

Novel Approaches in Regional Anesthesia & Pain Management

Chapter 3

Recent Advances in Labour Analgesia

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Abstract

Labour pain analgesia is ever evolving since its inception by etherisation of labour. Adverse effects of labour pain on both mother and foetus remain a major concern for care providers. Childbirth is associated with intense, excruciating pain and to overcome this unpleasant experience many strategies both pharmacological and non-pharmacological have been extensively researched and utilized. Non-pharmacological methods provide psychological support to cope with painful situations rather than mitigating the pain completely. Recent trends in labour pain relief includes use of remifentanyl IV-PCA, Nitronox, low concentration of local anaesthetics, use of levobupivacaine and ropivacaine along with adjuvants like clonidine, dexmedetomidine, neostigmine, dexamethasone. Technical advances such as computer integrated patient controlled epidural analgesia, programmed intermittent or automated mandatory epidural boluses and ultrasound guided neuraxial technique are other innovations. Skilled and supportive care during labour along with properly timed and framed, communication and information during the peripartum period can mitigate the unmet expectations of the labouring parturients, thus avoiding maternal dissatisfaction.

Keywords: Labour analgesia; Epidural, Ultrasonography; Neuraxial techniques; Computer integrated patient controlled labour analgesia; Programmed intermittent bolus.

I. Introduction

Attitude towards pain relief in labour depends on personal aspiration, prevailing cultural factors, religious beliefs and peer group influences. A wide repertoire of labour analgesia modalities both pharmacological and non-pharmacological, are being practised around the globe to provide pain free labour experience to humanize the process of childbirth. Epidural analgesia is irrefutably the most effective technique of labour analgesia which is widely accepted as a gold standard [1]. Several improvisations have been done over the last few decades to enhance safety, efficacy and acceptability of neuraxial labour analgesia [2]. Majority of women in developing countries go through this excruciating pain despite the availability of painless labour facilities. Communication gap between care provider and patients during antenatal visit is the main reason behind this wide gap. Information regarding various modalities of labour analgesia during these visits empowers the patient to make a well informed choice resulting in considerable improvement in maternal and perinatal outcomes. This chapter focuses on some of the newer modalities of labour analgesia, with a passing reference to the established practices.

2. Pain Pathways [3,4]: (Figure 1A & 1B)

First stage of labour: Pain in first stage of labour is mainly visceral, diffuse, poorly localized due to dilation of cervix, distention of lower uterine segments and uterine contractions; mediated by slow conducting unmyelinated C fibres traversing in T10, T11, T12, and L1 spinal nerves.

Second stage of labour: Pain during late first and second stage of labour incorporates both visceral (T12-L1) and somatic components arising from uterine contractions, cervical stretching, stretching of vagina, pelvic ligaments and pelvic floor. Rapidly conducting myelinated A δ fibres carry impulses via S2-S4 sacral nerves (pudendal nerves). Perineal branches of posterior cutaneous nerve of thigh, somatic fibres from the cutaneous branches of the ilioinguinal and genitofemoral nerves also carry afferent fibres to L1-L2.

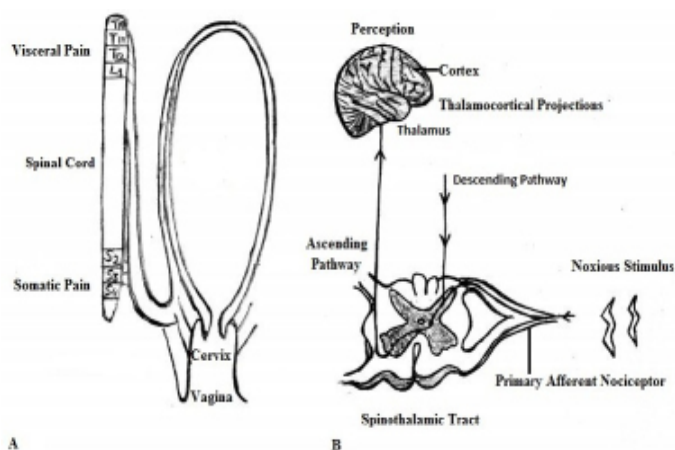


Figure 1: Labour Pain Pathway A) Visceral & somatic B) Supraspinal

3. Management of Labour Pain:

It includes both non-pharmacological and pharmacological methods of labour pain relief.

3.1. Non-pharmacological methods:

Non-pharmacological approaches enable those parturients to cope with labour pain who opt for unmedicated childbirth. These non-pharmacological techniques work by distracting parturients and also release of endorphins (natural pain killers). Continuous intrapartum psychological support decreases maternal dissatisfaction especially in those parturients having underlying anxiety traits. Ante-natal childbirth preparation helps in having realistic approach, awareness and positive attitude towards labour (**Table 1**).

Table 1: Non-pharmacological methods.

Specialized	Non-specialised
<ul style="list-style-type: none"> • Acupuncture • Transcutaneous electrical nerve stimulation (TENS) • Intradermal saline injection • Hypnosis • Virtual reality analgesia 	<ul style="list-style-type: none"> • Hydro-bath • Hot packs • Massage and aroma therapy • Ball exercises • Yoga breathing and relaxing techniques • Birthing partner for continuous emotional support • Prenatal classes

Table 2: Pharmacological Methods

Systemic		Regional		
Intravenous		Inhalational	Neuraxial	Other nerve blocks
Opioids	Nonopioids			
-Pethidine	-Nalbuphine	-Entonox (nitronox)	-Lumbar epidural	-Lumbar sympathetic block
-Meperidine	-Butorphanol	-Sevoflurane	-Combined spinal epidural analgesia (CSEA)	-Pudendal nerve block
-Tramadol	-Buprenorphine	(Sevox)	-Single Shot Spinal(SSS)	-Paracervical block
-Morphine		-Isoflurane	-Continuous spinal analgesia (CSA)	
-Fentanyl	NSAIDS	-Desflurane	-Dural puncture epidural technique (DPE)	
-Sufentanyl	-Paracetamol	-Enflurane		
-Remifentanyl	Dissociative or amnesic			
-Alfentanil	-Ketamine			

Table 3: Dose of commonly used adjuvants

Name of adjuvants	Intrathecal dose	Epidural dose	
		Bolus	Maintenance
Fentanyl	15-25 µg	50-100 µg	1-3 µg/mL
Sufentanil	1.5-5 µg	25-50 µg	0.2-0.4 µg/mL
Clonidine	15-30 µg	75-100 µg	0.75-1.5 µg/mL
Dexmedetomidine	5-10 µg	0.5-1 µg/kg	0.25-0.75 µg/mL
Neostigmine	Not recommended	500-700 µg	4µg/mL
Dexamethasone	4 mg	4-8 mg	-

3.1.1. Virtual reality analgesia

Immersive virtual reality is a extremely novel technology in the field of valid non-pharmacological techniques for labour analgesia which can potentially delay and decrease the use of intravenous medication. According to a recent pilot study immersive virtual reality (VR) is a potentially effective technique in decreasing sensory, affective pain and anxiety in unmedicated labouring parturients wearing VR goggles especially in 1st stage of labour. Rigorous scientific studies and database is lacking to prove the benefit of this technology [5,6].

3.2. Pharmacological methods: Parenteral opioids, nonopioids and inhalational anaesthetic agents in low concentrations have been used frequently to provide labour analgesia. This approach is routinely used where facilities for neuraxial analgesia are not available, or parturients do not opt for it or there are contraindications for its use. The administrations of local anesthetic agents with adjuvants are routinely used for neuraxial analgesia and also nerve block (Table 2).

3.2.1. Intravenous analgesia:

Remifentanyl: It is an ultra short acting, potent, synthetic opioid for parental analgesia during labour. Intravenous patient controlled analgesia (IV -PCA) with remifentanyl is a suitable method of labour analgesia in which neuraxial technique is contraindicated or refused by parturient though it does not provide complete analgesia as neuraxial analgesia [7,8].

Bolus dose of 20-50 µg on patient demand with lockout period of 2-3 min without background infusion or alternatively infusion in range of 0.03 - 0.1 µg/kg/min with PCA pump programmed for remifentanyl, connected to dedicated canula can be considered as a feasible option [9]. It has favourable pharmacokinetics like short onset of action (1min), peak action (2min), duration of action (20 min) and a context sensitivity half life of 2.5 min which is

independent of duration of infusion [10]. Remifentanyl has a high placental transfer, however it is extensively metabolized in fetus with no residual neonatal effects. Monitoring like SpO₂, BP, respiratory rate, Pain scores, cardiotocography (CTG) recording and one to one nursing care is required as maternal desaturation, hypoventilation and even apnoea remains the major concern with remifentanyl infusion and bolus dose [11]. It is indicated in cases of thrombocytopenia (platelet count < 80,000 per microliter of blood), patient on anticoagulation therapy; some neuropathies and anatomical deformities of back and as a salvage technique in failed epidural analgesia. It should be avoided in patients with allergy to opioids, other parenteral opioids in last 4 hrs, multiple pregnancy; severe cardiac and respiratory diseases.

3.2.2. Inhalational analgesia techniques

Nitronox: 50% Nitrous oxide and 50% Oxygen has been used for labour analgesia since ages. It regained popularity among midwives and obstetric care providers after advent of adequate scavenging systems in some centres in the US keeping the N₂O concentration less than 25 ppm and use of proper ventilation. Currently nitronox is the only FDA-approved apparatus for the self administration of N₂O [12]. It has separate sources for O₂ and N₂O, a blender device which delivers preset 50:50 mix of nitrous oxide and oxygen and a scavenging unit with wall suction for exhaled N₂O. It can be used in any stage of labour, self administered via hand held face mask. It has a long track of safety record, is fast acting, has a short duration of effect, with minimal sedation, maintenance of airway reflex and no observed immediate side effect on newborn. Nitrous oxide should not be used in known vitamin B12 deficiency and those who have methylene tetrahydrofolate reductase (MTHFR) gene mutation. N₂O provides a variable, inconsistent labour analgesia ranging from very poor to good, despite of this, high satisfaction is reported by parturients who use N₂O than in a subset of parturients experiencing inadequate neuraxial labour analgesia. The current data and evidences on environmental exposure, side effects and cost effectiveness suggest N₂O should be an option among available labour analgesia modalities [13,14].

3.2.3 Neuraxial analgesia

Owing to high efficacy, safety and overall improved quality of analgesia, neuraxial analgesia is considered a gold standard for labour analgesia.

3.2.3.1 Drugs used in neuraxial analgesia

The ideal local anaesthetic should be consistently able to produce a reliable sensory block, minimal or no motor blockade, without tachyphylaxis and good safety profile, in advertent overdose or accidental intravenous injection.

(i) Local anaesthetics

(a) Bupivacaine: The amide local anaesthetic bupivacaine is most commonly used drug for labour analgesia. It is a racemic mixture of 2 stereo-isomers. Bupivacaine provides good analgesia epidurally but dose dependent motor blockade and poor safety profile as compared to single enantiomer drugs. It is highly protein bound and has limited placental transfer. The onset of pain relief is within 8-10 min, peak action in 20 min with duration of action 90 min. Recently the minimum local anaesthetic volume (MLAV) of bupivacaine 0.125% has been researched as 13.6 ml and minimum local anaesthetic concentration (MLAC) of bupivacaine 0.25% as 9.2 ml. The MLAC (EC50) for bupivacaine is calculated 0.0625% with EC95 of 0.129%. MLAC is lower in early labour as compared to late labour, also lower with addition of opioids. Dose sparing effect can be achieved by using concept of MLAV and MLAC. On reducing the concentration of drug, an equivalent analgesia can be achieved by increasing the volume of low concentration solution [15,16].

(b) Ropivacaine: It is a propyl homologue of bupivacaine and single levo- rotatory enantiomer, and found to be less cardiotoxic, less arrhythmogenic and less neurotoxic. It is relatively less potent, with a potency ratio of 0.66 (ropivacaine to bupivacaine) suggesting ropivacaine does not have a superior sensory motor differential block as compared to bupivacaine. Ropivacaine has a longer duration of analgesia as compared to bupivacaine. Concentrations of 0.08% to 0.2% are being used to initiate epidural analgesia. In equipotent doses ropivacaine(0.15%) vs bupivacaine(0.1%) or ropivacaine(0.1%) vs bupivacaine(0.0625%) produces similar analgesia with similar motor block incidences [17-19].

(c) Levobupivacaine: Levobupivacaine is a Levo-rotatory enantiomer of bupivacaine which has emerged as a safer alternative. The potency ratio of levobupivacaine to bupivacaine is 0.98, making it almost equipotent to bupivacaine. It has less depressant effect on myocardium and central nervous system, therefore levobupivacaine is less cardiotoxic and neurotoxic than bupivacaine with a greater safety profile. It is highly protein bound so less unbound fraction is available for activity and it also has a high clearance of unbound fraction which explains shorter elimination half life of the drug.

When low doses are used, toxicity concern may seem irrelevant but total amount of local anaesthetic used may be high, during protracted labour and in case of operative delivery. The current evidence suggests a potency hierarchy of bupivacaine > levobupivacaine > ropivacaine. These drugs do not offer any clinical advantage over each other, when low dose techniques are used. Ropivacaine and levobupivacaine both being less cardiotoxic, cardiodepressant and less arrhythmogenic than bupivacaine, have increased margin of safety profile after inadvertent intravenous injection. Both newer drugs are approximately 5 times costlier and unavailability of drugs at places may prove hindrance for using these agents in resource limited setups. The

use of low concentration in labour epidural drug mixture decreases the incidence of assisted vaginal delivery which may be secondary to reduction in total dose of LA used and subsequent lesser motor blockade [20].

(ii) Adjuvants (Table 3)

(a) Opioids: Lipid soluble opioids like fentanyl and sufentanil have been used in combination with local anaesthetics to increase their potency, reduce MLAC, prolong duration, decrease latency, for LA sparing effects and to improve overall quality of analgesia. Epidural opioids provide analgesia primarily through spinal site of action [15]. Lower costs and easy availability of fentanyl makes it a popular choice as adjuvant in labour analgesia. Adverse effects like pruritis, nausea, maternal sedation and neonatal depression are usually not bothersome with use of low doses of fentanyl and sufentanil in neuraxial labour analgesia.

(b) Clonidine: Clonidine is a α_2 agonist which acts on dorsal horn of spinal cord to produce labour analgesia. It can be administered epidurally alone or in combination with LA, with or without opioids. Use of clonidine as adjuvant decreases the MLAC of local anaesthetics, reduces LA consumption, decreases breakthrough pain, and potentiates duration and quality of analgesia with no effect on motor blockade. It is useful when patient is sensitive to other epidural analgesics, and those having higher incidences of nausea and pruritis with opioids. Clonidine can cause hypotension, maternal sedation, bradycardia, fetal heart rate (FHR) changes especially with high doses $>150 \mu\text{g}$ [21].

(c) Dexmedetomidine: It is a highly selective potent α_2 adrenergic receptor agonist which has intrinsic analgesic properties. Dexmedetomidine owing to high placental retention does not significantly cross the placenta. It is known to prolong duration of analgesia when combined with local anaesthetics. It has a high safety profile, being a highly selective receptor agonist as compared to the nonselective α agonist clonidine. Dexmedetomidine promotes progress of labour as it increases frequency and amplitude of uterine contractions in a dose dependent fashion [22]. Some researchers have used dexmedetomidine as an adjuvant with local anaesthetics in doses of $0.25\mu\text{g}-1\mu\text{g}/\text{ml}$ for epidural infusion, $0.5\mu\text{g}-1\mu\text{g}/\text{kg}$ as epidural bolus for initiation and $5\mu\text{g}-10\mu\text{g}$ for intrathecal administration [23-29]. Caution regarding sedation, bradycardia and hypotension is warranted especially with high doses.

(d) Neostigmine: It is a cholinesterase inhibitor which indirectly stimulates muscarinic and nicotinic receptor in spinal cord by preventing breakdown of acetylcholine in synapse. Acetylcholine acts as an important neurotransmitter in the descending inhibitory pathway. Use of neostigmine neuraxially is reported to have dose sparing effect on LA [30] and prolongs duration of analgesia. Neostigmine may be a useful adjuvant in patients with extreme sensitivity (vomiting or pruritis) to opioids, patient with opioid addiction history, patient on buprenorphine and in cases of chronic exposure of opioid secondary to chronic pain. Side effects such as

motor blockade, dizziness, bradycardia, nausea and vomiting may occur. Combination of clonidine and neostigmine have also been used by some researchers based on synergistic antinociceptive effect of spinal α_2 adrenergic agonist and cholinesterase inhibitor to prolong the duration of labour analgesia [31].

(e) Dexamethasone: It is a glucocorticoid steroid which relieves pain through reducing inflammation, blocking nociceptive C fibres transmission and suppressing neural ectopic discharge. It increases duration of analgesia and decreases dose of local anaesthetics. It has antiemetic effect, with limited maternal and neonatal side effects [32-34].

3.2.3.2 Initiation of neuraxial analgesia

(a) Technical advances in neuraxial analgesia

(i) Role of Ultrasonography (USG):

Novel innovations in the form of USG guided neuraxial technique improves overall success rate of epidural placement in cases like scoliosis and other spinal anatomical abnormalities, obese patients, less experienced and trainee anaesthesia personnel, or as rescue in unanticipated difficulty in epidural placement [1]. Physiological changes of pregnancy leads to increase in procedure related complication like multiple puncture, difficulty in placing catheter, inadvertent dural puncture and PDPH. Intent of sono-anatomy is to improve technical, clinical outcome and forecasting difficult epidurals. It is helpful in identification of best epidural space, midline and depth of space, estimate and optimize the angle of needle insertion [35]. It can also be used as teaching tool to improve learning curve and safety of epidural insertion [16]. Increased procedure time in initial stage of learning, need of expertise, procurement of USG machine, can be deterrents for smooth implementation of USG in regular practice.

Novel epidural needles: These have optical fibres embedded in touhy needle shaft to analyze and identify the various tissue planes [1]. This method to track needle tip during ultrasound guided procedures, involves the use of fibre-optic ultrasound receiver that is fixed within the needle to communicate ultrasonically with external ultrasound probe. This provides a reliable device tracking during in and out plane needle insertion [36].

Real time three dimensional and four dimensional ultra-sonography: Real time visualization of needle while localising epidural space using 3D/4D probe have been described. Complex anatomy of spine and bone shadows, make it difficult to obtain good quality images. Further development in this field could establish it as a useful tool in future [36].

Various novel technologies are under trial to identify epidural space to accurately guide needle in epidural space, correctly identify the entry in epidural space and confirm the catheter location in epidural space [36]. Ultrasound through needle, machine vision using

artificial intelligence using computer to identify images and Acoustic radiation force impulse imaging based on acoustic impedance variations in tissues are currently being researched to evaluate their cost effective use in guiding needle in epidural space. Acoustic puncture assist device which measures the pressure at tip of needle and provides real time auditory and visual displays of pressure waveform and Bioimpedance to differentiate various tissue types are under evaluation for entry of needle in epidural space. For confirming catheter location, near-infrared tracking system, electrocardiography guided system and epidural pressure waveform analysis may be promising methods [36].

(ii) Loss of resistance technique [1,36,37]:

To eliminate subjective variation in identifying epidural space by visual observation of LOR violation the novel LOR methods have been employed recently; along with traditional loss of resistance technique (using saline or air) and tactile feedback.

a. Epidrum: This is an air operated device interposed between epidural needle and syringe, it has a thin diaphragm which deflates once needle tip enters epidural space for providing visual confirmation. Use of epidrum may reduce procedure time and number of attempts.

b. Episure (Autodetect syringe): Episure has a coaxial compression spring with portex pulsator LOR syringe which supplies a constant pressure while advancing the touhy needle. Visual confirmation of space is done by forward movement of plunger and emptying of syringe. It allows use of both hands of operator during insertion and takes less time for insertion.

c. Epidetection LED: This device has a pressure sensor which is attached to epidural needle and the colour of LED changes once needle enters the epidural space.

d. Epidural balloon: This modification of Macintosh balloon is a Y-shaped connector attached to the epidural needle with one end having balloon and other end attached to a syringe for charging the balloon with air.

(iii) Epidural stimulation test: It involves electrical stimulation of nerve which passes through the epidural space by using a saline column in epidural catheter. Motor and sensory responses generated by 1-10mA stimulation indicates epidural location of catheter tip. Pre-existing neuromuscular disease, local anaesthetic administration and neuromuscular blocking agent makes electrical stimulation ineffective. It is not widely accepted because of technical difficulties [36].

(iv) Wire reinforced catheter: In this novel catheter inner wire coil is designed to provide sufficient columnar strength for insertion and lumen patency. Resistance to kinking confers greater flexibility to minimize paresthesias and perforation of dura and vessels [38].

(b) Different neuraxial techniques:

- (i) Combined spinal epidural technique
- (ii) Dural puncture epidural technique
- (iii) Single shot spinal technique
- (iv) Continuous spinal technique

(i) Combined spinal epidural technique (CSE):

CSE (needle through needle technique) has advantage of both spinal and epidural in terms of rapid onset of analgesia including sacral analgesia and longer duration of analgesia. This technique is especially useful when initiated in 2nd stage of labour and parous parturient in whom progress of labour is rapid, in obese and difficult spine. Improved overall quality of analgesia even with opioid alone can be accomplished in early stage of labour henceforth avoiding motor blockade, hypotension and also of immense help in stenotic heart diseases. Incidence of unilateral block and need for rescue analgesia is lower with CSE, however possible side effects of dural puncture and incidence of pruritis are higher. In CSEA technique it is difficult to ensure correct placement of epidural catheter as the effect of intrathecal drug prevents diagnosis of misplaced catheter [2,15,39,40].

(ii) Dural puncture epidural technique(DPE):

Dural puncture epidural (DPE) technique is a technical modification of combined spinal epidural (CSE) technique. Dura puncture is done by 25G spinal needle while withholding the direct administration of drug, along with placement of epidural catheter which improves quality of analgesia by transfer of drugs in subarachnoid space from appropriate administration of medication in to epidural space. Variability of local anaesthetic used, concentration of drug, diffusion capacity of drug, bolus size, time of bolus administration, distance between the puncture location and epidural drug administration, pressure gradient between two compartments, size of dura puncture, pressure of epidural injection affects the extent of drugs reaching subarachnoid space and overall quality of analgesia. DPE technique thus provides rapid, reliable onset of analgesia, early sacral coverage, symmetrical analgesia, fewer top up requirement as compared to continuous epidural technique and better foetal and maternal side effect profile over CSE [3,41,42].

(iii) Single shot spinal technique (SSS):

This technique is easy to perform with success rate of 98%. Short procedure time and rapid onset of analgesia renders it beneficial in restless patient due to intense pain of 2nd stage

of labour or as rescue measure in failed epidural and in low resource set up. Main limitation of SSS is shorter duration of action. Since labour is unpredictable and process of labour is unique to each parturient, a second spinal block may be required. Low dose spinal analgesia by administering a combination of bupivacaine 2.5mg and fentanyl 25µg and morphine 250µg may provides analgesia up to 4 hours without hampering ambulation [43].

(iv) Continuous spinal analgesia technique (CSA):

Intentional insertion of epidural catheter in intrathecal space is done with infusing local anaesthetic and/or opioid in CSF. Suitable candidates for this technique are morbidly obese, in difficult airway providing reliable analgesia, spinal deformities, previous spinal surgeries in whom placement of epidural catheter is difficult and as salvage in accidental dural puncture while attempting epidural [15]. CSA can also be helpful in providing analgesia and anaesthesia in significant cardiac diseases with minimal hemodynamic effects. CSA has a high rate of failure because of dislodgement of catheter, a high incidence of postdural puncture headache and unavailability of suitable catheters; regrettably makes it difficult to advocate its routine use [15]. There are chances of accidental overdose of drug and high spinal if mistaken for epidural catheter. CSA can be initiated with either opioid only (fentanyl 15-25µg or sufentanil 1.5-5µg) or using a dose of 1.25-2.5mg bupivacaine/ 2-3.5mg ropivacaine with fentanyl 2µg/ml or sufentanil 0.3µg/ml as in CSE. For maintenance 0.06% bupivacaine with fentanyl 2µg/ml in doses of 0.5-3ml boluses is used to achieve T8-10 sensory level [15]. Association of cauda equina syndrome with use of micro-catheter smaller than 24G had been reported. Micro-catheters with their very small internal diameter limits the flow rate of injected local anaesthetic within CSF exposing some of the nerve roots to very high concentration of local anaesthetic [15,16,44].

(C) Maintenance of epidural analgesia: (Table 4 & 5)

Maintenance of epidural analgesia has witnessed technical advancement with use of novel drug delivery systems such as:

- a. Computer integrated patient controlled analgesia (CI-PCEA)
- b. Programmed or Automated intermittent epidural bolus (PIEB)

Regular practised technique for maintaining epidural labour analgesia include intermittent bolus dose, continuous epidural infusion and patient controlled epidural analgesia. Common

Table 4: Common epidural drug regimens used in different neuraxial techniques.

	Initial Bolus dose	Background Infusion	Top up dose	Lock out time interval
Lumbar Epidural Analgesia	10-15 mL LDM*	5-8 ml/h LDM	10-15 mL LDM	10-20 min
Combined Spinal Epidural Analgesia (CSEA)	Intrathecal 0.5% B (1-2.5 mg) + F (10-25 µg) or S (2.5-10 µg)	5-8 mL/h LDM	Epidural 5-10 mL LDM	10-20 min
Patient Controlled Epidural Analgesia (PCEA)	5-10 mL LDM	5-8 mL/h LDM	8-12 mL LDM	10-20 min

LDM (bupivacaine/levobupivacaine 0.0625%-0.125% or Ropivacaine 0.08-0.2%+fentanyl 1- 3 µg/ml)

Table 5: Dose of drugs used for epidural analgesia.

Name of drug	Initial Bolus	Maintenance infusion
Bupivacaine	10-15 ml of 0.125%-0.25% solution	0.0625%-0.125% solution given at rate of 8-15 mL/hr
Ropivacaine	10-15 ml of 0.1%-0.2% solution	0.2%-0.5% solution given at rate of 8-15 mL/hr
Levo Bupivacaine	10-15 ml of 0.2%-0.25% solution	0.1%-0.125% solution given at rate of 8-15 mL/hr
Fentanyl	50-100 µg	1-3µg/ml
Sufentanil	10-25 µg	0.2-0.4µg/ml

epidural drug regimens are given in **Table 4**.

a. Computer integrated patient controlled analgesia (CI-PCEA):

It is a novel innovative PCEA system in which pre-programmed algorithm is used to modify basal infusion rate on basis of previous hour's drug usage for patient administered boluses [15]. It converts a continuous infusion pump in to a computer integrated PCEA which is more responsive to parturient need. This interactive program records the history of the analgesic requirements over the past hour and according to number of boluses, it increases the magnitude of basal infusion proportionally. It may or may not be able to reduce the total LA consumption as compared to PCEA but it decreases breakthrough pain with better VAS scores and maternal satisfaction [45-47].

b. Programmed or Automated intermittent epidural bolus (PIEB):

PIEB is a novel technology which delivers preset boluses at timed interval (5-10 ml of LDM at 30-60 min) with a programmable pump for maintenance of labour analgesia. Provider

can modify volume of bolus, drug mixture, basal infusion rate, lockout interval, and maximum allowable dose per hour [48]. It has been suggested to be a superior mode for the maintenance of labour analgesia compared to conventional continuous epidural infusion. In PIEB, instead of background infusion, the hourly total amount of local anaesthetic solution normally used in a continuous epidural infusion is administered as intermittent boluses of low dose mixtures. Intermittent boluses improve uniform spread of drug in epidural space owing to higher injectate pressure, larger volumes and allows drug to spread through multiple orifices with improved parturient satisfaction. Longer duration of analgesia, lesser drug consumption with less motor blockade, lower incidences of breakthrough pain when compared to usage of same amount of drug via continuous infusion is also achieved [16,49-52]. PIEB can be combined with PCEA as background infusion, which results in reduced consumption of local anaesthetics and less PCEA demand boluses, when compared to PCEA with standard continuous background infusion, while maintaining similar analgesic efficacy. The anesthesia provider can modify the infusion solution by changing local anaesthetic and opioid concentration, patient-controlled bolus volume, lockout interval, background infusion rates and maximum allowable dose per hour.

4. Future Prospects

Pharmacogenetics enables us to have better understanding and knowledge of variability in drug response, drug requirement and sensitivity. Effect of single nucleotide polymorphism (SNP) 304A >G (substitution of adenine for guanine at position 118) of gene encoding μ opioid receptor (OPRM1) has been researched. Nulliparous women who are heterozygous or homozygous for this gene have lower ED50 for fentanyl and sufentanil. Clinical implications of genetic polymorphism still remain unclear and is subjected to further research [15,16,53,54]. Pharmacogenetics may open up new avenues for knowledge and understanding of genetic variation and polymorphism in ethnic groups and their clinical implication in tailoring the customized therapy to suit need of patients.

4.1 Myths and controversies with neuraxial analgesia:

a) Timing of epidural analgesia

ACOG and ASA have jointly emphasized that there is no need to wait till cervical dilation reached 4-5cm. Maternal request is sufficient indication for pain relief in labour. Early vs late initiation of labour analgesia have no difference in operative delivery rates and duration of labour [55,56].

b) Epidural test dose

Standard test dose practise with epinephrine is better to be avoided in labour patients as

it may lead to hypertension and uteroplacental insufficiency. The low concentration and dilute volume of epidural drugs dose (LA and opioids) of local anaesthetic can be used as test dose to check a functioning epidural catheter [15].

c) Duration of labour

Various studies demonstrate that effective neuraxial analgesia may slightly prolong the second stage of labour [57], because of inhibition of Ferguson reflex and pelvic muscle relaxation [58]. Analgesia related prolongation of labour, if it occurs is short, has not been shown to have adverse maternal and neonatal effects and is probably of minimal clinical significance [15].

d) Early vs delayed pushing

Passive descent and monitoring during labour with delayed pushing has been advocated in parturient using neuraxial labour analgesia. Delayed pushing decreases maternal exhaustion by allowing passive descent have positive impact on vaginal birth and instrumental delivery by effective bearing down [59,60].

e) Discontinuation of analgesia in late labour

Many RCTs conclude that discontinuation of epidural late in labour to maintain parturient ability to push effectively does not show any significant effect on reduction of instrumental delivery as compared to continuation of same epidural regimen until delivery. This practise significantly increases inadequate pain relief and it is difficult to re-establish same level of analgesia subsequently [61,62].

f) Incidence of operative or instrumental delivery

RCT and data base systemic trials failed to show significant association between epidural and C-section [56,57,63]. Many meta-analysis and COMET study even suggested lower incidence of instrumental delivery after low concentration opioid and LA mixtures [56,64,65].

Additionally a number of factors are known to affect progress and outcome of labour including degree of analgesia during 2nd stage of labour, local anaesthetic concentration, method of epidural analgesia, parity, artificial rupture of membranes, use of oxytocin and also obstetric provider's intervention and status of patient. Greater pain intensity in early labour and high demand of analgesic doses appears to be risk factors for operative delivery [66].

g) Vaginal birth after caesarean delivery(VBAC) and epidural

Epidural analgesia should be considered early in these parturient as adequate pain

relief may encourage to attempt VBAC and it can be used to convert for surgical anaesthesia if needed for operative delivery. Epidural analgesia is not expected to mask sign of uterine rupture [3,67].

h) Maternal fever

A modest, gradual rise in core temperature in subset of patients receiving epidural analgesia has been consistently reported. Mechanism of temperature elevation is likely to be an inflammatory process. Sterile inflammation is caused in the absence of pathogens, driven by endogenous molecules named alarmins which are released upon tissue damage that activates the inflammasome. Inflammasome promotes maturation of proinflammatory cytokines such as IL β 1 and IL18 with induction of fever which is attributed to bupivacaine [68-69]. Risk factors for maternal fever are nulliparity, prolonged rupture of membrane, prolonged labour, frequent intervention and in view of both maternal and neonatal safety patient should be evaluated for clinical chorioamnionitis [15,69].

i) Chronic backache

Many prospective studies [63,70-72] have not shown significant association between use of epidural and long term backache, disability and limitation of movement [15]. The most significant factors for long term backache are antepartum backache, inability to achieve pre-pregnancy weight and physical heavy work [70-72]. Local tissue trauma at skin puncture site during epidural placement can cause short term backache.

j) Breast feeding success

Several trials and studies failed to demonstrate significant association between breast feeding and epidural analgesia. Lactation failure is multifactorial, like intention of mother to breast feed, psychological status of mother, need to return to work, maternal fever, instrumental delivery, use of oxytocin and social support; further research is needed to assess the impact and strength of association of these factors. In clinical practice low dose local anesthetic and small doses of commonly used opioids does not adversely affect breast feeding success rate at 6 weeks [16,73,74].

k) Postpartum depression

Epidural labour analgesia was found to be associated with a decreased risk of postpartum depression. Intensity of labour pain and mode of pain relief are reported to be associated with mood disorder in early postpartum period [75]. Parturient with severe acute pain have 2.5 fold increased risk of persistent pain and 3 fold increased risk of postpartum depression [76]. Postpartum depression is not only associated with maternal morbidity but also associated with emotional, cognitive and behavioral development of child [77]. Managing the intrapartum

and postpartum pain significantly decreases the risk for depression. The risk for postpartum depression is also known to decrease by attending prenatal childbirth classes, emotional support and continued breast feeding [78].

5. Conclusion

Labour pain is a complex multifactorial physiological and psychological phenomenon. Labour analgesia has evolved from ether anaesthesia to very efficient neuraxial analgesia. Newer modalities using low dose local anaesthetics mixture in combination with adjuvants administered via CI-PCEA and PIEB-PCEA have made neuraxial analgesia more safer for both mother and neonate with least effect on progress of labour. Ultrasonography guided placement of epidural catheter improves success rate in difficult cases and can also be used as teaching tool. Innovations to improve appreciation of LOR and real time visualization of needle by sonography are undergoing rigorous scientific research. Pharmacogenetics may further help in understanding individual variation in drug responses and help in tailoring epidural analgesia in individual cases.

6. References

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