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COMPARISON OF EPIDURAL AND INTRAVENOUS FENTANYL PATIENT-CONTROLLED ANALGESIA AFTER CESAREAN SECTION UNDER EPIDURAL ANESTHESIA WITH CHLOROPROCAINE

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A thesis submitted in partial fulfillment of the requirements for the degree of Master of Science at Virginia Commonwealth University

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Abstract

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This study compared two methods of postcesarean fentanyl patient-controlled analgesia (PCA). Fentanyl was administered intravenously (PCA_I) or epidurally (PCA_E) following cesarean section under epidural chloroprocaine anesthesia. Twenty-one ASA I and II parturients were randomly assigned to receive fentanyl PCA_I ($n = 9$) or PCA_E ($n = 12$). At surgical completion fentanyl 1.0 mcg/kg was given and the PCA initiated with a dose of 30 mcg, a lock-out interval of 10 minutes, a maximum dose of 180 mcg/hr, and no basal rate. Data were collected over 24 hours including visual analog scale (VAS) pain scores, plasma fentanyl levels, total fentanyl usage, and side effects.

Surgical time was significantly longer for the PCA_I group ($p = 0.0213$). There was no difference in VAS scores until 24 hours when the PCA_E group's were significantly lower ($p = 0.0295$). The PCA_E group

almost always had lower VAS scores. Total fentanyl usage was significantly lower for the PCA_E group ($p = 0.050$). There was no significant difference in plasma fentanyl levels, side effects, or patient satisfaction. The data revealed that both methods provided adequate postoperative analgesia and epidural fentanyl provided both local and systemic mediated analgesia.

Chapter One

Introduction

Introduction

The epidural catheter technique is the anesthetic method of choice for women undergoing cesarean section due, in part, to the normal physiologic changes of pregnancy that place women at a higher risk under general anesthesia. The epidural catheter is also useful in providing postoperative analgesia. Studies demonstrate that epidural analgesia is comparable and possibly superior to intravenous (IV) analgesia (Grant et al., 1992; Welchew & Breen, 1991). Thus, epidural catheters are an ideal means to provide both anesthesia and analgesia for the parturient undergoing cesarean section.

Chloroprocaine (CP), an amino ester local anesthetic, is highly valued as an epidural agent in obstetric anesthesia because of its rapid onset, rapid metabolism, short duration, low toxicity, and minimal placental transfer (Shnider & Levinson, 1993). These characteristics make this the drug of choice in emergent cesarean sections and mild fetal distress scenarios. However, CP is not without problems. It appears that epidurally administered CP reduces the effectiveness of subsequently administered local anesthetics and mu-receptor agonists, such as bupivacaine (BP) and morphine, respectively (Hodgkinson, Husain, & Bluhm, 1982; Kotelko et al., 1983). This apparent antagonism may interfere with the quality of anesthesia and analgesia desired.

Chloroprocaine's opioid antagonism seems to be limited to fentanyl and morphine, both mu-receptor agonists. Kotelko et al. (1983) first described the antagonistic effect of CP on opioids. They compared postoperative epidural morphine analgesia after various epidurally administered local anesthetics for cesarean section and found a significant decrease in morphine's efficacy after CP anesthesia. Many researchers have confirmed these results. Malinow et al. (1988) found similar effects of reduced analgesic duration when epidural fentanyl was given after epidural CP anesthesia. It has since been reported that even when CP is used solely as a test dose, reduced opioid efficacy occurs (Eisenach, Schlairet, Dobson, & Hood, 1991).

Fentanyl is the preferred analgesic for many operative procedures, including cesarean section, because of its high potency, cardiovascular stability, absence of histamine release, and low incidence of late-onset respiratory depression when administered in the central neuraxis (Stoelting, 1991). Given the value of CP as an anesthetic and fentanyl as a postoperative analgesic, the ability to overcome CP's antagonism of fentanyl and determine the mechanism by which this occurs is of importance to anesthesia providers.

Though the exact mechanism of CP's opioid antagonism remains a mystery, Fragneto, Moore, Pan, Ross, and Long (1994) found that the antagonism may be overcome by administering an epidural fentanyl bolus and patient controlled epidural analgesia (PCA_E) after epidural CP anesthesia. In fact, when compared to the epidural lidocaine (LD) control group, there was no significant difference in the effectiveness of fentanyl between the two groups. Thus, at least one study supports the idea that CP's opioid antagonism may be overcome. The mechanism by which this occurs, however, is unknown.

Researchers have differing opinions about the site of action of epidural opioids. Some suggest that opioids act locally at the site of the nerve roots, whereas others suggest the opioid is absorbed by the epidural veins and acts systemically (Grant et al., 1992; Loper et al., 1990). Another possibility is that there is a combined mechanism of action. This study attempts to address the issue by comparing serum fentanyl levels and pain scores of parturients receiving either IV or epidural fentanyl after epidural CP anesthesia for cesarean section.

Statement of Purpose

The purpose of this study is to determine whether fentanyl PCA_E, when given after epidural CP for elective (nonlaboring) cesarean section, mediates analgesia through a local, systemic, or combined mechanism. A comparison to IV fentanyl patient controlled analgesia (PCA_I) is used to determine this effect.

Statement of the Problem

Chloroprocaine causes an antagonism of fentanyl when both are given epidurally. This antagonistic effect can be overcome with the use of a fentanyl PCA_E, but the mechanism of action is unknown. Does fentanyl act locally at the nerve roots and by diffusion into the cerebrospinal fluid (CSF) or is it absorbed into the systemic circulation by the epidural veins and act centrally? Or do both of these occur providing a combined mechanism of action?

Hypothesis

There is no difference in analgesia, plasma fentanyl levels, and side effects between fentanyl PCA_E and PCA_I after epidural CP for elective (nonlaboring) cesarean section.

Variables

The independent variables are fentanyl administered by PCA_E and PCA_I. Fentanyl PCA_I, which manifests itself systemically, is used as the comparison group. The dependent variables are visual analog scale (VAS) pain scores, side effects, serum fentanyl levels and total fentanyl usage. Side effects include sedation, nausea, vomiting, and pruritus.

Definition of Terms

Epidural catheter. An epidural catheter is a thin, flexible, plastic catheter which is threaded into the epidural space after puncturing the lumbar 2-3 or 3-4 vertebral interspace. The catheter is used to administer local anesthetics to provide surgical anesthesia for cesarean section and to administer opioids for postoperative analgesia.

Intravenous catheter. An IV catheter is a canulla inserted into a peripheral vein which is used to administer opioids for postoperative analgesia.

Patient controlled analgesia. Patient controlled analgesia (PCA) is a mechanical device which is programmed to deliver a specific dose of opioid by patient demand. The device is used to infuse opioids by the IV or epidural routes.

Assumptions

The following statements are valid assumptions about this study:

1. Patients were American Society of Anesthesiologists (ASA) class I and II without undiagnosed medical conditions.

2. Intrapartum complications involving visceral or uterine damage were nonexistent.

3. The anesthesia providers responsible for placement of the epidural catheter used for cesarean section and postoperative analgesia included student nurse anesthetists, staff nurse anesthetists, anesthesiology residents, and anesthesiologists.

4. A protocol was followed to assure thorough evaluation and assessment of patients prior to initiating anesthetic intervention, including patient counseling concerning this intervention.

5. Patients were compliant with the use of PCA.

6. All data recorded in the medical records were accurate.

7. Patients were honest in reporting a negative history of IV opioid abuse.

Limitations

The following statements are valid limitations for this study:

1. The population was limited to parturients undergoing elective (nonlaboring) cesarean section at a large, urban university hospital.

2. Variability exists in each individual's perspective of pain; the rating of pain is subjective.

3. The sample size was small which decreases the ability to generalize the results to a larger group.

4. Differences exist in the level of surgical expertise which may influence the level of postoperative pain.

5. Differences in the data collection techniques of nurses and data collectors may cause inaccuracies to exist.

Delimitations

This study consists of pregnant females undergoing elective (nonlaboring) cesarean section at a large, urban university hospital between February 1996 and August 1997. Though a target group of 40 women was desired for this study, data were collected on only 21.

Conceptual Framework

In order to understand CP's opioid antagonism, one must be familiar with several aspects of neural physiology and how pharmacologic agents are utilized within this system. First, nerve impulse propagation and conduction is discussed as well as how local anesthetics block this process. Second, a basic explanation of pain pathways is given with specific focus on the endogenous opioid receptor system. Third, epidural physiology and how local anesthetics and opioids act in the epidural space is discussed.

Nerve Physiology

The basic unit of the nervous system is the neuron, a cell which generates and conducts impulses to and from the central nervous system (Cousins & Bridenbaugh, 1988). Neurons are composed of a cell body, an axon, and dendrites, and are categorized as sensory (afferent), motor (efferent) and sympathetic (efferent). Axons generate and conduct impulses. Sensory neurons send impulses from specialized peripheral branches to the spinal cord. Motor neurons send impulses from the spinal cord to various effector organs. Sympathetic neurons are

controlled by the autonomic nervous system but work in conjunction with the entire central nervous system.

Since the axon generates and conducts impulses, certain characteristics of this part of the neuron must be understood. Whether or not an axon is myelinated affects how the impulse is transmitted and the speed at which this occurs. Impulses travel along unmyelinated axons in a uniform manner. A change in the permeability of ionic channels in the axonal membrane causes a change in electrical voltage, depolarizing the cell (Cousins & Bridenbaugh, 1988). Myelinated axons have regular interruptions called nodes of Ranvier; it is only here that changes in membrane permeability and depolarization can occur. Thus, impulses spread from node to node on a myelinated axon, allowing for significantly faster conduction velocities.

Nerve impulses are generated and conducted along an axon partly because of differences in the concentration gradient of ions (mainly sodium and potassium) across the axonal membrane. Potassium ions (K^+) are contained mainly in the intracellular space while sodium ions (Na^+) are mainly extracellular. Potassium ions selectively move out of the cell causing a slight negative charge inside the cell and a slight positive charge outside the cell. This is called the resting membrane potential (Berne & Levy, 1993). When an action potential (impulse) larger than threshold is generated Na^+ rushes into the cell, via Na^+ channels, causing it to depolarize. The cell becomes positively charged inside causing K^+ to efflux out of the cell, repolarizing it. Depolarization is associated with skeletal muscle contraction and repolarization with relaxation.

Local Anesthetics and Nerve Impulse Conduction

Local anesthetics are bases which exist *in vivo* in an equilibrium state between a nonionized, neutral species and an ionized, charged species. The ionized species can block nerve impulse conduction at the axon by interfering with Na^+ channel function (Cousins & Bridenbaugh, 1988). It is thought that the neutral form of the local anesthetic passes through the axonal membrane, where it becomes ionized at its site of action. The ionized form of the drug blocks the Na^+ channel's ability to generate and to propagate impulses.

Local anesthetics have pKa values between 7.5 and 9.5, thus existing more as a charged than an uncharged species while in solution (Cousins & Bridenbaugh, 1988). Because of this, the pH in the body can impact the potency of these drugs. An alkaline extracellular pH favors the neutral species, allowing more local anesthetic to pass through the axonal membrane and collect at its site of action. An acidic cytoplasmic pH favors the ionized species allowing a more potent blockade at the site of action.

The ability of a local anesthetic to block nerve conduction depends on many factors, including the diameter of the nerve and whether or not it is myelinated. Nerve fibers are classified according to their function and size (see Table 1). In general, the larger the fiber the more difficult it is to block because local anesthetic must diffuse through the entire nerve in order to completely block its core fibers. Myelinated fibers are also more difficult to block than unmyelinated fibers. Myelin acts as a barrier between the local anesthetic and the nerve fibers, delaying the diffusion process. This relationship is variable. For example, even though B fibers are myelinated, they are blocked first because of their small size. This explains the early sympathetic block seen after epidurally administered

local anesthetics. The intermediate sized A-delta and C fibers, myelinated and unmyelinated respectively, are the next to be blocked. These moderate pain and sensation. Finally, the large, myelinated A-alpha motor neurons are the last to be blocked.

Table 1

Nerve Fiber Classification and Characteristics

Fiber Type	Myelination	Size (micrometers)	Conduction Velocity (meters/sec)	Function
A-alpha	yes	12-20	70-120	Motor
A-beta	yes	5-12	30-70	Touch Pressure
A-gamma	yes	5-12	30-70	Proprioception
A-delta	yes	1-4	12-30	Pain Temperature
B	yes	1-4	14.8	Preganglionic autonomic (sympathetic)
C	no	0.5-1	1.2	Pain Temperature

Note. Adapted from Neural Blockade in Clinical Anesthesia and Management of Pain (p. 36), by M. J. Cousins and P. O. Bridenbaugh, 1988, Philadelphia: J. B. Lippincott. Copyright 1988 by J. B. Lippincott Company.

Pain Pathways and the Opioid Receptor System

Nociceptive (pain) pathways are complex and not fully understood. Nociceptive impulses are transmitted from the periphery via primary afferent nerve fibers (mainly A-delta and C fibers) to the dorsal horn of the spinal cord where various systems modulate this information (Cousins & Mather, 1984). One of these is the endogenous opioid

receptor system. There are three basic types of opioid receptors in the body: mu, kappa, and delta (Murkin, 1991). These receptors are found in the periphery, spinal cord, and brain with varying distributions. For instance, mu and kappa receptors predominate in the substantia gelatinosa of the dorsal horn of the spinal cord, which is the primary site for integrating nociceptive afferent information from A-delta and C nerve fibers (Murkin, 1991).

Exogenous opioid agonists act by binding to these receptors. Morphine and fentanyl, both mu-receptor agonists, activate these receptors which then exert their analgesic effects as well as other side effects. These side effects include miosis, bradycardia, and respiratory depression. The route of administration helps to determine the primary site of receptor stimulation and action. For instance, it is postulated that epidurally administered opiates primarily bind to receptors in the substantia gelatinosa of the dorsal horn of the spinal cord, while those administered IV act mainly on receptors in the brain. Intrathecal (and therefore epidural) opiates selectively block pain by inhibiting presynaptic neuronal excitation without blocking sensory, motor and sympathetic function (Cousins & Mather, 1984).

Epidural Blockade

Epidural blockade, commonly used in obstetrics, requires that a catheter be inserted into the epidural space of the spinal column, usually through a lumbar interspace. The epidural space is a potential space between the ligamentum flavum and the dura which separates the epidural and subarachnoid spaces. It contains the epidural veins and spinal nerves, as well as other tissues and structures.

When local anesthetics and opioids are injected into the epidural space, nerve blockade and analgesia takes place by several mechanisms.

Local anesthetics diffuse into the CSF through the dura and the dural cuff region, the area where the spinal nerves leave the subarachnoid space. They also bathe the spinal nerve roots as they pass through the epidural space and seep into the paravertebral spaces where the spinal nerves travel. Depending on the concentration of local anesthetic, sympathetic, sensory, and motor blockade occurs. Lipid soluble opioids, such as fentanyl and sufentanil, diffuse through the dura and dural cuff regions to the substantia gelatinosa of the dorsal horn of the spinal cord where they stimulate mu receptors and cause analgesia.

Chloroprocaine and Opioid Antagonism

Several theories have been postulated about CP's opioid antagonism but the mechanism of this effect remains unresolved. The focus has centered around the pH of CP, CP metabolite interference and mu-receptor antagonism. It is necessary to understand these theories as a basis for explaining the antagonism.

Chloroprocaine is a weak base with a pH of 2.7-4.0 in plain solution, the lowest of all local anesthetics (Cousins & Bridenbaugh, 1988). Its significantly lower pH is thought to be a possible contributor to the antagonism of opioids. An agent with a low pH injected into the epidural space could transiently alter the effectiveness of subsequently injected agents such as fentanyl.

Chloroprocaine is hydrolyzed by plasma cholinesterase resulting in two inactive metabolites, 4-amino-2-chlorobenzoic acid (ACBA) and 2-diethylaminoethanol (Stoelting, 1991). Though ACBA has no intrinsic neuronal effect of its own, it is possible that it may interfere with opioid receptors in some way. Along with CP itself, it could cause conformational changes at the opioid receptor, making it unreceptive to an opioid agonist.

Chloroprocaine or its metabolites could also act as an opioid receptor antagonist, specifically at the mu-receptor (Naughton et al., 1988). If a direct mu-receptor antagonism is the culprit, the effect, in theory, could be overcome with a sufficient quantity of mu-receptor agonist. Thus, repeated boluses or an infusion of fentanyl should be able to overcome CP's opioid antagonism.

Summary

Chloroprocaine has an opioid antagonist effect which is not fully understood. Theories include CP metabolite interference, mu-receptor antagonism, and a pH effect. It is necessary to understand nerve physiology, pain pathways, and how local anesthetics and opioids work in these systems as a basis for understanding this antagonism.

Chapter Two

Review of Literature

Intravenous Versus Epidural Analgesia

Numerous studies have attempted to determine if one form of postoperative analgesia is superior. Intramuscular (IM), IV and epidural analgesia have all been proven effective. However, both PCA_E and PCA_I opioids have been more effective than IM opioids in providing adequate pain relief, probably due to the maintenance of serum or CSF levels of the drug (Eisenach, Grice, & Dewan, 1988; Lomessy, Magnin, Viale, Motin, & Cohen, 1984).

Several researchers have reported more effective analgesia with epidural opioids when compared to IV opioids, as evidenced by lower pain scores (Grant et al., 1992; Vella et al., 1985; Welchew & Breen, 1991). Cohen, Subak, Brose, and Halpern (1991) performed an uncontrolled study on 684 cesarean section patients who chose their own form of postoperative pain control. They chose between subarachnoid, epidural, PCA_I, or IM analgesia. The best analgesia was reported by the subarachnoid and epidural groups.

In contrast, Ellis, Millar, and Reisner (1990) compared IV and epidural fentanyl infusions in post-cesarean patients and found no difference in mean pain scores. However, three patients in the IV group were dropped from the study due to inadequate analgesia at the maximum infusion rate. The absence of data from these three patients

could have affected the study results, considering the study comprised only 28 patients.

Though epidural opioids have been shown to provide one of the most effective forms of analgesia, disadvantages have been reported. One of these was the apparent increased incidence of pruritus associated with the administration of either fentanyl or morphine (Cohen et al., 1991; Harrison, Sinatra, Morgese, & Chung,1988; Vella et al., 1985). Other researchers reported no difference in the incidence of pruritus (Ellis et al., 1990; Fragneto et al., 1994; Loper et al., 1990). In general, there seemed to be no difference in the incidence of nausea, vomiting, and level of sedation (Grant et al., 1992; Loper et al., 1990; Welchew & Breen, 1991). Cohen et al. (1991) reported a higher incidence of nausea and vomiting in the subarachnoid and epidural groups, but this could be related to hypotension from the sympathectomy associated with these forms of anesthesia rather than a direct central neuraxis opioid effect.

Another reported disadvantage of both epidural and IV opioids is their effect on ventilation. Renaud et al. (1988) found that epidural fentanyl caused a significant decrease in the ventilatory response to carbon dioxide, but these changes were similar in magnitude to IV opioids and were not clinically significant. Another study, comparing IV and epidural morphine in post-thoracotomy patients, revealed that while both groups had a decrease in forced vital capacity and forced expiratory volume in the first second, the epidural group had significantly less decrease (Shulman, Sandler, Bradley, Young, & Brebner, 1984). They suggested that epidural narcotics may have a slight advantage over IV narcotics, but it may not be clinically significant.

History of Chloroprocaine

Chloroprocaine, an ester-linked local anesthetic, has had a tumultuous history. After its original release into clinical practice in the late 1970s the agent was associated with reports of arachnoiditis and was thought to be neurotoxic when used epidurally (Ravindran, Bond, Tasch, Gupta, & Luerssen, 1980; Reisner, Hochman, & Plumer, 1980). Research indicated that the antioxidant sodium bisulfite which had been added to the preparation was the culprit. The drug was reformulated and again enjoys a useful place in obstetric anesthesia.

Epidural Chloroprocaine for Cesarean Delivery

Epidural anesthesia for cesarean delivery is preferable to general anesthesia for many reasons. Pregnant women are at increased risk for pulmonary aspiration of stomach contents because of normal physiologic changes which occur during pregnancy. Intragastric pressure and gastric acid secretion are increased, gastric pH is decreased, gastric emptying is delayed, and the pressure difference at the gastroesophageal junction is reduced (Shnider & Levinson, 1993). Though not a guarantee, epidural anesthesia probably reduces the risk for aspiration by maintaining the mother's protective airway reflexes and avoiding intubation (Cousins & Bridenbaugh, 1988). Epidural anesthesia also lessens intraoperative blood loss, suppresses the mother's endocrine stress response, and allows earlier mother-infant contact (Shnider & Levinson, 1993). In the presence of a uterine incision to delivery time of greater than 90 seconds, the fetus maintains a stable acid-base balance with epidural anesthesia, but not general anesthesia (Cousins & Bridenbaugh, 1988). Postoperatively, the epidural provides quality analgesia with a low risk of sedation.

Factors to consider when choosing a local anesthetic for cesarean delivery by epidural include onset, duration, therapeutic index, systemic toxicity, cumulation, and quality of blockade. Chloroprocaine has proven itself a valuable agent in obstetric anesthesia for several reasons. It provides a rapid onset block and has the lowest systemic toxicity of all the local anesthetics due to its rapid serum hydrolysis (Shnider & Levinson, 1993). It also has a high therapeutic index, short duration of action, and negligible cumulation (Cousins & Bridenbaugh, 1988). Fetal blood levels of CP after injection for neural blockade are minimal (Cousins & Bridenbaugh, 1988). These qualities make it an ideal agent for emergent cesarean deliveries.

Chloroprocaine also has several disadvantages. The early sympathetic block seen with epidural blockade combined with the rapid onset of CP anesthesia cause an increased incidence of hypotension (Shnider & Levinson, 1993). Because of its short duration, frequent redosing is necessary to maintain the required T4 level of anesthesia and tachyphylaxis can occur, making it difficult to maintain an effective surgical block (Shnider & Levinson, 1993). CP has also been found to decrease the effectiveness of subsequently administered local anesthetics and opioids, which can be a problem if tachyphylaxis occurs or postoperative epidural analgesia is desired (Hodgkinson et al., 1982; Kotelko et al., 1983).

Hodgkinson et al. (1982) demonstrated that epidural CP reduced the effectiveness of subsequently administered BP. In this study, stage I labor patients were given 10 milliliters (mL) of either 2% CP or 0.25% BP. When pain recurred, eight mL of 0.5% BP was given. The CP group experienced a longer time to onset and a shorter duration of the subsequent BP, and required more frequent supplemental doses.

Corke, Carlson, and Dettbarn (1984), treating isolated rat nerves, found that both CP and its primary metabolite, ACBA, significantly reduced the recovery time of subsequently administered BP. He concluded that ACBA, and possibly CP itself, were responsible for reducing the duration of BP, lending support to the clinical impression that CP antagonized BP. Since this study was performed on rat nerves, it is questionable that it can be generalized to the obstetric population. However, the duration of action of BP in the control group was similar to that seen in the clinical setting using humans.

Chloroprocaine was thought to be an ideal agent for test dosing, especially in the obstetric population, because of its low systemic toxicity and rapid metabolism. One study revealed that the IV injection of 100 milligrams (mg) of CP produced specific CNS symptoms in all 20 of their healthy male volunteers, suggesting it provides an effective test dose (Grice, Eisenach, Dewan, & Mandell, 1987). Two studies have shown that even when CP is used only as a test dose, the duration of action of the primary local anesthetic is shortened, as well as the duration of opioid analgesia (Eisenach et al., 1991; Grice, Eisenach, & Dewan, 1990).

Chloroprocaine and Opioid Antagonism

Kotelko et al. (1983) was the first to report the apparent opioid antagonistic effects of CP. His group found that when 3% CP was given as the primary epidural anesthetic for cesarean section, postoperative epidural morphine provided less satisfactory analgesia, additional opioids were required sooner, and total opioid usage was higher than if BP or LD were used. They concluded that the use of epidural CP

interferes with the efficacy of epidural morphine in providing postoperative analgesia.

Several researchers have since confirmed Kotelko's results. All of these studies were performed on cesarean section patients who received fentanyl 50 micrograms (mcg) epidurally either after delivery of the fetus or at the end of surgery. Naulty et al. (1986) found that the duration of epidural fentanyl analgesia after epidural CP anesthesia was significantly less than if BP, LD, or lidocaine with epinephrine (LD/E) were used. Malinow et al. (1988), in a similar study, supported these results. Another research group has shown that when CP was used as a top up agent after BP anesthesia, there was a decreased duration of epidural fentanyl (Ackerman & Juneja, 1989).

Phan, Azar, Osborn, Salter, and Lear (1988), using five mg of morphine epidurally after either CP or LD epidural anesthesia, reported a higher incidence in late onset analgesia, but no difference in duration of analgesia or pain scores. They also claimed that those women who received CP experienced poorer quality analgesia. However, they failed to define late onset analgesia, nor was any data provided to support their claim of poorer quality analgesia. The delayed analgesic effect could have been produced by the rapid offset of CP anesthesia and the slow onset of epidural morphine analgesia, causing a "window" of time in which analgesia was inadequate.

Early theories on CP's antagonism of opioids centered around its pH. Some researchers suggested that the low pH of CP, as compared to the other local anesthetic agents, was a possible cause (Naulty et al., 1985; Phan et al., 1988). Malinow et al. (1988), in two different studies, reported the effect of alkalinized CP on the duration of epidural fentanyl and found there was still a diminished analgesic

effect. They concluded, as did others, that pH was not the primary basis for the opioid antagonism.

Another theory was that CP acted as a mu-receptor antagonist. A study using dogs as the experimental model revealed that ACBA, the principle metabolite of CP, did not possess mu-receptor antagonist activity (Naughton, Pelligrino, & Albrecht, 1988). In contrast, Camann, Hartigan, Gilbertson, Johnson, and Datta (1990) compared epidural fentanyl, a mu-receptor agonist, and butorphanol, a kappa-receptor agonist, after either LD or CP epidural anesthesia. The group which received CP and fentanyl experienced higher pain scores and a shorter duration of analgesia than the other three groups. These results supported a possible mu-receptor antagonism.

Though the exact mechanism of CP's opioid antagonism was still undefined, some thought the effect could be overcome. In previous studies, a one time dose of opioid was given and the effect measured, but no one had tried a repeat dose of opioid or an opioid infusion. Malinow et al. (1988) was the first to suggest that repeat epidural injections or a continuous infusion of opioids may overcome the antagonism. Fragneto et al. (1994) compared epidural LD and CP anesthesia for cesarean section followed by an epidural fentanyl bolus and PCA_E for postoperative pain. They found no difference in pain scores, mean fentanyl usage, patient satisfaction, or side effects. They claimed that by administering fentanyl PCA_E, CP's antagonism of opioids could be overcome. Since serum fentanyl levels were not drawn in this study, it was unknown whether the epidural fentanyl was acting on a local or systemic level.

Local Versus Systemic Effects of Epidural Opioids

A conflict has existed in the literature as to whether epidural opioids act locally by diffusion into the CSF, systemically by absorption through the epidural veins, or by a combination of these. Researchers have come to varying conclusions. Lomessy et al. (1984), using a cross-over study design, gave either IM or epidural fentanyl and compared plasma fentanyl levels after each. They reported higher fentanyl levels after IM injection but better analgesia after epidural injection. Thus, they suggested the mechanism of action of epidural fentanyl is not through systemic absorption. Vella et al. (1985) concurred with these results. They compared IV and epidural fentanyl and found higher plasma fentanyl concentrations in the IV group with lower pain scores in the epidural group. Other researchers have found similar results (Ellis et al., 1990; Grant et al., 1992).

Loper et al. (1990), when comparing IV and epidural fentanyl, had contrasting results. They found no significant difference in plasma fentanyl levels and suggested that systemic absorption was a major contributor to analgesia. However, in this study the only blood level drawn occurred at 18 hours, allowing significant time for systemic absorption to occur. Ellis et al. (1990) also demonstrated no difference in plasma fentanyl levels at 24 hours, though a difference did occur at 12 hours.

Welchew and Breen (1991) compared fentanyl via IV or thoracic epidural routes. They found that the IV group used twice as much fentanyl as the epidural group and had higher pain scores. They suggested that fentanyl provides locally mediated analgesia.

Gourlay et al. (1989) measured fentanyl concentrations in CSF after lumbar epidural administration. Though the study only consisted of six patients, all had significant concentrations of fentanyl in

lumbar CSF within 20 minutes of administration. They also compared serum fentanyl concentrations and found that only two of six patients had barely detectable fentanyl levels, suggesting there is minimal vascular uptake of fentanyl immediately after epidural injection.

Summary

Chloroprocaine has proven itself to be a valuable local anesthetic for obstetric surgery, while epidural opioids have been shown to be an effective means of providing postoperative analgesia. Early studies reported that epidural CP used for cesarean section caused an antagonism of subsequently administered epidural mu-receptor opioids. A further study revealed that this antagonism could be overcome with a continuous epidural fentanyl infusion. It was not known, however, if the fentanyl was providing locally or systemically mediated analgesia since plasma fentanyl levels were not drawn. Evidence in the literature has supported the theory that epidural fentanyl has both local and systemic effects. This study has attempted to address the issue of the site of action of epidurally administered fentanyl after epidural CP anesthesia for elective cesarean section delivery.

Chapter Three

Methodology

The purpose of this study was to determine if epidural fentanyl, administered subsequent to epidural CP for cesarean section, mediated analgesia through a local, systemic, or combined mechanism of action. Prior to this study, CP has been shown to interfere with the analgesic effect of mu-receptor agonists such as morphine and fentanyl. It was found that this effect can be overcome with a continuous infusion of the opioid, but the mechanism remains unknown.

Research Design, Population, and Treatment Groups

This study utilized a quasi-experimental design and took place in a large, urban university hospital. Approval for the study was obtained from the Committee on the Conduct of Human Research. A convenience sample of nonlaboring parturients undergoing elective cesarean section participated. Upon entering the study, subjects were randomly placed in one of two treatment groups. The PCA_I group served as the comparison group and the PCA_E group as the experimental group.

Procedure

Written informed consent was obtained from ASA I and II parturients undergoing elective (nonlaboring) cesarean section and consenting to epidural anesthesia. Women with a history of IV opioid

abuse were excluded from the study. Patients were randomly assigned to receive fentanyl by PCA_I or PCA_E for postoperative analgesia.

After routine patient preparation, an epidural catheter was placed in the lumbar 2-3 or 3-4 interspace to a depth of two to four centimeters. After a test dose of three mL of 2% LD to ensure proper placement, the epidural catheter was incrementally dosed with 3% CP to obtain a T4 sensory level bilaterally. The T4 level was maintained intraoperatively with a continuous epidural infusion of 3% CP at 10 mL/hour from the time of skin incision to skin closure.

Intraoperative discomfort was treated with ketamine 10 to 20 mg IV. Patients who required more than 50 mg of ketamine were considered to have inadequate epidural anesthesia and were excluded from the study. No epidural or IV fentanyl (or other analgesic) was used intraoperatively.

Upon completion of surgery, a 1.0 mcg/kilogram (kg) bolus of fentanyl was given either IV or epidural, according to treatment group assignment. Repeat boluses of fentanyl were administered by the same route until patient comfort was achieved, but not in excess of 200 mcg. At completion of surgery, a fentanyl PCA_E or PCA_I was also started, according to treatment group, with a dose of 30 mcg, a lock-out interval of 10 minutes, and a maximum dose of 180 mcg per hour. No basal infusion was given. If pain was experienced by the patient while being treated with the PCA_E or PCA_I, a 1.0 mcg/kg fentanyl bolus was given by the same route. Repeat boluses were given every 20 minutes if discomfort persisted, to a maximum of 200 mcg of fentanyl. If rebolusing failed to relieve the discomfort, the fentanyl PCA was considered a failure; an alternative form of analgesia was provided. Anesthesia providers administered all fentanyl boluses and initiated

the appropriate PCA treatment. All fentanyl boluses were given according to treatment group assignment.

Beginning at completion of surgery, a blinded observer assessed sensory levels of anesthesia every 15 minutes until a T12 level was present bilaterally. Then, pain levels were assessed using a VAS every 15 minutes for the first two hours after surgery completion and then at 4, 6, 12, and 24 hours. The level of sedation was monitored by a blinded observer at 1, 2, 4, 6, 12, 18, and 24 hours postoperatively. The incidence of side effects from fentanyl was recorded including nausea, vomiting, pruritis, and respiratory depression.

A heparin lock IV was placed to obtain blood samples for plasma fentanyl levels. If the patient was in the IV group, the heparin lock was placed in the arm opposite the infusion. Plasma fentanyl levels were obtained at 1, 4, and 24 hours after initiation of the fentanyl PCA. The total fentanyl PCA dose used by the patient was recorded at 1, 2, 4, 6, 12, 18, and 24 hours postoperatively. At the end of the 24 hour period, patients were asked to rate their overall satisfaction with the method of pain control they used.

Instrumentation

A data collection form was completed for each patient (see Appendix). Demographic data included age, height, weight, gravidity, parity, and weeks of gestation. Intraoperative data consisted of the volume of CP required to establish surgical anesthesia and the total volume used during surgery. Total surgical time, initial sensory level obtained, additional drugs (e.g., ketamine) used during surgery, and the patient's satisfaction with their anesthesia were also recorded.

A VAS was used to measure postoperative pain. The VAS is an instrument commonly used to measure subjective clinical symptoms.

Patients were educated in its use and asked to indicate on the scale the intensity of their pain. The scale was then flipped over and a numerical amount was assigned to their level of pain.

Data Analysis

Demographic data, pain and sedation scores, total volume of fentanyl used, and plasma fentanyl levels were analyzed using an independent samples t-test. A Fisher's exact test was used to determine differences in conversion to another form of analgesia, incidence of nausea and pruritis, and patient satisfaction. A value of $p \leq 0.05$ was considered significant.

Chapter Four

Results

Demographic Data

Of the 21 participants, nine were in the PCA_I group and 12 in the PCA_E group. An independent samples t-test was used to compare mean age, height, weight, and total surgical time between the two groups (see Table 2). Their was no significant difference in age, height, or weight. However, the PCA_I group had a significantly longer surgical time, an average of 20 minutes. Data on surgical time were missing for two patients, one from each group.

Table 2

Mean Demographic Characteristics

Characteristics	PCA_I Group	PCA_E Group	p-value
Age (years)	29.9	30.4	0.8543
Height (inches)	62.9	63.6	0.5121
Weight (pounds)	195.1	194.9	0.9909
Surgical Time (min)	91.5	71.0	0.0213*

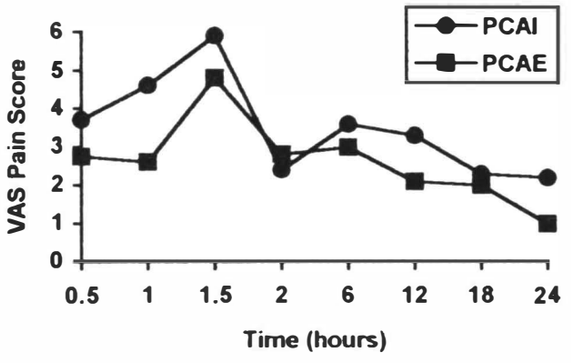
Note. * Statistical significance $p \leq 0.050$.

VAS Pain Scores

Mean pain scores are depicted in Figure 1. Data were available on 16 patients, eight from each group. The PCA_E scores were consistently lower than the PCA_I scores, except at two hours, in which the PCA_E scores were higher. An independent samples t-test revealed there was no significant difference in these scores except at 24 hours, when the PCA_I group experienced significantly higher pain scores (p = 0.0295).

Figure 1

Mean VAS Pain Scores



One patient in the PCA_I group and four patients in the PCA_E group required conversion to another form of analgesia. The patient's IV from the PCA_I group had come out for an extended period of time while three patients from the PCA_E group had dislodged epidural catheters. A Fisher's exact test demonstrated that this was not significant (p = 0.3383). Of the remaining 16 patients, five from each group required additional fentanyl boluses to obtain adequate analgesia.

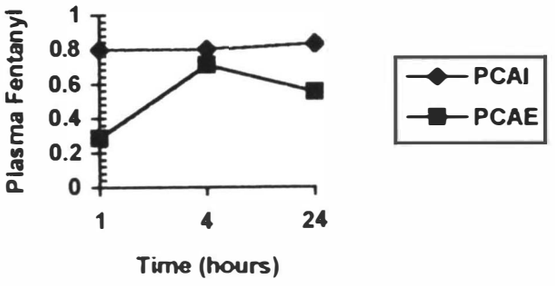
Fentanyl Usage and Plasma Levels

An independent samples t-test was used to compare the total amount of fentanyl used, with and without boluses. The mean total volume of fentanyl used after 24 hours was 106 mL for the PCA_I group and 84 mL for the PCA_E group. This approached significance (p = 0.0654). The mean total volume of fentanyl used including boluses was 110 mL for the PCA_I group and 88 mL for the PCA_E group. The p-value was significant at 0.050.

Plasma fentanyl levels were assessed using an independent samples t-test for ten of the 16 patients (see Figure 2). There was no significant difference in plasma fentanyl levels, but significance was approached at 24 hours (p = 0.0729). The plasma fentanyl levels of the PCA_E group were always lower than the PCA_I group.

Figure 2

Mean Plasma Fentanyl Levels



Side Effects and Patient Satisfaction

Data on side effects and patient satisfaction with their assigned analgesia were collected on the 16 patients who completed the study (eight from each group). Sedation scores were evaluated using a repeated measures t-test and revealed no significant difference between the two groups. A Fisher's exact test was used to compare the incidence of nausea and pruritis. In the PCA_I group, one patient experienced pruritis and no one reported nausea. Four patients in the PCA_E group reported pruritis and one patient was nauseated. There was no significant difference between the groups. When asked about their satisfaction with the form of analgesia used, all reported either excellent or good. Four people from the PCA_I group and six from the PCA_E group reported satisfaction as excellent. Using the Fisher's exact test, there was no significant difference in patient response (p = 0.6084).

Chapter Five

Discussion

The purpose of this study was to determine if fentanyl PCA_E provided analgesia locally, systemically, or in a combined manner after epidural CP for cesarean section. A comparison was made to patients receiving PCA_I analgesia. The hypothesis stated that there is no difference in analgesia between fentanyl PCA_E and PCA_I after cesarean section under epidural anesthesia with CP.

Conclusions

Though the demographic variables were similar between the two groups, total surgical time was an average of 20 minutes longer for the PCA_I group. VAS pain scores were also generally higher for the PCA_I group, though not significantly until 24 hours. There may have been a relationship between the longer surgical time and the generally higher pain scores.

Though the PCA_I group had generally higher pain scores than the PCA_E group, the scores of both groups were fairly low. There was no difference in patient satisfaction with their assigned form of analgesia. Thus, both methods were effective in providing adequate postoperative analgesia.

The total amount of fentanyl used in the 24 hour study period, including boluses, was significantly less in the PCA_E group. The VAS pain scores were also lower for this group, except at two hours when

the PCA_I scores were lower. Again, the scores were significantly lower for the PCA_E group at 24 hours. These two trends, a lesser volume of fentanyl used with generally lower pain scores, supported the theory that fentanyl PCA_E provided locally mediated analgesia at the spinal cord.

Plasma fentanyl levels were not significantly different between the two groups. However, the PCA_E group always had lower levels than the PCA_I group, approaching significance at 24 hours. This finding suggested that fentanyl PCA_E was systemically absorbed by the epidural veins to some extent and provided systemically mediated analgesia. It was interesting to note that the plasma fentanyl levels peaked in the PCA_E group at four hours and were at their lowest at 24 hours. A possible explanation for this observation was that after systemic absorption into the general circulation, fentanyl was either metabolized or redistributed back into the CSF.

Comparison to Other Studies

Grant et al. (1992) compared pain scores and total fentanyl usage in thoracotomy patients receiving either an epidural or IV fentanyl bolus and PCA infusion, initiated before chest closure. They reported significantly higher fentanyl usage and VAS pain scores at six and 14 hours postoperatively in the IV group. They suggested that epidural fentanyl had a direct analgesic effect on the spinal cord. Their results were similar to those found in this study, though the patient populations and the anesthetic techniques used were different.

Comparing fentanyl administered either IV or via thoracic epidural in postoperative upper abdominal surgery patients, Welchew and Breen (1991) also reported significantly lower pain scores and less fentanyl usage in the epidural group. They concluded that epidural

fentanyl provides locally mediated analgesia. Again, though patient populations and anesthetic techniques differ, the data results and conclusions were similar.

Lomessy et al. (1984) found similar results when they compared IM and epidural fentanyl after a postoperative bolus. They found lower pain scores after the epidural injection and greater plasma fentanyl levels after the IM injection, suggesting a spinal site of action. However, they failed to report the significance of the plasma fentanyl levels.

Loper et al. (1990) found no difference in plasma fentanyl levels and pain scores between IV and epidural groups given a fentanyl bolus and PCA infusion postoperatively. The only plasma fentanyl level drawn was at 18 hours. These results were similar to this study with respect to plasma fentanyl levels, but not pain scores. One explanation for the difference in pain scores may be that they studied patients undergoing knee surgery, a different population than the one currently under study. Ellis et al. (1990) also reported no difference in pain scores after studying IV or epidural fentanyl infusions in postoperative cesarean section patients. They collected plasma fentanyl levels and found a significantly higher level in the IV group at 12 hours, but not 24 hours, the only two levels drawn. They reported no difference in total fentanyl usage. However, three patients from the IV group were dropped from the study due to inadequate pain relief at maximum PCA infusion rates. The absence of this data could have significantly affected the study results and conclusions. Thus, past studies have provided evidence that epidural fentanyl mediates analgesia both locally and systemically.

Limitations

This study was significantly limited by the small sample size (N = 21) and the amount of missing data. Since five patients required conversion to another form of analgesia, data (other than demographic) were only available on 16 patients. In addition, a complete set of plasma fentanyl samples were available on only 10 patients (four from the PCA_I group and six from the PCA_E group) because of missing samples. Since the initial sample size was small to begin with, the lack of this data could seriously compromise the results. A small sample size tends to produce a less accurate assessment of the general population than a large sample. With a large sample, sampling error and the likelihood of getting a deviant sample decreases.

A limitation also existed in the patient population chosen for this study. Only non-laboring parturients scheduled for elective cesarean section were allowed to participate. The study took place at a large, urban university hospital and was limited to patients receiving medical care at this facility. Therefore, study results can only be generalized to these particular populations.

Inherent limitations exist in the nature of the data collected and the data collectors. Pain is a subjective entity and is experienced differently from person to person. The people who collected the data are subject to their own interpretations and biases. Bias was minimized by several methods. First, patients were randomly assigned to a treatment group. Data collection specific to anesthesia practice, such as assessing sensory levels, administering fentanyl boluses, and obtaining plasma fentanyl levels were done by trained anesthesia providers. Data such as assessing pain by VAS scale, sedation, and incidence of side effects was collected by specialized nurses who are knowledgeable and familiar with data collection methods.

Recommendations for Future Study

The results for this study are promising, but a larger sample size is needed to confirm and clarify the results. This study could be broadened to include parturients undergoing non-elective cesarean section, which is when CP is most likely to be used. Studies collecting both plasma and CSF fentanyl levels after either IV or epidural fentanyl would probably provide the most accurate data in determining the site of action of epidural fentanyl. However, it may not be ethically appropriate to put a patient at risk in collecting multiple CSF samples.

Summary

In conclusion, both PCA_E and PCA_I provided effective postoperative analgesia after elective cesarean section under epidural chloroprocaine anesthesia. VAS pain scores were generally lower in the PCA_E group and were significantly lower at 24 hours. However, VAS pain scores of both groups were low and patient satisfaction was equivalent, suggesting both methods provide adequate postoperative analgesia. The total volume of fentanyl used, including boluses, was significantly lower in the PCA_E group. This, combined with the low VAS pain scores, suggested that fentanyl PCA_E provided locally mediated analgesia. Plasma fentanyl levels were not significantly different, suggesting that systemic analgesia probably also occurred with PCA_E. There was no difference in the incidence of sedation, pruritis, or nausea and vomiting.

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List of References

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Appendix

Data Sheet: Epidural versus IV Fentanyl PCA for Postcesarean Analgesia After Use of Chloroprocaine

Patient Name_____ Study No._____

Medical Record Number_____ Date_____

Age_____ Race_____ Height_____ Weight_____

Gravidity_____ Parity_____ Weeks Gestation_____

C-section: (circle) repeat primary

Reason for C-section:_____

Surgery Start time_____ Surgery End time_____

Total Surgery time_____

Volume of Chloroprocaine to establish block:_____

Total Volume of Chloroprocaine Used:_____

Maximum Sensory Level: L:_____ R:_____

Additional Drugs Used During C-section (list name and dose):_____

_____

> 50 mg Ketamine Used: (circle) yes no

Quality of Anesthesia for Surgery (per patient): (circle)

excellent good fair poor

Fentanyl PCA: (circle) epidural IV

Time PCA Started:_____

Repeat bolus of Fentanyl (1.0 mcg/kg) required for initial analgesia:

(circle) yes no

Sensory Levels: (beginning of PCA initiation until < T12)

Time	R	L	Time	R	L
0 min	____	____	75 min	____	____
15 min	____	____	90 min	____	____
30 min	____	____	105 min	____	____
45 min	____	____	120 min	____	____
60 min	____	____			

VAS Pain Scores: (beginning at PCA initiation)

Time	Score	Time	Score	Time	Score
0 min	____	75 min	____	6 hr	____
15 min	____	90 min	____	12 hr	____
30 min	____	105 min	____	18 hr	____
45 min	____	120 min	____	24 hr	____
60 min	____	4 hr	____		

Sedation Score (beginning at PCA initiation)

Time	Score	Time	Score	Time	Score
0 hr	____	4 hr	____	18 hr	____
1 hr	____	6 hr	____	24 hr	____
2 hr	____	12 hr	____		

Did patient require bolus during 24 hr period? (circle) yes no

If yes, include dose and time:_____

_____

Did patient require conversion to alternative mode of analgesia? (circle) yes no

If yes, time converted and mode of alternate analgesia:_____

_____

If required conversion, was evidence of dislodged epidural or IV? (circle) yes no

PCA Usage

Time	Attempts/Doses	Time	Attempts/Doses	Time	Attempts/Doses
1 hr	_____	9 hr	_____	17 hr	_____
2 hr	_____	10 hr	_____	18 hr	_____
3 hr	_____	11 hr	_____	19 hr	_____
4 hr	_____	12 hr	_____	20 hr	_____
5 hr	_____	13 hr	_____	21 hr	_____
6 hr	_____	14 hr	_____	22 hr	_____
7 hr	_____	15 hr	_____	23 hr	_____
8 hr	_____	16 hr	_____	24 hr	_____

Total Volume PCA Used at 24 hours:_____

Plasma Fentanyl Levels Drawn (please record time):

1 hr _____ 4 hr _____ 24 hr _____

Side Effects:

Pruritis: (circle) yes no

Record any Rx required for pruritis and time of administration:

_____

Nausea or Vomiting: (circle) yes no

Record any Rx required for nausea and time of administration:

_____

Resp. Rate < 10: (circle) yes no

Narcan administered: (circle) yes no

If yes, dose and time:_____

Patient satisfaction with analgesia: (circle)

excellent good fair poor

Would patient have this type of analgesia again: (circle) yes no

Vita