0.743
		Females (%)	23 (23%)	26 (26%)		
3.	ASA grade	I (%)	49(49%)	41 (41%)	Fisher's test	0.256
		II (%)	51 (51%)	59 (59%)		
4.	Body mass index (mean ± SD)		26.14±4.47	26.31±4.1	Sample-t test	0.239
5.	Type of surgery	Lower abdomen (%)	53 (53%)	43 (43%)	Chi-square test	0.367
		Lower limb (%)	43 (43%)	52 (52%)		
		Scrotal (%)	4 (4%)	5 (5%)		
6.	Baseline pulse rate (mean ± SD)		85.64±20.05	82.81±18.06	Sample-t test	0.296
7.	Baseline mean arterial pressure (mean ± SD)		97.58±15.73	98.76±12.23	Sample-t test	0.554

*SD-standard deviation

**p < 0.05- significant and < 0.005- very significant

Both the groups were comparable with respect to demographic characteristics like age, sex, ASA grade, BMI, type of surgery (table-1).

Table-2: Sensory and motor blockade characteristics; post-operative analgesia; patients with hypotension and doses of vasopressors in both groups.

Sl.no	Characteristics	Group-B	Group-L	Test	**p
1.	Sensory onset time-L1 (seconds) (mean ±* SD)	111.9± 49.75	114.43± 80.37	Sample-t test	0.789
2.	Motor onset time (seconds) (mean ± SD)	128.87± 78.13	123.76± 87.83	Sample-t test	0.664
3.	Maximum sensory level(mean ± SD)	7.04± 1.59	7.16± 1.58	Sample-t test	0.594
4.	Time to attend maximum sensory level (seconds) (mean ± SD)	365.6± 108.6	361.95±97.86	Sample-t test	0.803
5.	Time to attend maximum motor level (seconds) (mean ± SD)	451±133.7	450.95± 121.86	Sample-t test	0.997
6.	Postoperative analgesia duration (minutes) (mean ± SD)	249.55±70.7	270.7±92.9	Sample-t test	0.072
7.	Number of patients with hypotension (%)	19 (19%)	17 (17%)	Chi- square test	0.713
8.	Total number of doses of ephedrine given	81 (81%)	83 (83%)	Chi-square test	0.765
	0				
	1	7 (7%)	8 (8%)		
	2	9 (9%)	8 (8%)		
	3	3 (3%)	1 (1%)		

*SD- standard deviation

**p < 0.05- significant and < 0.005- very significant

There was no statistical significant difference in the onset time of sensory blockade or onset time of motor blockade between HB and HL. With both our study drug onset of sensory blockade was faster than motor blockade. (table-2).

Maximum sensory level attended was also not statistically significant with both the groups as the mean of sensory level attended was nearing seventh thoracic segment. Mean sensory blockade level was 7.04± 1.59 and 7.16± 1.58 with HB and HL respectively (table-2).

Even there was no statistical significant difference between the time to attend maximum sensory and motor blockade or in postoperative analgesia period with both the study drugs (table-2).

lthough more number of patients with HB developed intraoperative hypotension after SAB and needed increased frequency of ephedrine doses, this difference was not statistically significant when compared to HL (table-2).

Discussion:

There are factors causing changes in density of CSF and LA solution. CSF component is similar to any interstitial fluid which is isotonic. CSF density ranges between 1.0000 to 1.0006 g.litre^{-1} at 37^{0}C [9]. According to Anne et al. study, mean CSF density was 1.00059 ± 0.00020 g.ml^{-1} with 95% confidence limits upper and lower as 1.00019 and 1.00099 respectively[10]. Pregnant women have lower CSF density compared to men and non-pregnant women[9]. Most of these changes in density are minor, which is well noticed at the fourth numerical place after decimal.

Theoretically, hypobaric solutions have density lower than the upper confidence limits of CSF density whereas hyperbaric solutions have density higher than the lower confidence limits of CSF density[10]. Approximately LA with baricities below 0.9990 or above 1.0010 is considered as hypobaric and hyperbaric respectively.

Earlier there was availability of only bupivacaine as hyperbaric. Levobupivacaine and ropivacaine were available as isobaric solutions. But in recent days, preformed 0.5% HL is available. We have analysed its effects during SAB.

In our study sensory and motor blockade characteristics like sensory and motor onset; peak sensory level and time to attend maximum sensory and motor blockade, were similar with preformed 0.5% 3 ml HB and HL, both with 0.2 ml buprenorphine.

We added 0.2ml (60µg) buprenorphine as adjuvant to our study drug which perhaps has negligible effect on baricity of study drug combination based on Jasinski et al.study. Jasinski et al. in their study assessed the density of various LA and opioid combinations. Their study showed that, combining LA with opioid reduced density, but the reduction was not to an extent of converting LA from hyperbaric to isobaric [11].

As there were no earlier studies with preformed 0.5% HL in literature, we compared the results obtained in our study with the isobaric levobupivacaine converted to hyperbaric using dextrose and saline in the operation theatre by the anaesthesiologist just before SAB.

Different formulations were used in different studies to prepare the HL using isobaric levobupivacaine and various concentrations of dextrose solution. 2.7 ml of 0.75% isobaric levobupivacaine with 1 ml of 33% dextrose (330 mg.ml^{-1} glucose) with 0.3 ml of normal saline gives total volume of 4 ml solution with 0.5% HL having 82.5 grams per ml of glucose is one such kind of preparation[7]. In another study 0.48 ml of 50% dextrose (240 mg glucose) was mixed with 2.52 ml (12.6 mg) of 0.5% isobaric levobupivacaine to give total 3 ml of 0.42% HL with 80 mg.ml^{-1} glucose concentration[4].

HB and HL efficacy were assessed by Alley et al. in their crossover study among 18 healthy volunteers. 24 hours was the interval between either of the study drugs for SAB[12]. Besides conventional methods like pinprick and MBS, some advanced methods were also used for blockade evaluation. Transcutaneous electric stimulation, thigh tourniquet tolerance were used for sensory blockade and electromyography at abdomen and isometric force dynamometry at quadriceps were used for motor blockade assessment. With all these modalities, they inferred that HB and HL had equivalent clinical efficacy, which is coherent to our study[12].

Casati et al. compared unilateral SAB with 0.5% HB and HL for inguinal herniorrhaphy among 60 patients using very low dose of 8 mg. Here onset of sensory blockade and maximum sensory blockade attained with both the drugs were similar without any statistical significance[8]. These observations in their study are consistent with our study results, but sensory onset time was highly prolonged in Casati et al. with both HB and HL compared to our study[8]. This can be because of lower dose of both the study drugs and unilateral position maintained after SAB.

Luck et al. in their study among 60 patients concluded that SAB characteristics like sensory blockade onset at T10, maximum sensory level and the time to attain it via HB and HL were indistinguishable[13]. This result matches to our study findings and can thoroughly be extrapolated to our study results as the subjects

(patients posted for infraumblical surgeries) were similar. But compared to Luck et al. our sensory onset time was shorter with both study drugs as we considered the onset time for sensory blockade, when L1 dermatome was blocked rather than T10 in their study [13].

Haken et al. compared lower dose HB with HL among 60 patients posted for urological surgeries[14]. In their study, motor blockade attained was statistical significantly lower MBS and of shorter duration with HL compared to HB. This is contradictory result compared to our study. This might be associated with the lower dose of drug (7.5mg) and lower glucose concentration (around 6%) which they used unlike around 8% which we used[14]. In their study, HB and HL solutions had 120mg of glucose diluted to 2ml resulting 60 $mg.ml^{-1}$ concentration (6% glucose). This change in glucose concentration can alter the baricity and spread of the LA. Also, as we got the result from a larger sample size of 200 subjects; it can be of more considerable.

In Thakore et al. study, among 90 patients posted for medical termination of pregnancy with SAB, there was statistical significantly slower sensory and motor blockade onset and lower sensory level attained with HL than HB[15]. This variation in finding compared to our study result could be because of difference in composition of both the study drugs in their study. In Thakore et al. study, to make HL solution, 1 ml of 5% dextrose was diluted to 3ml whereas HB solution was made using 1.5 ml of HB with 8% glucose diluted to 3 ml. Hence there was lower glucose concentration in HL compared to HB which alters its baricity and eventual spread in CSF[15]. In our study, glucose concentration was kept constant as we used preformed hyperbaric solution of both study drugs with 8% glucose diluted up to 3.2 ml with 0.2 ml buprenorphine.

According to McLeod's study, at 37^0C, density of 0.5% HB is 1.02424 ±0.00163 and 0.5% HL is 1.02487 ± 0.00348 with $80mg.ml^{-1}$ of glucose[16]. LA density increases with drug concentration. Also its baricity increases linearly as there is increase in glucose concentration. As the temperature of LA decreases, there is increase in its density[9]. Thus baricity of LA varies with the temperature. We did not measure the density of our study drugs and assumed it to be coherent with the McLeod study. Increase in baricity of LA agents makes it to act differently in CSF leading to more settling of drugs in CSF due to gravitational effect according to the position of the patients[17]. Thus controlled level of sensory and autonomic blockade attained perhaps for longer duration with hyperbaric solutions, unlike with isobaric solutions. With isobaric solutions, level of blockade attained is not influenced by gravity and hence drug gets distributed at the same level where injected or it may rise up, against the gravity in case of hypobaric solutions[16].

Difference in duration of post-operative analgesia was not significant in our study. Many studies comparing HB and HL emphasised on complete sensory regression time rather than post-operative analgesia. We stressed more on post-operative analgesia duration because, up to this period there would be blockade of pain signals carrying, sensory fibres. This is utmost crucial to be known in post-surgical patients to supplement analgesia and prevent various systemic adverse effects of pain[18]. Complete sensory regression implies the sparing of all variety of sensory fibres; carrying touch, pressure and pain signals. Complete sensory regression up to T10 level was also similar with both the study drugs in Luck et al. study.

Though levobupivacaine is known to be cardio-protective, it causes hypotension after SAB which can be easily managed. In our study, there were equal tendencies of hypotension to be caused by both the study drugs. Similar study results were reported with Casati et al. and Luck et al. in their studies. In Glaser et al. study, even with isobaric solution of bupivacaine and levobupivacaine, there were no difference in patients with hypotension in both the groups[19]. Two patients in each group had bradycardia which was managed with atropine in our study.

There were some limitations in our study. We did not assess the post- operative ambulatory time or voiding time in the patients, which was essential to know the impact on duration of motor blockade by LA. This is because patients operated for fractured lower limb were immobilised with the splint or pre-operatively catheterised. More studies are needed to know the ambulatory time with preformed 0.5% HL. We didn't compare the complete sensory regression time as we wanted to restrict our study parameters and concentrate on post-operative analgesia duration for the reasons already stated above. We could not measure the density of the study drugs due to limited resources. Measuring of density would have shown the exact density of our study drugs. But we referred to the Mc Leod et al. study for the reference value of the density of study drugs[16].

Conclusion

Preformed 0.5% HL with 8% glucose combined with 0.2 ml buprenorphine is similar to preformed 0.5% HB with 8% glucose combined with 0.2 ml buprenorphine for SAB in infraumblical surgeries as both these drugs has identical sensory and motor blockade characteristics and similar duration of post- operative analgesia. Both HL and HB can produce hypotension; which is

easily manageable with fluids and vasopressors. More studies are needed with individual varieties of surgeries and larger sample size to know about its effect

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