Non-neuraxial analgesia in labour

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Abstract

Pain in labour is often described as one of the most severe pains experienced. Neuraxial techniques provide the most effective form of labour analgesia. However, not all women wish to have this or indeed want complete pain relief in labour. There are also subgroups of women in whom neuraxial techniques are contraindicated or attempted placement is unsuccessful. Therefore delivery units must be able to offer a range of non-neuraxial analgesia options for labour.

Keywords Analgesia; diamorphine; Entonox; labour; non-neuraxial; opioids; patient-controlled; pethidine; remifentanil

Royal College of Anaesthetists CPD Matrix: 1A02, 1D02, 2B01

Learning objectives

After reading this article, you should be able to:

- state the options available for non-neuraxial analgesia for labour
- outline the efficacy of the non-pharmacological and pharmacological methods of labour analgesia described
- outline the adverse effects of each of the methods of non-neuraxial analgesia

Women in labour expect to have effective analgesia and are disappointed when this is not the case. The degree of analgesia desired varies widely, with two-thirds of women questioned wanting the minimum amount of drugs to allow them to cope with the pain of labour.[1] It is therefore important that we are able to offer a range of analgesic options and ensure we give good-quality information about the different options available to aid women in making a choice most appropriate to their needs.

This article will focus on non-neuraxial techniques of analgesia: non-pharmacological and pharmacological (Table 1).

Non-pharmacological

Labouring women use a range of non-pharmacological techniques for pain relief with varying effects and evidence for their use. There is some evidence to support the use of relaxation, immersion in water, acupuncture and massage, but insufficient evidence for the use of transcutaneous electrical nerve stimulation (TENS), sterile water injections, aromatherapy, biofeedback and hypnotherapy.[2] Even the techniques with poor evidence of efficacy are found useful by many women and can improve maternal satisfaction.

Relaxation

Relaxation techniques (breathing exercises) are often taught in antenatal classes. By focussing on breathing, it helps women to stay in control and conserve energy. Relaxation techniques are thought to provide analgesia and better maternal satisfaction with childbirth.[3]

Immersion in water

The Changing Childbirth Report by the Department of Health in 1993 led to the acceptance of immersion in water for labour and birth by the Royal College of Midwives in 1994. Baths are used to allow sufficient warm water (<37.5°C) to completely cover the pregnant abdomen. The use of birthing pools in the first stage of labour reduces the need for neuraxial techniques but does not affect the requirements for opioids, the duration of labour, the need for operative delivery or neonatal outcome.[4]

Transcutaneous electrical nerve stimulation (TENS)

A TENS machine consists of electrodes attached to a portable, hand-held device. The electrodes are attached to the skin over the dermatomes responsible for the painful stimulus (lower back) and an electrical current is applied and increased as required. TENS uses Melzack and Wall's gate control theory of pain and is a common treatment modality for both acute and chronic pain.

NICE does not support the use of TENS in established labour.[5] In 1994, it was used by 16% of low-risk primiparous labouring women.[6] Despite the limited evidence for TENS providing labour analgesia, most women said they would use TENS again in the future.[6]

Injections of sterile water

Injections of sterile water, also known as water blocks, are injections of approx 0.1 ml of sterile water, injected intracutaneously or subcutaneously, into four areas of the lower back. They are performed at the peak of contraction to minimize the pain from the injection itself. Water blocks became popular for relieving back pain in labour but a 2012 Cochrane review found no evidence of benefit.[7]

Pharmacological

Inhalational

Entonox: nitrous oxide (N_2O) was discovered in the 1700s but it was not until 1961 that Tunstall introduced it as Entonox: 50% nitrous oxide (N_2O) and 50% oxygen (O_2) to obstetric practice. Entonox is now the most commonly used method of analgesia for labour in the UK and is available in 100% of UK obstetric units[8] but it is not commonplace in the USA or many European countries.

Nitrous oxide is a colourless, odourless gas with a minimum alveolar concentration (MAC) of 105 and a blood gas partition

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Methods of non-neuraxial analgesia in labour

Non-pharmacological	Relaxation techniques
	Immersion in water
	Acupuncture
	Massage
	Transcutaneous electrical nerve stimulation (TENS)
	Sterile water injections
	Aromatherapy
	Biofeedback
	Hypnosis
Pharmacological — inhalational	Entonox
	Volatile anaesthetic agents
Pharmacological — parenteral opioids	Bolus
	Patient-controlled analgesia

Table 1

coefficient of 0.46 giving it the benefit of rapid onset and offset of action. Onset of action is within 30 seconds with full analgesic effect by 50 seconds and as it is eliminated via the lungs, it does not accumulate. It is thought to act via non-competitive inhibition of N-methyl-D-aspartate (NMDA) subtype of glutamate receptors.

Entonox is self-administered by breathing through a demand valve attached to either a mask or mouthpiece. As well as analgesia, Entonox can cause euphoria. The side effects: dizziness, hallucinations, nausea and vomiting and drowsiness, can sometimes limit use. Methionine synthase activity may be completely inhibited after a few hours of nitrous oxide administration.

A 2014 systematic review found very few good-quality studies on nitrous oxide use for labour pain and concluded that there was insufficient evidence for the effectiveness of nitrous oxide in managing labour pain.[8]

Most studies have not found adverse outcomes in the babies of mothers using nitrous oxide for labour but the quality of the studies has been poor. APGAR scores are no different between babies born to mothers who used nitrous oxide for labour and those mothers who used other or no pharmacological labour analgesia. Animal studies have found that fetal exposure to mixtures of anaesthetic drugs including nitrous oxide can cause significant neuroapoptosis during periods of rapid synaptogenesis (mid-gestation to several years old). We do not know the human relevance of these effects yet.

Entonox can be stored in cylinders making it suitable for women who choose to have home births. It has a pseudocritical temperature of −5.5°C at 137 bar. At this temperature it separates out into its two constituent components: N_2O and O_2. If the cylinder is then used, initially the woman will get little analgesia as most of the gas will be oxygen and then subsequently she will be at risk of inhaling a hypoxic mixture of nitrous oxide. This is important knowledge for community midwives — if their Entonox cylinder has been exposed to temperatures below freezing, it should be warmed at room temperature and the contents adequately mixed prior to use.

Volatile anaesthetic agents: A survey in 2007 found that 3% of obstetric units in the UK[9] were using volatile anaesthetic agents for labour analgesia. The fluorinated agents (e.g. isoflurane and sevoflurane) can be used at sub-anaesthetic doses to provide analgesia while maintaining airway reflexes. Inspired fractions of 0.8% sevoflurane have been found to provide optimum analgesia[10] with no increase in the incidence of post-partum haemorrhage. However, the use of volatile agents requires specialist equipment such as a draw-over Oxford miniature vaporizer and adequate scavenging in the labour room, which has practical and financial implications.

Opioids (Tables 2 and 3)

Bolus: About 95.5% of UK obstetric units use either intramuscular (IM) pethidine or diamorphine. Units usually co-administer antiemetics (73.7%) with IM opioids.[11] Tramadol, meptazinol and pentazocine are not widely used in the UK and there is no current evidence that they confer any advantage over pethidine.

Pethidine: Developed in 1939, pethidine (meperidine) has been approved for independent use by midwives since 1950. It was introduced into practice without any evidence from randomized controlled trials on its efficacy for labour pain and there have been concerns that its main effect is sedation rather than analgesia. In 2008, it was found to be the most commonly used intramuscular opioid analgesic in UK consultant-led maternity units (84.4%).[11]

Intramuscular pethidine acts within 40 minutes to give 2—3 hours of clinical effect. It is metabolized in the liver to norpethidine and pethidinic acid, which are further conjugated before being excreted in the urine. Norpethidine is an active metabolite with half the analgesic effect of pethidine. However, its effects cannot be reversed with naloxone.

Pethidine is highly lipid soluble and crosses the placenta: at delivery, the mean cord blood concentration is 75—90% of the maternal venous concentration. Maternal administration of pethidine has significant effects on the fetus: there is maximal risk of neonatal respiratory depression if delivery occurs within 2—3 hours of the maternal dose. Altered neonatal neurobehaviour, decreased wakefulness and attentiveness and impaired breast-feeding are associated with maternal pethidine use.

Diamorphine is a highly lipid-soluble prodrug which itself has no analgesic properties. Between 2005 and 2006, it was used in

Side effects of opioids

Maternal side effects	Fetal/neonatal side effects[a]
Nausea and vomiting	Loss of fetal heart variability
Sedation	Respiratory depression
Dizziness	Sedation
Respiratory depression	Delay in breast-feeding
Euphoria/dysphoria	Decreased neurobehavioural scores
Delayed gastric emptying	
Hallucinations	
Urinary retention	

[a] No current evidence for these fetal/neonatal side effects with remifentanil.

Table 2

Properties of commonly used opioids in obstetric analgesia

	Pethidine	Diamorphine	Remifentanil
Dose	50–150 mg	5–10 mg	10–40 μg bolus every 2–3 minutes
Most common route for obstetric analgesia	IM	IM	IV PCA
Type of opioid	Synthetic phenylpiperidine derivative	Semi-synthetic diacetylated morphine derivative	Synthetic phenylpiperidine derivative
Receptor	Mu agonist (kappa and delta to lesser extent)	Mu agonist (kappa and delta to lesser extent)	Mu agonist (pure)
Introduced	1940	1898	1997
Degree of protein-binding	60%	40%	70%
Potency compared with morphine (morphine = 1)	0.1	2	200
Metabolism	Liver	Plasma	Plasma
Metabolites	Norpethidine (active) pethidinic acid	6-Monoacetylmorphine (active)	Remifentanil acid (1/300th–1/4600th potency remifentanil)
Excretion	Urine	Urine 7–10% biliary excretion	Urine
Elimination $t_{1/2}$	4 hours	3 minutes	5–30 minutes
Context sensitive $t_{1/2}$			3.5 minutes
Caution with use	Renal/hepatic impairment Epilepsy (proconvulsant effect of pethidine and norpethidine) Avoid if had monoamine oxidase inhibitor in last 2 weeks	Renal/hepatic impairment	Other opioids administered within the last 4 hours, intrauterine fetal death, high or low BMI, obstructive sleep apnoea, concurrent magesium sulphate administration, prematurity

Table 3

34.1% of consultant-led maternity units[11] but this percentage is likely to be higher now as there was a diamorphine shortage in the UK in 2005.

In the plasma, it undergoes ester hydrolysis to form the active metabolite 6-monoacetylmorphine which is then converted to morphine. A small amount of diamorphine is excreted unchanged in the urine while 50–60% of diamorphine is excreted as morphine.

A blinded, randomized, controlled trial compared 7.5 mg IM diamorphine to pethidine 150 mg IM and found that diamorphine provided slightly improved pain relief after 1 hour but was associated with longer labours overall. Of note is that both intramuscular diamorphine and pethidine had limited analgesic effects, with the mean visual analogue scale score for the diamorphine group decreasing from 8 to 6, and the pethidine group from 8 to 7 at maximal effect. There were no significant differences between APGAR scores or the need for neonatal resuscitation between the two groups.[12]

Patient-controlled opioid analgesia for labour: Many opioids have been used for labour pain via intravenous patient-controlled systems (PCAs) with much interest in remifentanil in this setting due to its favourable pharmacokinetic profile. Remifentanil is the most common drug used for labour PCA in the UK where a live birth is anticipated with 36% of delivery units in the UK offering remifentanil PCA as a labour analgesia option in 2011.[9,13]

Remifentanil PCA: *Pharmacology*: Remifentanil is an ultra-short-acting, synthetic mu-opioid receptor agonist. It has a rapid onset with effect-site concentrations peaking at 1.2 minutes. Due to its ester linkage it can be hydrolysed by non-specific tissue and plasma esterases to remifentanil acid (1/300th–1/4600th of the potency of remifentanil), which is then excreted in the urine.

Practical set-up: Remifentanil PCA should be administered via a dedicated cannula. Reported bolus doses vary but a common regimen is a 10–40 μg bolus with a lockout of 2–3 minutes. Continuous pulse oximetry is required and one-to-one midwifery care is mandatory.

Efficacy: Remifentanil PCA lowers pain scores more effectively than Entonox or intramuscular pethidine but not as much as epidural analgesia. Maternal satisfaction scores with remifentanil are higher than with other IV or IM opioids and slightly lower than with epidurals. Many units allow the concurrent administration of remifentanil PCA and Entonox.

The RESPITE trial found that the women receiving remifentanil patient-controlled analgesia had half the conversion rate to epidural (19%) than the intramuscular pethidine group (41%) and interestingly, the rate of instrumental delivery was 26% with IM pethidine and 15% with remifentanil PCA.[14]

Several studies have shown that VAS (visual analogue scale) pain scores fall in the first hour of remifentanil PCA analgesia but then rise again in the following few hours. This could be due to increasing pain as labour progresses, tolerance to remifentanil or both. Background infusions have been used but carry a higher

risk of arterial desaturation. A potential solution to this may be to use a stepwise bolus regime where the size of the remifentanil bolus can be increased if required as labour progresses as long as maternal side effects allow.[16]

Maternal side effects: Mild nausea or itching is relatively common with remifentanil PCA but rarely requires medical intervention. Remifentanil PCA carries a risk of maternal desaturation with the remiPCA SAFE group reporting oxygen saturation <94% in 24.7% of patients.[15] There have been case reports of respiratory and cardiorespiratory arrest with remifentanil PCA for labour but with strict protocols for its use, such as those used by the remiPCA SAFE network, severe adverse effects in the mother are extremely rare; the remiPCA SAFE group found no need for maternal ventilation or cardiopulmonary resuscitation in 9500 patients receiving remifentanil PCA for labour analgesia.[17]

Fetal effects: Remifentanil crosses the placenta to a significant degree (umbilical vein:maternal artery ratio = 0.88) but the mean umbilical vein:umbilical artery ratio of 0.29 suggests a combination of rapid metabolism and rapid redistribution of remifentanil in the fetus. No studies have found any excess of non-reassuring cardiotocograph traces. The 6-year audit of outcomes from the remiPCA SAFE group found that neonatal severe adverse events (need for cardiopulmonary resuscitation) potentially related to remifentanil were rare, documented in 13/4559 neonates (0.3%), compared to other large retrospective studies where neonatal resuscitation was necessary in 0.08% to 1.48% of live births without remifentanil PCA. Supplemental oxygen was required in 5% of neonates (5.0%). In 2013, the remiPCA SAFE group recommended discontinuing remifentanil PCA 5-10 minutes prior to cord clamping.[15] ◆

REFERENCES

1 Green JM. Expectations and experiences of pain in labour: findings from a large, prospective study. *Birth* 1993; **20:** 65–72.

2 Jones L, Othman M, Dowswell T, et al. Pain management for women in labour: an overview of systematic reviews. *Cochrane Database Syst Rev*, 2012. Art. No.: CD009234.

3 Smith CA, Levett KM, Collins CT, Crowther CA. Relaxation techniques for pain management in labour. *Cochrane Database Syst Rev*, 2011. Art. No.: CD009514.

4 Cluett ER, Burns E. Immersion in water in labour and birth. *Cochrane Database Syst Rev*, 2009. Art. No.: CD000111.

5 National Institute for Health and Clinical Excellence. Intrapartum care: management and delivery of care to women in labour. CG55. 2007, http://guidance.nice.org.uk/cg190 (accessed December 2015).

6 Dowswell T, Bedwell C, Lavander T, Neilson JP. Transcutaneous electrical nerve stimulation (TENS) for pain management in labour. *Cochrane Database Syst Rev*, 2009. Art. No.: CD007214.

7 Derry S, Straube S, Moore RA, Hancock H, Collins SL. Intracutaneous or subcutaneous sterile water injection compared with blinded controls for pain management in labour. *Cochrane Database Syst Rev*, 2012. Art. No.: CD009107.

8 Likis FE, Andrews JC, Collins MR, et al. Nitrous oxide for the management of labour pain: a systematic review. *Anaesth Analg* 2014; **118:** 153–67.

9 Saravanakumar K, Garstang JS, Hasan K. Intravenous patient controlled analgesia: a survey of UK practice. *Int J Obstet Anesth* 2007; **16:** 221–5.

10 Yeo ST, Holdcroft A, Yentis SM, et al. Analgesia with sevoflurane during labour: II. Sevoflurane compared with entonox for labour analgesia. *Br J Anaesth* 2007; **98:** 110–5.

11 Tuckey JP, Prout RE, Wee MYK. Prescribing intramuscular opioids for labour analgesia in consultant-led maternity units – survey of UK practice. *Int J Obstet Anesth* 2008; **17:** 3–8.

12 Wee MYK, Tuckey JP, Thomas PW, Burnard S. A comparison of intramuscular diamorphine and intramuscular pethidine for labour analgesia: a two-centre randomised blinded controlled trial. *Br J Obstet Gynaecol* 2014; **121:** 447–56.

13 Howie KM, Millar S. Usage of remifentanil patient controlled analgesia in labour in the UK. *Int J Obstet Anesth* 2011; **20**(supp 1)**:** S36.

14 Wilson MJA, MacArthur C, Hewitt CA, et al. Intravenous remifentanil patient-controlled analgesia versus intramuscular pethidine for pain relief in labour (RESPITE): an open-label, multicentre, randomised controlled trial. *Lancet* 2018; **392:** 662–72.

15 Melber AA, et al. Remifentanil patient-controlled analgesia in labour: six-year audit of outcome data of the RemiPCA SAFE Network (2010–2015). *Int J Obstet Anesth* 2019; https://doi.org/10.1016/j.ijoa.2018.12.004. Accessed on 18/05/2019.

16 Tveit TO, Halvorsen A, Seiler S, Rosland JH. Efficacy and side effects of intravenous remifentanil patient-controlled analgesia used in a stepwise approach for labour: an observational study. *Int J Obstet Anesth* 2013; **22:** 19–25.

17 Melber AA. Remifentanil patient-controlled analgesia (PCA) in labour – in the eye of the storm. *Anaesthesia* 2019; **74:** 277–9.

