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## 21.1 Introduction

Since biblical times, the labor process has been recognized as being one of the most painful human experiences. Early treatments varied widely, according to the cultural and religious practices of the time. In the middle ages, treatments such as amulets, magic girdles, and readings from the Christian liturgy were considered to be appropriate treatment. More invasive pharmacologic treatments such as the use of soporific sponges (a mixture of biologically active plants, inhaled or ingested) were sufficiently potent to cause unconsciousness. Of interest, bloodletting was used until the middle of the nineteenth century to cause swooning and thus pain relief [1].

Physicians and midwives that wished to relieve labor pain had to overcome a number of obstacles. Pain, although severe, was known to be self-limited and was not thought to be inherently dangerous to the health of the mother and newborn. In contrast, many treatments of the day carried significant risks to both. It is small wonder that a non- interventional approach was preferred.

Over the last 100 years, pain relief options have become safer and more effective. It became clear that medications that are given to the mother may influence the course of labor and may depress the baby at the time of delivery. Regional analgesia became an important method of providing effective pain relief. However, questions persisted about the effect on the progress of labor and subtle changes in the newborn. Often, fears of harm are based on poorly designed studies that were more likely to demonstrate the researchers' biases than truth.

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In this chapter, we will review the evidence base for providing labor analgesia. We will begin with a definition of “evidence-based medicine.” We will then discuss how to formulate a clinical question and to formulate a plan for best practice. Finally, we will discuss some of the topics that have a clear evidence base and areas for future research.

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## 21.2 Evidence-Based Medicine

### 21.2.1 Definition

*Evidence-based medicine* is “the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients” [2]. This approach must take the available clinical expertise and experience into account. In addition, patient preferences and expectations must be integrated into the process.

### 21.2.2 How to Use an Evidence-Based Approach

This approach can be broken down into four well-defined steps.

#### 21.2.2.1 Ask a Clinical Question

Often, one is faced with a patient with a clinical condition that requires treatment. When considering labor analgesia, one is faced with a number of choices each with different advantages and disadvantages depending on the patient’s expectations, skills, and preferences of the healthcare providers, resources available and other considerations. The “PICO” format is often used as a template to help formulate the question. When considering labor analgesia, the Population must be considered. Are the subjects nulliparous, multiparous, or mixed? Are they healthy or are there obstetric or medical factors that place the patients at risk for adverse outcome? The Intervention is usually the experimental treatment. Examples might be method of initiation of analgesia (*combined spinal/epidural*, *epidural* alone), timing of the analgesia (early in labor or later), or drug used (ropivacaine, bupivacaine). The Comparator is the control. It is rare for *placebo* to be used as a comparator in this setting except for some non-pharmacologic treatments such as *transcutaneous electrical nerve stimulation* (TENS) or *intra-dermal sterile water* injections [3, 4]. In other trials, the control is almost always at least thought to be active. It could be *parenteral opioid* analgesia, a different form of regional block, or a different mode of maintaining analgesia. The main Outcomes should be clearly defined. Often, when drugs are compared, the main outcome is a measure of quality of analgesia. Sometimes, the main outcome is a particular side effect (operative delivery, motor block, nausea) or benefit (cord pH, maternal satisfaction). An example of how the

**Table 21.1** The table illustrates how to use the “PICO” format to answer a clinical question

Item	Example (from Wong et al. [5])
Population	Healthy nulliparous patients requesting epidural analgesia for pain relief
Intervention	Intrathecal fentanyl, followed by an epidural test dose before 4 cm dilation. Standard epidural infusion and patient controlled bolus maintenance
Comparison group	Parenteral opioid before 4 cm dilation, followed by epidural analgesia with standard infusion and patient controlled bolus maintenance
Outcome (primary)	Incidence of cesarean section

The question in this case is: Is there harm in initiating epidural analgesia early in labor?

PICO format could be used to help formulate a treatment plan is shown in Table 21.1.

When designing a clinical trial, the best type of study (randomized controlled trial, cohort study, etc.) will depend on the clinical question and feasibility. Therefore, the “*PICOT*” format (with the “T” for Type of study) is often used to formulate research questions.

### 21.2.2.2 Search for the Best Evidence

Once the clinical question has been formulated, the next step is to search for the most reliable information available. A hierarchy of evidence has been formulated, with information at the highest level being (theoretically) the least susceptible to bias. In general, the hierarchy of evidence is shown in Table 21.2.

The type of information available will depend on the exact question. For example, the question posed in Table 21.1 describes two treatments (early vs. late epidural analgesia) and asks about common treatment harms (cesarean section). In that case, the most reliable information, as shown in Table 21.2, is a systematic review of randomized controlled trials. However, questions concerning diagnostic tests (e.g. will a test dose before epidural labor analgesia prevent harm?), or prognosis (e.g. what is the natural history of dural puncture headache with a large gauge needle?), may require other types of information. A summary of the hierarchy of evidence, depending on the clinical question, has recently been published [7]. However, the hierarchy in Table 21.2 pertains to the most common issues in labor analgesia therapy.

### 21.2.2.3 Critically Appraise and Combine the Evidence

Fortunately, clinicians rarely have to rely on individual studies to formulate a treatment plan. Many topics related to pain relief in labor have recently been systematically reviewed and are available in evidence-based guidelines [8, 9]. These are examples of guidelines that were created using recognized methodology by experts in the field and tested for validity by clinicians. In addition to making recommendations, the strength of the recommendations, using a modification of Table 21.2, is also reported. These guidelines are updated periodically to take into account new information.

**Table 21.2** The hierarchy of evidence (adapted from [6])

Level	Type of information
1a	A systematic review of well-designed, homogeneous randomized controlled trials
1b	Single large randomized controlled trial
1c	All or none trial
2a	A systematic review of homogeneous cohort studies
2b	Individual cohort study or low quality RCT
2c	Outcome studies
3a	Systematic review of case controlled studies
3b	Individual case controlled studies
4	Case series or seriously flawed studies of other designs
5	Expert opinion
6	Nonhuman (animal/in vitro) studies

#### 21.2.2.4 Determine the Best Treatment for Your Patient

While randomized controlled trials and systematic reviews can often be used as a guide to treatment, they do not give the whole picture. Factors such as the expertise of the clinician, expectations of the patient, and the resources available must also be considered when treating individual patients. For example, epidural analgesia initiated with a low concentration of *local anesthetic* may reduce the incidence of instrumental vaginal delivery [10], but it may not be the best treatment for a patient with rapidly progressing labor.

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### 21.3 Topics in Analgesia for Labor with Systematic Review or Large RCT Support (Level 1)

There have been many randomized controlled trials that help guide practice in providing labor analgesia for our patients. Some are quite large and definitive, while others are small and yield a less precise estimate of effect. Taken together in a systematic review, a consistent pattern often emerges. Table 21.3 summarizes some of the questions that have been thoroughly studied and have level 1 evidence to support recommendations.

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### 21.4 Conclusions

The optimal provision of analgesia in labor requires application of evidence-based medicine, “the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients.” This involves four steps:

- (1) Asking a clinical question; the “PICO” format can be used as a template where the clinician considers the *Population*, the *Intervention*, the *Comparator*, and the *Outcomes* when formulating a question.

**Table 21.3** Topics in analgesia for labor

Clinical question	Reference #	Level of evidence	Best evidence	Recommendation
Compared to other forms of analgesia, how does epidural analgesia affect the progress of labor?	[11]	1A	<ul style="list-style-type: none"> <li>– No effect on cesarean section rate</li> <li>– May increase the risk of operative vaginal delivery rate</li> <li>– No effect on length of first stage of labor</li> <li>– Prolongation of second stage of labor by about 13 min</li> </ul>	<ul style="list-style-type: none"> <li>– Epidural analgesia provides the most effective analgesia compared to other forms</li> <li>– Fear of an increased incidence of cesarean section is unfounded</li> <li>– There may be an increased incidence of operative vaginal delivery</li> </ul>
Compared to opioid analgesia, what is the efficacy of epidural analgesia and incidence of major side effects?	[12]	1A	<ul style="list-style-type: none"> <li>– Epidural analgesia provided superior analgesia during the first and second stages of labor and superior maternal satisfaction with analgesia</li> <li>– There was no difference in the incidence of long term back pain</li> <li>– There was a higher incidence of maternal fever and hypotension in the epidural group</li> <li>– There was a higher incidence of naloxone use and low 1 min Apgar scores in the opioid group</li> </ul>	
Does administration of epidural analgesia early in labor increase the incidence of cesarean section or operative vaginal delivery compared to later administration?	[13]	1A	There was no difference in the incidence of cesarean section or operative vaginal delivery when epidural analgesia was administered in the latent phase of labor compared to the active phase of labor	There is no need to delay epidural analgesia until the active phase of labor

(continued)

**Table 21.3** (continued)

Clinical question	Reference #	Level of evidence	Best evidence	Recommendation
What are the effects of higher concentrations (>0.1 % bupivacaine) of local anesthetic compared to lower concentrations (≤0.1 % bupivacaine) when used for maintenance of epidural labor analgesia?	[10]	1A	<ul style="list-style-type: none"> <li>– No difference in maternal pain scores, maternal nausea, hypotension, or fetal heart rate abnormalities</li> <li>– No effect on cesarean section rate</li> <li>– Higher operative vaginal delivery rate</li> <li>– Increased incidence of lower limb motor block, with fewer patients able to ambulate</li> <li>– Increased incidence of urinary retention</li> <li>– Prolonged second stage of labor</li> </ul>	<ul style="list-style-type: none"> <li>– Low concentrations of local anesthetic are equally effective but cause fewer adverse effects than higher concentrations</li> <li>– Initial concentrations of bupivacaine should be less than 0.1 %</li> </ul>
What are the advantages and disadvantages of combined spinal–epidural compared to an epidural alone for initiation of labor analgesia?	[14]	1A	<ul style="list-style-type: none"> <li>– CSE has a faster onset of analgesia (~3 min), but increases the risk of pruritis</li> <li>– No differences in maternal satisfaction, hypotension, mode of delivery, or neonatal outcome</li> </ul>	Overall there is little difference between the two methods of analgesia, and it is not possible to recommend either method as superior
How does patient-controlled epidural analgesia (PCEA) compare with continuous epidural infusion alone for maintenance of analgesia?	[15]	1A	Patient controlled analgesia required fewer unscheduled clinician interventions, used less local anesthetic, and caused less lower limb muscle weakness than continuous infusion	Where possible, patient controlled analgesia is preferred for maintenance of labor analgesia compared to continuous infusion alone
What is the best strategy for maintaining	[8, 16]	1A	– The addition of a continuous infusion to PCEA	A continuous infusion should be

(continued)

**Table 21.3** (continued)

Clinical question	Reference #	Level of evidence	Best evidence	Recommendation
epidural analgesia with PCEA?			provides better analgesia and reduces clinician workload compared to PCEA alone – There are a large number of regimens that specify different bolus doses, lockout intervals, and infusion rates, but there is insufficient evidence to show one is superior	added to PCEA regimens
What is the efficacy of intermittent mandatory boluses and PCEA compared to continuous background infusion and PCEA for maintenance of analgesia?	[17]	1A	– Intermittent mandatory boluses may reduce the dose of local anesthetic, reduce second stage of labor duration, and increase maternal satisfaction – Too few patients studied to determine effect on clinician workload and other outcomes	This is a new and promising mode of maintenance of epidural labor analgesia, but more studies are required to make definitive recommendations on its use
Are there clinically important differences between the use of bupivacaine or ropivacaine for epidural analgesia?	[18, 19]	1A 1B	– Low concentrations of both local anesthetics provide effective labor analgesia – Bupivacaine has a higher incidence of motor block compared to ropivacaine after prolonged usage – There is no significant difference between the two	There is insufficient information to recommend either ropivacaine or bupivacaine as superior for routine labor analgesia

(continued)

**Table 21.3** (continued)

Clinical question	Reference #	Level of evidence	Best evidence	Recommendation
			agents in maternal satisfaction, mode of delivery, or neonatal outcomes – Currently, ropivacaine is more costly than bupivacaine – Overall there is little difference between the two agents in clinically used concentrations for epidural analgesia	
What is the effect of systemic opioids for labor analgesia?	[20, 21]	1A 1B	– Systemic opioids provide minimal analgesia for labor – They are associated with maternal nausea, vomiting, and sedation – There is insufficient evidence for the superiority of particular opioids in terms of analgesia – Pethidine is associated with a higher incidence of drowsiness and nausea compared to other opioids	– Systemic opioids are less effective than regional techniques and are associated with adverse maternal effects – They may be considered if regional techniques are contraindicated
Compared to no analgesia or placebo what is the effect of nitrous oxide on labor pain, progress of labor, and maternal side effects?	[22]	1A	– Nitrous oxide provides some pain relief during the first and second stages of labor – There was no effect on the progress of labor, incidence of cesarean section, or incidence of operative vaginal delivery	Nitrous oxide is a reasonable alternative for labor analgesia in institutions equipped to limit exposure to healthcare personnel

(continued)



**Table 21.3** (continued)

Clinical question	Reference #	Level of evidence	Best evidence	Recommendation
			<ul style="list-style-type: none"> <li>– There is an increased incidence of nausea, vomiting, drowsiness, and dizziness</li> </ul>	
What is the effect of transcutaneous electrical nerve stimulation (TENS) compared to placebo or standard care for the treatment of labor analgesia?	[23]	1A	<ul style="list-style-type: none"> <li>– TENS does not reduce the severity of labor pain or increase satisfaction with labor pain management</li> <li>– No difference in the incidence of cesarean section or operative vaginal delivery</li> <li>– No difference in neonatal outcomes</li> </ul>	TENS has a limited role to play in treatment of labor analgesia
What is the effect of sterile water papule injections compared to placebo or standard care for the treatment of labor analgesia?	[24]	1A	<ul style="list-style-type: none"> <li>– No evidence of analgesic efficacy</li> <li>– No significant adverse effects or differences in maternal or neonatal outcomes</li> </ul>	Further study is required to determine whether or not intradermal sterile water papules are effective for labor analgesia
What is the effect of acupuncture or acupressure compared to placebo or standard care for the treatment of labor analgesia?	[25]	1A	<ul style="list-style-type: none"> <li>– Some pain reduction reported compared to placebo, standard care, or no treatment</li> <li>– May reduce the need for pharmacologic intervention</li> <li>– No significant adverse effects reported</li> <li>– There were no studies in the analysis that had a low probability of bias</li> </ul>	Insufficient data to determine the role of acupuncture or acupressure in the treatment of labor pain

- (2) Searching for the best evidence; this will depend on the exact question formulated. There are established hierarchies of evidence based on study design which guide clinicians in determining the most suitable evidence base.
- (3) Critically appraising and combining the evidence; systematic reviews, meta-analyses, and evidence-based guidelines can provide clinicians with useful combined results and recommendations from a broad evidence base.
- (4) Determining the best treatment for specific patients taking into consideration their unique characteristics or clinical situations.

There are a number of topics in labor analgesia which have been extensively studied, with high level evidence available to support clinical practice. Neuraxial regional analgesia remains the most effective available modality for labor pain relief. Epidural analgesia does not increase the risk of cesarean delivery, although the second stage of labor may be prolonged, and there may be an increased risk of instrumental delivery. Epidural analgesia may be provided early in labor without affecting labor outcome. Although systemic opioids and nitrous oxide have some analgesic efficacy and may be considered if neuraxial techniques are contraindicated, they are less effective and can cause significant maternal adverse effects. There is little evidence to suggest that non-pharmacological techniques of analgesia (e.g., TENS, acupuncture, sterile water injections) are efficacious.

When initiating neuraxial analgesia, there is little difference between a combined spinal-epidural technique and epidural technique alone. Low concentrations of local anesthetic (e.g.,  $\leq 0.1\%$  bupivacaine) should be used for maintenance of analgesia to reduce the risks of motor block and instrumental delivery. Either ropivacaine or bupivacaine used at low concentrations can be safely and effectively used for epidural analgesia. PCEA along with background infusion is an effective and safe maintenance strategy. There is developing evidence that intermittent mandatory boluses may be superior to continuous infusion when combined with PCEA for maintenance of epidural analgesia; however, further research is required in this area.

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