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NON-REGIONAL LABOUR ANALGESIA

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INTRODUCTION

Labour pain is multifaceted as it is influenced by many physiological, psychosocial, and cultural factors. For most parturients it is the most painful event in their lives, fortunately for many it is forgotten with time. In 1971 Melzack, on the McGill Pain Questionnaire, rated it as more painful than cancer pain. Furthermore, he demonstrated that in nulliparous patients without prepared childbirth training it was nearly as painful as an amputation of the digit without anaesthesia. (1)

Therefore, all parturients should be offered and given the right to choose from the available labour pain management options. Undoubtedly neuraxial techniques, particularly epidural analgesia, is still the gold standard in labour as it is the most efficacious with high maternal satisfaction and a relatively good safety profile. (2) However regional analgesic strategies may be unavailable or contraindicated in some circumstances.

It is therefore important that health care workers are aware of the different non-regional analgesia methods used and their efficacy, side effects and adverse effects on the parturient, fetus/neonate and progress of labour. These are divided into pharmacological and non-pharmacological methods.

Most non-pharmacological methods have been used for centuries and mainly focus on how to make an individual cope with pain rather than alleviating it. In the mid-1800s Dr James Young Simpson introduced the administration of ether and chloroform to labouring parturients. It became more popular and acceptable after Dr John Snow administered chloroform to Queen Victoria for the birth of her eightieth and ninth child.

PHYSIOLOGY OF LABOUR PAIN

Labour is a physiologic process characterized by regular, painful uterine contractions which increase with frequency, duration, and intensity as it progresses. This is associated with cervical changes and ultimately delivery of the fetus and placenta. (3, 4)

It is divided into three stages. The first stage is from the onset of labour to full cervical dilation i.e., 10 cm. The first stage is further divided into two phases: the latent phase, from the onset of uterine contraction to 4 cm cervical dilation; and the active phase, which is from 4 cm to 10 cm cervical dilation. The second stage of labour begins from full cervical dilation until delivery of the fetus. Stage three is from the delivery of the fetus to that of the placenta. (3, 4)

Labour pain is divided into two components – visceral and somatic pain. Visceral pain, which arises from dermatomes T10-12, is dull, poorly localized and felt in the lower abdomen, sacrum and back. It occurs in early in the first stage and second stage when cervical and lower uterine segment dilation release chemical mediators (bradykinin, histamine, serotonin, acetylcholine, and potassium ions) that activate the unmyelinated C fibres. These travel through the uterine, cervical, and hypogastric nerve plexus into the main sympathetic chain, which synapse in the dorsal horn gray matter of the spinal cord through T10-L1 nerve roots. (3, 4)

The somatic pain, which arises from dermatomes T10-L1, is sharp, well localised, and felt in the vagina, rectum and perineum. It occurs late in the first stage and second stage because of the stretch and distension of the pelvic floor, vagina and perineum which releases chemical mediators that activate the myelinated A delta fibres. These travel through the pudendal, genitofemoral, branches of the posterior cutaneous nerve and ilioinguinal nerves and ultimately synapse in the dorsal horn grey matter of the spinal cord through L1-L2 and S2-S4 nerve roots. (3, 4)

Both visceral and somatic pain pathways cross to the contralateral ventral white matter of the spinal cord and ascend through the spinothalamic tract to the hypothalamus, limbic system and cerebral cortex for the autonomic, emotional response and pain perception. (3)

CONSEQUENCES OF LABOUR PAIN

Painful contractions may lead to stimulation of the maternal respiratory system causing hyperventilation and respiratory alkalosis, which compromises fetal oxygen delivery by causing uterine vasoconstriction and a leftward shift of the maternal oxygen haemoglobin dissociation curve. Pain also stimulates maternal cortisol and catecholamine release, which further reduces uterine blood flow and prolongs labour via $ß_2$-mediated uterine smooth muscle relaxation. These factors compromise oxygen supply to the fetus, leading to fetal hypoxemia and acidosis. (5, 6)

Pain-mediated sympathetic stimulation results in an increase in maternal blood pressure, heart rate, oxygen consumption, carbon dioxide, systemic and pulmonary vascular resistance, delayed gastric emptying, ileus, nausea and vomiting(5). Some of these changes may cause detrimental effects in parturients with pre-existing cardiopulmonary conditions e.g., pulmonary hypertension. (7) Labour pain may also result in psychological and behavioural problems. These may include anxiety and stress resulting in delayed labour. (7)

INDICATIONS OF NON-REGIONAL LABOUR ANALGESIA

Regional analgesia is absolutely contraindicated if the parturient has actual or anticipated serious maternal hemorrhage, refractory hypotension, coagulopathy, increased intracranial pressure, skin or soft tissue infection at the site of regional analgesia placement. Regional analgesia is also contraindicated in cases of patient refusal. Some parturients decline analgesia completely to have a natural birth experience and others prefer less invasive pain management options. (4, 8)

Sometimes an attempt to place a regional analgesia is unsuccessful due to technical difficulty e.g., a parturient with severe scoliosis or previous spine surgery. In certain circumstances the regional might be inadequate therefore other pain relief options can be used as adjuncts.

In 2001 more than 90% of parturients in the United States received labor analgesia the majority being regional techniques. In contrast, in developing countries, pain relief during labour is sparse due to unavailability of appropriately skilled health professionals and lack of supplies and equipment. e.g. spinal, and epidural needles. (8, 9) Thus, delivery units must ideally be able to offer a range of non-neuraxial analgesia options for labour.

PHARMACOLOGIC METHODS

There are limited options for analgesia in labour because drugs**,** particularly opioids**,** may have dose-dependent maternal and fetal/neonatal adverse effects (due to utero-placental transfer) and at lower doses may provide suboptimal analgesia. They are either given parenterally or by inhalation. These methods usually need special equipment for administration and careful monitoring with trained staff.

Opioid Drugs

Opioid receptors are found in the central and peripheral nervous system and gastrointestinal tract. Opioids bind to these to inhibit neurotransmitters (noradrenaline, acetylcholine, neuropeptide and substance P) by G-protein-coupled receptor activation which leads a reduction in nerve transmission of nociception. (10)

- **Pethidine**
  In 1950 it became lawful for midwifes in United Kingdom to administer pethidine independently. Globally it is the most administered and researched opioid drug for labour analgesia because of its familiarity and affordability. Pethidine is a synthetic, highly lipid soluble opioid which is mainly alpha 1 glycoprotein bound and broken down into a proconvulsant metabolite norpethidine. (11)

  Pethidine is generally prescribed at 1mg/kg (maximum 150mg) intramuscularly (IM). Its maximal analgesic effect occurs in about 15 minutes and lasts up to 3 hours. Its analgesic efficacy has been challenged by many studies which found it to have more sedative than analgesic effects.(11)
  It can cause maternal confusion, loss of control, sedation, nausea, vomiting, urine retention, delayed gastric emptying and dose-dependent respiratory depression. The fetal/neonatal effects depend on the dose and time of administration to the parturient with peak plasma levels occurring 2 to 3 hours after IM injection. (11)

  The neonate is more susceptible to hypoventilation due to underdeveloped respiratory centres and higher plasma levels due to ion trapping of the weak base in the more acidic fetal circulation.(11) Volikas *et al* tried to compare the efficacy of pethidine patient-controlled intravenous analgesia (PCIA) set at a bolus dose of 10mg and lockout time of 10 minutes against remifentanil PCIA with a bolus dose of 0.5mcg/kg and lockout time of 5 minutes but had to end their study after recruiting 17 parturients because pethidine resulted in significantly low APGAR scores.(12) Pethidine -exposed neonates with normal APGARS are found to be drowsy and have a delay to commencing effective breastfeeding. Others discouraged its use during labour and delivery or permit its use with the proviso of immediate availability of naloxone if needed. (8)
  Pethidine minimally interferes with labour progress.

- **Morphine**
  Historically, a combination of morphine and scopolamine was administered in labouring parturients for analgesia, known as twilight sleep. This method was associated with several maternal and neonatal adverse effects. (13) Morphine is a potent natural opioid that exerts its analgesic effects by mainly binding to mu opioid receptors in the central nervous system. In the liver, morphine is metabolized into morphine-3-glucuronide (70%) and morphine-6-glucuronide (30%) these are then excreted via the kidneys.

The active metabolite morphine-3-glucuronide, has a higher potency than morphine and an elimination half-life of 120 minutes. (10)
For labour, morphine administered at doses of 2-5mg IV or 5-10mg IM have maximal analgesic effects at 20 minutes and 2 hours respectively and lasts for 4-6hours. (11)(8) Morphine is not ideal for labour due to slow onset of analgesia and increased risk of neonatal respiratory distress. Parturients experience side-effects similar to those of pethidine. (11) Olofsson *et al* parturients repeated IV morphine boluses at total of 0.15mg/kg found minimal pain severity reduction and significant sedation. (14)

- **Remifentanil PCIA**
  The administration of remifentanil for labour analgesia is relatively a new method merely over 20 years old and is unlicensed. It is an ultra-short acting opioid with several advantages, such as its rapid onset (about 30-60 seconds) and offset times. Remifentanil is metabolised by plasma and tissue esterase into inactive metabolites and has a short context sensitive half-life (3.5 minutes) of 5 to 10 minutes of stopping infusion with no residual effect therefore delivery can occur without neonatal respiratory depression. In addition, despite easily crossing the placenta, it's rapidly metabolized and redistributed in fetus by fetal esterases, which are nearly fully developed by birth. (11)

  Compared to other potent systemic opioids, remifentanil causes fewer side effects on the fetus. It minimally affects fetal heart rate, neonatal APGARS, cord gases and neonatal vital signs. (15) However fetal monitoring is recommended in many guidelines.

  The best dose regime with the most analgesic but minimal adverse effects is unknown. Dose regimes in studies have included bolus doses of 0.1 to 1mcg/kg/dose with lockout times ranging from 1 to 4.5 minutes, with or without a background infusion. Dose adjustments may be needed as labour progress. PCIA settings with bolus doses of 0.25-0.5mcg/kg with 2-minute lockout period and no background infusion is acceptable. The use of background infusion is associated with an increase in maternal side effects – however, when needed, a low dose of 0.025-0,05mcg/kg/min may be used. (10, 11) Volmanen *et al* achieved VAS scores of 3-5 of 10 with doses of 0.2-0.8mcg/kg but 94% of parturients desaturated to less than 94%. (16)

  Maternal adverse effects of remifentanil include respiratory depression and cardio-respiratory arrest. Therefore, close maternal monitoring is mandatory to identify and manage hypoxemia. This includes continuous one to one observation, respiratory rate, continuous maternal oxygen saturation and/or ideally end tidal carbon dioxide monitoring for apnea. The initiation and titration of remifentanil PCIA should only be performed under direct supervision of obstetric anesthesiologists. They must also obtain an informed consent and ensuring availability of appropriate emergency drugs and equipment. Accordingly its use should not be routine. (17)

  Discontinue immediately if desaturate to less than 94% despite supplemental oxygen, respiratory rate less than 8b/m and/or oversedation. (15) It is absolutely contraindicated in parturients who are allergic to remifentanil and avoid if other opioid drugs were administered within 4 hours prior. Remifentanil offers superior analgesic efficacy compared to nitrous oxide and other parenteral opioids but is inferior to epidural analgesia. However it is associated with more maternal apnea, hypoventilation and sedation. (10, 15) Other problems are its cost and difficulty in timing dose administration to achieve optimal analgesic effects.

- **Fentanyl PCIA**
  Fentanyl is a potent and highly lipid soluble synthetic opioid. Its maximal analgesic effect occurs within 3-4 minutes of administration and lasts for 30-60 minutes but will accumulate in the parturient and fetus if administered repeatedly or in large doses. The ideal loading and bolus dosage, lockout time and background infusion rate still undetermined. (11)

  Nikkola *et al* compared fentanyl PCIA (50mcg loading dose and 20mcg bolus dose with a 5-minute lockout time) to epidural analgesia in parturients, and had a 30% conversion rate from fentanyl PCIA to epidural mainly due to inadequate analgesia. (18)

  Fentanyl PCIA is associated with more neonatal adverse effects when compared to remifentanil PCIA such as desaturation (<90%) lasting up to 12 hours post-delivery. Therefore, cautious monitoring is advised. (10, 11)

Non-Opioids Drugs

- **Ketamine**
  A N-methyl-D-aspartate receptor antagonist with analgesic effects observed at subanaesthetic doses. In 2014 Joel and colleagues published a randomized, placebo control trial involving 70 parturients. They were further divided into 2 groups. Half were administered ketamine with a bolus of 0.2mg/kg IV slowly followed by an infusion at 2mg/kg/hour and the other group received 0.9% normal saline. Their results showed lowered pain scores of less than 3 out of 10 (from baseline pain scores of 10) without any significant maternal or fetal effects. (19)

  Side effects of ketamine include hallucinations, sleep disturbances, unpleasant dreams, nystagmus, blood pressure elevation(3) Ketamine should be avoided in eclampsia, preeclampsia, hypertension, heart disease, epilepsy, and psychotic disease. (5)

- **Paracetamol**
  Paracetamol is either administered as sole agent or adjunct depending on the severity of the labour pain. Parturients are usually given 1g IV 4 hourly and seldom have adverse effects at these therapeutic doses. Its analgesic effects occur within 15 minutes and last around 2 hours. Paracetamol provides better maternal analgesia and satisfaction compared to placebo. (8). A random, double blind study compared the efficacy and safety profile of paracetamol 1g IV to tramadol 1mg/kg IM when administered in the active phase of labour. Both drugs showed similar analgesic and neonatal effects, however the tramadol group had a higher incidence of maternal side effects. (20)

Inhalational Analgesia

This is the inhalation of anaesthetic agents at subanaesthetic concentration, while still maintaining an awake state and intact airway reflexes. The exact mechanism of action is still unknown. It needs frequent monitoring of exposure of health care providers and an active scavenging system for excess and exhaled gases.

- **Nitrous oxide**
  The administration of nitrous oxide in labour for analgesia begun in 1880. A century later it is available in almost all delivery units in the United Kingdom and is administered in up to 60% of labouring parturients. Nitrous oxide is generally available as a mixture of 50% nitrous oxide and 50% oxygen (Entonox) which is nonflammable, odourless, tasteless and has no risk of malignant hyperthermia. (11) It has a low blood-gas solubility coefficient of 0.47 thus has fast onset and offset of action of analgesia. (8)

  It is easy to administer, the parturient is firstly instructed how to self-administer it by holding the facemask or mouthpiece with a demand valve (stops gas flow when not administered), takes a breath in to generate the flow of nitrous oxide then breathes out into facemask or mouthpiece. In takes approximately 30 to 40 seconds for peak brain concentration to occur. It is then quickly removed from lungs therefore minimally accumulates. (11, 21)

  Nitrous oxide can be used for analgesia in any of the stages of labour including post delivery procedures e.g., manual removal of the placenta and episiotomy repair. It can be used as an adjunct to epidural and non-pharmacological analgesia, however concomitant opioid administration should be avoided. It should be avoided in those with respiratory compromise, neurological injury, and pulmonary hypertension. (22)

  It is generally safe for parturients; however, a few can experience nausea, vomiting, drowsiness, disorientation, and loss of consciousness is associated with concomitant opioid administration or prolonged exposure e.g. continuous self or assisted administration, like face straps or another person holding mask. (21) Intrapartum nitrous oxide has no effect on fetal heart rate, umbilical cord gas and APGAR scores. If present in the fetal circulation at delivery, the neonate is able to eliminate it by breathing. (21)

  Prolonged exposure to staff (if unscavenged nitrous oxide exposure exceeds 5 hours per week), increases the possibility of infertility, miscarriage, preterm labour, and vitamin B12 deficiency. Accordingly, nitrous oxide occupational exposure is monitored by badge dosimeter and an infrared N_2O analyser. The safety limit differs amongst various countries, ranging from 25 to 100ppm. (22) Nitrous oxide contributes 0.05% to the greenhouse effect, and its main sources are agriculture, fossil fuel combustion and industrial sources. The exact contribution of the health sector is unknown. (22)

  Studies show conflicting results regarding its efficacy. A study involving 501 parturients showed a 69% conversion rate from nitrous oxide to other forms analgesia, primarily due to inadequate pain control, and majority were given a neuraxial analgesia. (21)

- **Halogenated agents**
  These are used in a few centres in the UK, administered either intermittently or continuously through an agent specific vaporiser and the concentration is monitored by agent analyers. If administered intermittently, the patient only must administer during each contraction. Contractions can be monitored by either by palpation or intrauterine pressure tracing. Continuous administration (even inhales between contractions) is given during the second stage of labour under supervision of an anaesthetist, owing to the risk of reduction in level of consciousness, vomiting and aspiration. (5)

- **Isoflurane**
  This agent has an unpleasant smell and has an occupational exposure limit of 50ppm. Its continuous administration during the second stage of labour at 0.2 to 0.7% concentration shows comparable maternal analgesia and satisfaction to nitrous oxide.
  However intermittent administration at higher concentration of 0.75% provides more analgesia with increased risk of sedation. When 0.2-0.25% isoflurane is added to nitrous oxide it provides more analgesia compared to nitrous oxide alone. (11)

- **Desflurane**
  It has a low blood/gas partition coefficient of 0.42 therefore has a rapid onset and offset of action. When 0.1-4.5% desflurane in oxygen is administered during the second stage of labour it provided comparable analgesic effects as nitrous oxide but had higher amnesia occurrence. (11)

- **Sevoflurane**
  A pilot study involved 50 parturients, intermittently administered 2-3% sevoflurane in oxygen and air to target an expired fraction of 1-1.5. It showed significant pain reduction but an anesthetist was required for monitoring. (11)

NON-PHARMACOLOGIC OPTIONS FOR LABOUR ANALGESIA

Some parturients in labour choose to avoid the use of drugs or invasive methods for analgesia. Despite many non-pharmacological methods and some having been in use throughout history there is often insufficient scientific evidence to support their use especially in moderate to severe pain. However, it is still important health care providers can provide valid information to parturients about the efficacy and limitations of each method. Most are affordable, easy to administer and low risk to parturient and fetus/neonate.

1) Continuous Intrapartum Support

Long ago parturients went through labour in the presence of other women from the community. However, over the years the hospital setting has led to little support to the labouring parturient especially in low-income countries.The Cochrane review states that it includes offering emotional support, coping, and comforting strategies and being parturients' advocate when necessary. It can be used during all the stages of labour by either a designated health care provider, partner/relative/friend or even doula, i.e. nonmedical support of the parturient by trained person. (23) Some studies showed reduction in the following analgesia requirements, dissatisfaction during labour and operative birth rates. (24) Continuous intrapartum support is associated with no maternal or fetal adverse effects. (23)

2) Transcutaneous Nerve Stimulation (TENS)

The Scandinavians introduced its use in labour in the 1970s. A low intensity electric current is administered via skin surfaces to inhibit nociceptive transmission to the higher centres and stimulates the descending inhibitory pathways of pain (pain gateway theory). It is thought TENS also produces endogenous endorphin release. (25)

In the labouring parturient the electrodes are attached on her lower back (first set at about 2 cm at T10-L1 dermatomes on either side of spinous process and second set place at S2-S4 dermatomes) and she controls the electrical impulses which she can change the frequency and intensity using a battery powered handheld device. Labour specific TENS device have an additional booster button to intensify the stimulation and automatically increase intensity by 20% during a contraction. (3, 24)
In 2010 Mello *et al* published a review of nine studies, 49% of parturients received TENS and the rest either no TENS or placebo treatment. They concluded that TENS had no impact on the parturient, fetus/neonate or the labour and did not reduce use of additional analgesia. (25)

3) Water Immersion (WI)

It has been used for centuries and mostly used in midwifery-led delivery units. This is immersion of the parturient in warm water (< 37.5 C) with a minimum level above the abdomen. It can be done during the first or second stage of labour and for any period. WI could also occur in the third stage of labour (waterbirth). It is done in a pool or larger bathtub either at home or hospital. It is believed to work by increasing uterine blood flow and the release of endogenous endorphins and oxytocin. The buoyancy of water allows for better maternal mobility. (8)

Some studies showed reduction in pain and duration of the first stage of labour. Water immersion is generally safe for both parturient and neonate. However, there are few case reports of neonatal cord avulsion, drowning and near drowning or water aspiration and bacterial infection. (13) Therefore, it is only permitted in low-risk pregnancies and should be done under supervision of a qualified midwife. (24)

4) Massage

This is the rubbing and kneading of body's soft tissue with hands. Some Chinese hospitals have touch rooms to do the massage by significant others. A Cochrane review of 14 trials found low quality to suggest massage offered significant reduction in pain, labour duration or operative birth rates. (24)

5) Acupuncture/Acupressure

Originated from East Asian countries many years ago and is commonly used for management of chronic pain disorders. Acupuncture is the insertion of fine needles (by specifically trained practitioner) at a depth of about 2.5-3 cm into different parts of body(3). Most of these acupuncture points are either connected to/located near neural structures. The needles are either manually manipulated (classic acupuncture) or a low voltage is passed through them (electropuncture) for stimulation. Acupressure has the same acupuncture points but instead the therapist uses their fingers and hands. (24)

During labour it is usually used in the first stage and the acupuncture points in labour pain are located on the hands, feet, and ears(24).In Germany almost all the maternal units provide it and either done by a professional acupuncturist or trained midwife (180 hours on average). (26) Disadvantages of acupuncture include that it is time consuming, limits parturient mobility and the additional wires and machinery may interfere with maternal or fetal monitoring. There is limited evidence to support use for labour pain. (27)

6) Water Blocks/Intradermal Sterile Water Injection

It is administered during the first stage of labour or when parturient experiences significant back pain. Under aseptic technique 0.05 to 0.1 ml of sterile water is injected lower back at four sites with a 25-gauge needle. Post injection a burning/stinging sensation is felt for about 20 t0 30 seconds then analgesic effect occur which last for up to 2 hours. Water blocks can be repeated within 30 minutes. (28)

In 2018 Choudhary *et al* published a case report of a parturient diagnosed with peripartum cardiomyopathy (ejection fraction 25-30%), known with controlled diabetes mellitus type 2 and unilateral lower limb neurology undergoing investigation. She went into spontaneous labour, during the active phase she reported VAS of 8 then intradermal sterile water blocks were done and within 15 minutes had VAS 3 until delivery. (29)

7) Hypnosis/Hypnobirthing

It has been used in labour for over a century. Hypnosis is the process of conscious awareness alteration which involves focusing an individual's attention inward, less awareness to their surroundings and becoming more responsive to suggestions. Suggestions are verbal and non-verbal communications that can change perception, thoughts, and mood of an individual. However, these can still be rejected by the hypnotised individual because they are still conscious. (8)

During labour, the goal is to change the perception of pain. The parturient either does self-hypnosis or uses a hypnotherapist and certain medical terms are avoided and replaced with words that are unlikely to be associated with negative perception or thought e.g., birthing coach=birthing companion, catching the baby =receiving the baby, uterine contraction= uterine surge. (8)

For self-hypnosis, the parturient attends classes either alone or in groups on an average of once per week for 2 hours for about a month. (30) There is insufficient evidence to make a decision about its efficacy for labour pain. (24)

8) Aromatherapy

The use of essential oils from plants to improve physiological and psychological wellbeing, various types are in use including lavender, rose, peppermint and citrus. These can be as massaged into the skin, added to a bath or inhaled following aerosolization. (8)

Its exact mechanism of action is unknown. Generally safe but possible side effects include skin irritation or allergic reactions. A Cochrane review involving 535 parturients comparing aromatherapy with placebo, no treatment or other non-pharmacological methods found no difference in pain intensity, use of pharmacological methods and neonatal outcome. (8, 31)

CONCLUSION

Labour analgesia management is challenging as it requires providing sufficient analgesia whilst avoiding adverse effects to both the parturient and fetus/neonate. Epidural analgesia is the gold standard method however it might be inappropriate, inadequate, or unavailable in certain circumstances, so remifentanil PCIA can be administered provided extensive maternal monitoring and appropriate drugs and equipment are readily available. The advantages of non-pharmacological methods include minimal side effects and most address the psychological aspect of pain such as fear and anxiety which makes them great adjuncts. Therefore, it is important relevant health care providers are aware of the various available methods to discuss their benefits and risks, ideally antenatally, to obtain a more informed consent.

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