Review Article

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Comparative Analysis of Bupivacaine and Ropivacaine during Epidural Analgesia

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Abstract

IASP defines pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of the actual damage." This definition embraces various concepts especially the subjectivity of the symptoms which is the basis of the non-pharmacologicaloptions in the treatment of labour pain. We conducted this study to compare the efficacy of the equipotent 0.125% Bupivacaine and 0.2% Ropivacaine in labour.

Keywords: Bupivacaine; Ropivacaine.

Introduction

Bupivacaine has been the widely used local anaesthetic drug for Labour epidural analgesia but Albright in 1979 published an alarming editorial which associated bupivacaine with cardiac arrest. The search for a long acting local anaesthetic devoid of cardio toxicity led to the synthesis of Ropivacaine a new amino amide local anaesthetic which has been shown to cause less intense motor blockade and less cardiotoxic and is rapidly evolving as local anaesthetic of choice in labour Analgesia.

Review of Literature

Evron S, Glezerman et al studied a prospective Randomised double blind study comparing low doses of Bupivacaine & Ropivacaine concluded that Ropivacaine 0.2% was equialgesic with 0.125% Bupivacaine & produced less motor block (P<0.001) without any difference in duration of labour, deliver type or neonatal outcome.Fernandez C Et al study compared the efficiency and extent of motor block with 0.2% Ropivacaine and Bupivacaine 0.125% on 60 women in labour and concluded that both the drugs are equally effective for pain control. Motor block was seen in 8 patients with Bupivacaine and 1with Ropivacaine (P<0.05). Ropivacaine reduced motor block and offers an advantage in situations when walking Epidural is desired.

W.D.R Writer et al showed a prospective meta analysis using 0.25% Bupivacaine & Ropivacaine and concluded that Spontaneous Vaginal delivery occurred more frequently with Ropivacaine than with Bupivacaine (58% vs. 49% P<0.05) & fever infants with NACS (Neurological and Adaptive Capacity Scores) less than 35 in Ropivacaine compared with Bupivacaine group (2.8% vs. 7.6% P<0.05). P.D.W Fettes Et study concluded that the intermittent group required fewer supplementary injections and less drug to maintain similar pain scores, Sensory and motor block compared with continuous group. Hence concluded that intermittent topups remain a more efficacious mode of analgesia.

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Stephen H. Halpem et al study a Meta analytical study in 2074 patients and concluded that there is no statistically significant difference between the two drugs in the incidence of any obstetrical or neonatal outcome.Bee Beng Lee et al Study a prospective Randomised double blind study examining the effectiveness of five different doses of Ropivacaine (10, 20, 30, 40 & 50 mg) in labour analgesia and concluded that in a traditional dose–response study, the ED50 of Ropivacaine required to initiate epidural analgesia in early labour was 18.4 mg (95% confidence Interval 13.4–25.4 mg). J.M Porter Et al study on Epidural Ropivacaine during labour and its protein binding, placental transfer and neonatal outcome. They concluded that there was no significant Correlation between Maternal unbound Ropivacaine concentration and neonatal (cord) Ropivacaine concentration and no association between mean (SD) Umbilical venous Ropivacaine concentration and NACS of the neonates.Nicola S Wallace Retrospective study of 100 random post natal women who had received labour analgesia 98% of those who had received epidural analgesia said they would request this in subsequent labours, compared with 76% of those who had used Entanox only and 66% of those who had received Pethidine.

They conclude that: Most women in labour wants epidural analgesia, Friends are more influential requesting Labour analgesia than prenatal classes, Anaesthesiologist should be flexible in the mode of Labour Analgesia, Maternal satisfaction with Epidural analgesia in labour means that anaesthesiology work load in labour ward will increase. Halpem S H et al this study was conducted to know the effect of labour analgesia on breast feeding success. It was concluded that Epidural labour analgesia with local anaesthetics and opioids does not impede breast feeding success. Beilin Y Anesth Analg the study concluded that, Epidural Bupivacaine is equally as safe as, of equal or less toxicity than and significantly more potent and more economical than Epidural Ropivacaine. They say that newer does not mean better. N. Fratelli et al, The study evaluated the effects of Epidural analgesic with bolus doses on Uterine artery Pulsatality index (UtA-p1) during labour and concluded Epidural Analgesia using Ropivacaine 1mg/ml (20 ml)significantly reduced placental blood flow only transiently during uterine contraction 30 minutes after the injection. These changes did not seem to affect neonatal outcomes. D. Benhamou et al, The study concluded that Ropivacaine 2mg/ml was effective and well tolerated when given as a continuous extradural infusion at 6-8 ml/hr and may be used as the sole analgesic during labour. Linda S. Polley et al, Analgesic potencies of Ropivacaine and bupivacaine for epidural analgesis, The minimum local analgesic concentration of Ropivacaine was 0.111% wt/vol, and the minimum local analgesic concentration of bupivacaine was 0.067% wt/vol. They concluded that Ropivacaine was significantly less potent than bupivacaine, with a potency ratio of 0.6(95% confidence interval, 0.49-0.74), for epidural analgesia in the first stage of labour.

Ropivacaine may be less cardiotoxic than bupivacaine yet bupivacaine induced cardiac arrest is an exceedingly rare event especially in the labouring patient or in clinical settings utilising dilute concentrations used to produce analgesia. The benefits of Ropivacaine are theoretical at best but they are not worth their cost. Michael P. Nageotte et al, study concluded that as compared with lumbar epidural analgesia, the combination of spinal and epidural analgesia is not associated with an overall decrease in the incidence of caesarean delivery. G. Capogna et al. Relative potencies of bupivacaine and Ropivacaine for analgesia in labour, The analgesic potency of Ropivacaine was 0.60 relative to bupivacaine. Claims for reduced toxicity and motor block must be considered with differences in analgesic potency in mind. D. Bruce Scott et al,The acute CNS and CVS effects of Ropivacaine and bupivacaine were compared in 12 human volunteers in a randomised double blind manner with IV infusions at a rate of 10mg/min up to a maximal dose of 150 mg. They concluded that Ropivacaine is a less toxic compound than bupivacaine, but their relative therapeutic ratios must await the results of clinical trials in humans to assess the potency of Ropivacaine compared with that of bupivacaine.

Pharmacology of Bupivacaine

Bupivacaine hydrochloride is a long-acting local anaesthetic of the amide type. It is an amide linked local anaesthetic synthesized by B.A.F Ekenstam in 1957 and introduced into clinical practice by Talivuo in 1963. Bupivacaine HCl which is chemically designated as 2-piperidinecarboxamide, 1-butyl-N-(2,6-dimethylphenyl)-monohydrochloride, monohydrate.

Bupivacaine occurs as a 50:50 racemic mixture of the R- and S-enantiomers and is commercially available as bupivacaine and levobupivacaine, the S-enantiomer of bupivacaine.

Bupivacaine hydrochloride is a local anaesthetic of the amide type with a long duration of action. Bupivacaine hydrochloride differs structurally from

mepivacaine hydrochloride only in the substitution of a butyl group for the Methyl group. Bupivacaine hydrochloride occurs as a white, odourless, crystalline powder and is freely soluble in water and in alcohol. The pKa of bupivacaine hydrochloride is 8.1

Mechanism of Action

The base form is in equilibrium with cationic form outside the axoplasmic membrane. Base form diffuses inside the cell and recalibrates with cationic form. It then reaches the local anaesthetic receptor in the Na channel by reversing channel pore while it is in an open state. It prevents Na ions moving intracellularly. In addition to this simple sodium channel blockade, it also affects second messenger system such as adenylatecyclase and guanylatecyclase and also inhibits synaptic transmission by modification of post synaptic receptor (or) presynaptic calcium channel blockade in epidural / subarachnoid blockade.

Physiochemical Properties

Property Value

- Molecular weight 288
- Potency ratio 15
- Toxicity ratio 10
- pKa (25.C) 8.16

Protein Binding in %

- Maternal 95
- Fetal 66

% Non Ionizedat

- pH 7.4 – 17, pH 7.2 - 11

Partition Co-efficient

- (25.C, pH7.4) 346, Anaesthetic index 3.0-4.0

Pharmacokinetics of Epidural Bupivacaine

The uptake of local anaesthetic into blood vessels in the area where it has been deposited and its subsequent transfer into systemic circulation is referred to as systemic absorption. A biphasic absorption pattern has been found for epidural bupivacaine. The rapid initial absorption following epidural administration is most likely related to high concentration gradient between the drug in the solution and in the blood. In addition profound increases in epidural blood flow observed during epidural administration of bupivacaine may contribute to its fast initial absorption rate. Later on, after the local anaesthetic has been taken up into local tissues such as epidural fat, absorption will become dependent on tissue blood partitioning, resulting in marked slowing of absorption. Estimated total fraction of the dose ultimately absorbed into general circulation is 0.94 with mean absorption time 8.6 hours.Absorption of local anaesthetic is directly related to the amount of drug injected, vascularity, site injected and tissue binding of local anaesthetic at injection site. Bupivacaine will produce lower Cmax than less potent and less lipid soluble agents.Distribution of local anaesthetic has special emphasis in the pregnant patient, because one of the organs that will be exposed to the absorbed drug is fetoplacental unit.

Adverse Effect and Complications

Central Nervous System Toxicity

Potentially toxic blood level can occur when a drug is injected intravenously, intra arterially or a large dose of drug is given into highly vascular area. Risk of CNS toxicity is more because bupivacaine is a highly protein bound drug. Pregnancy is associated with 30% reduction in protein binding. This allows for higher brain level of bupivacaine for a given dose of drug.

Symptoms

Slow speech, jerky movements, tremors, hallucination, and seizure.

Cardiovascular Toxicity

1. Dose dependant depression of contractility
2. Dose dependent depression of conduction and velocity in all conducting tissues.

Progressive Prolongation of Ventricular Conduction

3. Predisposition to re-entry phenomenon followed by sudden onset of ventricular fibrillation.
4. More affinity for cardiolipin

Toxic plasma concentration is 4-5μg/ml

Ropivacaine

Ropivacaine is a new aminoamide local anaesthetic. It is the monohydrate of the hydrochloride salt of 1-propyl-2',6'- pipecoloxylidide

and is prepared as a pure S enantiomer. Pipecoloxylidides were first synthesized in 1957 and have been in clinical use for more than 30 years. Ropivacaine has a propyl group on the piperidine nitrogen atom of the molecule. The pipecoloxylidides are chiral drugs because the molecules possess as asymmetric carbon atom and they may have left - (Sinister) or a right (rectus) handed configuration.

Ropivacaine is produced as the single "S" enantiomer. It has an enantiomeric purity of 99.5% and is prepared by alkylation of `S' enantiomer of dibenzoyl - L – tartaric acid.

The Physiochemical Properties of Ropivacaine are as Follows

1. Molecular weight (base) : 274
2. pKa: 8.1
3. Partition coefficient (N Heptane/ buffer):2.9
4. Mean uptake ratio (rat sciatic nerve): 1.8
5. Protein binding %: 94

The relative lipid solubility of Ropivacaine as measured by partitioning studies between N-heptane buffer and relative mean uptake into rat sciatic nerves, shows Ropivacaine to be intermediate between bupivacaine and lignocaine. Plasma–protein binding is marginally less than that of bupivacaine but the pKa is identical.

Onset: Moderate

Relative Potency: 6

Duration: Long acting

Ropivacaine blocks the generation and the conduction of nerve impulses, presumably by increasing the threshold for electrical excitation in the nerve, by slowing the propagation of the nerve impulse, and by reducing the rate of rise of action potential. The progression of anaesthesia is related to the diameter, myelination and conduction velocity of affected nerve fibres. is reached in regard to unbound concentration.

Metabolism

Ropivacaine is extensively metabolised in the liver, predominantly by aromatic hydroxylation mediated by cytochrome P4501A to 3- hydroxy Ropivacaine. Approximately 37% of the total dose is excreted in the urine as both free and conjugated 3-hydroxy Ropivacaine. Low concentrations of 3-hydroxyRopivacaine have been found in the plasma. Urinary excretion of the 4-hydroxy and both the 3-hydroxy and 4-hydroxy Ndealkylated metabolites accounts for less than 3% of the dose. An additional metabolite, 2-hydroxy methyl Ropivacaine has been identified but not quantified in the urine. Both 3-hydroxy and 4-hydroxy Ropivacaine have a local anaesthetic activity in animal models less than that of Ropivacaine. There is no evidence of in vivo racemization in urine of S (-) Ropivacaine to R (+) Ropivacaine.

Elimination

The kidney is the main excretory organ for most local anaesthetic metabolites. In total, 86% of the Ropivacaine dose is excreted in the urine after intravenous administration of which only 1% relates to unchanged drug. Ropivacaine has a mean total plasma clearance of 387±107 ml/min. The mean ±SD terminal half life is 1.8 ±0.7h after intravascular administration and 4.2±1.0h after epidural administration.

In-Vivo Studies

The effect of local anaesthetics on the electrophysiology of the heart has been defined. The maximal rate of increase in the cardiac action potential (Vmax) is largely dependent on sodium ion influx via the sodium channels. All local anaesthetics are known to depress Vmax in a dose dependent manner. Ropivacaine is intermediate between lignocaine and bupivacaine in decreasing Vmax. Exogenous progesterone has no additional effect on depression of Vmax.

Ropivacaine administered by the intravenous route was found to be less toxic than bupivacaine Mild CNS symptoms and minor cardiovascular toxicity occur at lower dosage and lower plasma concentrations with bupivacaine compared with Ropivacaine. Two human volunteer studies of lumbar extradural block using 0.1%, 0.2%, or 0.3% of Ropivacaine 10ml or 0.25% Bupivacaine 10ml followed by continuous infusion of 10ml/hr of the same drug for 21 hours showed a similar spread of sensory block, reduced intensity of motor block and quick recovery which offers a distinct advantage in the clinical setting during extradural analgesia for labour or post-operative pain.

Adverse Reactions

A major cause of adverse reactions may due to excessive plasma levels which may be due to over dosage, unintentional intravascular injection or slow metabolic degradation. Most adverse events reported were mild and transient.

Central Nervous System Reactions

These are characterized by excitation and/or depression. Restlessness, anxiety, dizziness, tinnitus, blurred vision or tremors may occur, possibly proceeding to convulsions. However, excitement may be transient or absent with depression being the first manifestation. This may quickly be followed by drowsiness, unconsciousness and respiratory arrest. Other effects may be nausea, vomiting, chills and constriction of pupils.

Cardiovascular System Reactions

High doses of accidental intravascular injection may lead to high plasma levels and related depression of myocardium, decreased cardiac output, heart block, and hypertension, bradycardia ventricular arrhythmias including ventricular tachycardia and ventricular fibrillation and possibly cardiac arrest.

Results

Data were analysed using SPSS 15 software. Descriptive analysis for nonparametric variables was expressed in *proportion* and parametric variables in *mean* and *standard deviation*. The treatment difference was assessed using *ttest*for independent samples for parametric variables and by *Chi square test* for non-parametric variables. Statistical significance was assessed using p at 0.05 cut off or 95% confidence interval. (95% CI).

The total duration of labour in both groups were comparable. The duration of first, second and third stage of labour were also comparable. Student T-test was done on duration on total and each stage of labour. The P-values were all >0.05 implying that differences were not statistically significant.

Table 1: Time for Onset of Analgesia

A - Group(Mean ± S.D)	B –Group(Mean ± S.D)	P - Value
11.9	11	0.406

A - Group		B -Group	
Minimum	Maximum	Minimum	Maximum
15	8	13	8

The time for onset of analgesia shows no statistical significance.p> 0.05

Table 2: No. of Rescue Boluses

A - Group(Mean ± S.D)	B – Group(Mean ± S.D)	P - Value
0.27± 0.521	0.40 ± 0.675	0.395

A - Group		B - Group	
Minimum	Maximum	Minimum	Maximum
0	2	0	2

The number of rescue boluses required showed no statistical significance in the t test.

Table 3: Maximum Sensory Level Achieved

A - Group(Mean ± S.D)	B – Group (Mean ± S.D)	P - Value
9.20± 0.761	9.03 ± 0.765	0.401

A - Group		B - Group	
Minimum	Maximum	Minimum	Maximum
8	10	8	10

The minimum and maximum sensory levels achieved in both Group A and Group B were T8 and T10 respectively and showed no statistical significance in the t test.

Table 4: Duration of Labour

Stage of Labour	A - Group		B - Group		P - Value
	Mean (Mins)	SD	Mean (Mins)	SD	
First Stage	314.20	71.604	302.13	50.469	0.454
Second Stage	63.07	8.242	65.13	8.283	0.337
Third Stage	6.93	2.318	7.37	2.076	0.449
Total	384.20	69.906	374.47	49.624	0.537

Stage of Labour	A - Group		B - Group	
	Minimum	Maximum	Minimum	Maximum
First Stage	185	480	200	365
Second Stage	50	79	50	89
Third Stage	3	12	3	11
Total	245	540	261	430

Conclusion

Bupivacaine has stood the test of time as bedrock of labour analgesia because of its longer duration of action and lesser degree of motor block for a comparable degree of sensory analgesia. The newer local anaesthetic Ropivacaine has advantages over Bupivacaine because of its motor-sparing properties and its lower systemic toxicity. Ropivacaine is a local anaesthetic with lower cardiotoxic potential [1,2,3,4,6] and higher threshold for neurtoxicological symptoms [4,5,6] than racemic bupivacaine. Themajority of published data on ropivacaine are on its use in the epidural space [8,9]. In the context of above mentioned developments we have undertaken a study to compare 0. 20% Ropivacaine with 0.125% Bupivacaine without any additives for epidural labour analgesia.

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