COMPARATIVE STUDY BETWEEN INTRAVENOUS PARACETAMOL AND PETHIDINE AS POST-CESAREAN SECTION ANALGESIA

Thesis

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Presented By

Sameh Fathy Gad Elseed

Resident of Obstetrics & Gynecology -
Nasr City Hospital for Health Insurance
M.B.B.Ch. 2007, Faculty of Medicine, Ain Shams University

Supervised By

Prof. Dr. Hassan Tawfek khairy

Prof. of Obstetrics & Gynecology
Faculty of Medicine, Ain Shams University

Dr. Mohamed Elmandooh Mohamed

Assistant Prof. of Obstetrics & Gynecology
Faculty of Medicine, Ain Shams University

Dr. Sherif Hanafy Hussin

Lecturer in Obstetrics & Gynecology
Faculty of Medicine, Ain Shams University

Faculty of Medicine
Ain Shams University
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LIST OF ABBREVIATIONS

Abbrev.		Full term
5-HT	**:**	5-hydroxytryptamine
CB1	**:**	Cannabinoid receptor 1
CNS	**:**	Central nervous system
COX-2	**:**	Cyclooxygenase-2 enzyme
DOP	**:**	Delta opioid peptide receptor
EEG	**:**	Electroencephalography
IASP	**:**	The international association for the study of pain
INR	**:**	International normalized ratio
KOP	**:**	Kappa opioid peptide receptor
MOP	**:**	mu opioid peptide receptor
NAPQI	**:**	N-acetyl-p-benzo-quinine-imime
NMDA	**:**	N-methyl-Daspartate
NNT	**:**	The number needed to treat
NO	**:**	Nitric oxide
NOP	**:**	Nociceptinorphanin
NOS	**:**	Nitric oxide synthase
NSAIDs	**:**	Nonsteroidal anti-inflamatory drugs
P	**:**	Projection cells
PAG	**:**	Peri-aqueductal gray area
PCA	**:**	Patient controlled analgesia
PG	**:**	Prostaglandins
PGG2	**:**	Prostaglandin G2
PGH2	**:**	Prostaglandin H2
SDS	**:**	Simple descriptive scale
SG	**:**	Substantia gelatinosa
Tmax	**:**	Time to maximum plasma concentration
UGT	**:**	UDP glucuronosyl transferase
VAS	**:**	Visual analogue scale
VRS	**:**	Verbal rating scale

INTRODUCTION

Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage**.** Medical and technological advances have made pain more manageable today than ever before. Pain management has been established as one of the benchmarks of quality health care ***(Kingdom and Kizior, 2002).***

Pain is a major problem in surgery including cesarean section. Post cesarean section pain is a common cause of acute pain in obstetrics, although pain relief and patient satisfaction are still inadequate in many cases. Today, cesarean section is one of the most frequently performed surgeries in the world**.** Cesarean births are more common than most surgeries, due to many factors. The first factor of course is that nearly 50% of the world populations are women, and pregnancy is still a very common condition. However, more important is the fact that a cesarean section may be life saving for the baby, or mother or both ***(Anna'na', 2005).***

Pain in the postoperative period is an important impediment to recovery from surgery and anesthesia. Hence, reducing the pain after cesarean section (C/S) or any other surgery is very important ***(Ng et al., 2002)***. However, managing the pain after C/S is more complicated because the patients are always young, healthy and active women who are eager to care for their

infants since the first postpartum hours and days are important for interaction between mother and newborn, pain should not interfere with the mother's ability to nurse the baby ***(Lim et al., 2001)***.

Post-operative pain pathophysiological processes, include the activity of neurotransmitters, are operative at multiple sites along this structural pathway to aid in conveying the signal. This process is referred to as nociception. Nociceptive process begins at peripheral level. When damage occurs, biochemical agents that initiate or sensitize the nociceptive response are released. These agents include potassium, substance P, bradykinin, and prostaglandin among others ***(Kingdom and Kizior, 2002).*** The initial injury provokes a series of physiologic events what is known as pain phases ***(Bourlert, 2004).***

Management of acute pain after cesarean section has evolved considerably over the past decade. In many institutions, with intravenous patient controlled analgesia and neuraxial opioids, have replaced traditional intramuscular opioid injections. The general approach to pain after cesarean section is changing, shifting away from traditional opioid-based therapy toward a (multimodal) or (balanced) approach. Multimodal pain therapy involves the use of a potent opioid regimen, such as patient controlled analgesia or neuraxial opioids, in combination with other classes of analgesic drugs such as acetaminophen and non steroidal anti-inflammatory drugs, with the variable addition of local anesthetic techniques. Despite current advances in

postoperative pain therapy, pain relief may still be inadequate for a substantial number of women ***(Kuhnet, 2004).*** This may be particularly true as they make the transition from relative dependency on potent opioid regimens to full dependency on oral analgesics on the second postoperative day ***(Power, 2003).***

Most parturient women request analgesia, whether pharmacologic or non-pharmacologic ***(Thurlow et al., 2002)***. Typical analgesic regimens include opioids; nonopioid analgesics, such as paracetamol and non- steroidal anti-inflammatory drugs, with the variable addition of local anesthetic techniques ***(Kuhnet, 2004).*** Opioid analgesia includes Morphine, Pethidine, fentanyl, tramadol, butorphanol, remifentanil, and ketamine, which is currently the current gold standard for obstetric analgesia ***(Pandya, 2010)***.

Whilst opioids are the main stay for relief of severe pain, they are far from perfect analgesics as they have many significant adverse effects ***(Stein et al., 2000)***. The common opioid side-effects of respiratory depression, sedation, depression of gastrointestinal motility, nausea and vomiting, and the potential risk of abuse reflect the striking and generalized role endogenous opioids play in general human physiology ***(Bodnar and Hadjimarkou, 2003).*** High cost and difficult availability are other reasons of avoiding the use of these drugs as routine analgesics medications after surgery ***(Movahed and Poorrostamy, 2003).***

Pethidine, like morphine exerts its analgesic effects by acting as an agonist at the mu opioid receptor. It also has a kappa opioid receptor action, which is of unknown clinical significance. It has structural similarities to atropine and other tropane alkaloids and may have some of their effects and side effects. In addition to these opioidergic and anticholinergic effects, it has local anesthetic activity related to its interactions with sodium ion channels ***(Bryant and Knights, 2010).***

Paracetamol is another type of analgesics and is the most commonly prescribed analgesic for the treatment of acute pain and the efficacy of single-dose paracetamol as a postoperative analgesic has been confirmed by various studies, the mechanism of action remains unclear as, unlike opioids and NSAIDs respectively, paracetamol has no known endogenous binding sites and does not inhibit peripheral cyclooxygenase activity significantly. There is increasing evidence of a central antinociceptive effect, and potential mechanisms for this include inhibition of a central nervous system (COX-2), inhibition of a putative central cyclooxygenase (COX-3) that is selectively susceptible to paracetamol, and modulation of inhibitory descending serotinergic pathways ***(Koppert et al., 2004)***.

However, oral paracetamol has a slow onset of analgesia and the non-availability of the oral route immediately after surgery limits its value in treating immediate postoperative pain ***(Salonen et al., 2009)***. The introduction of an intravenous preparation and reports of the analgesic and anti-inflammatory

properties and safety advantages of a nitric oxide (NO) releasing form may represent significant advances in the use of this drug in treatment of acute pain ***(Sachs, 2005)***. Also, Perfalgan (IV paracetamol) provides onset of pain relief within 5 to 10 minutes after start of administration. The peak analgesic effect is obtained in 1 hour and the duration of this effect is usually 4 to 6 hours. The maximal plasma concentration of paracetamol observed at the end of 15 minutes IV infusion of 500 mg and 1g of perfalgan is about 15µg/ml and 30µg/ml respectively ***(emc, 2008)***.

Despite the availability of analgesic medication, inadequate pain treatment continues to be an important problem in many clinical setting one of the major contributing factors is a lack of routine pain measures that could indicate to medical staff how much pain patient are experiencing so accurate estimation of the patient's pain is crucial in the process of pain relief ***(Choiniere, 1994)***.

In the last two decades, the visual analogue scale (VAS) has come to be one of the most popular methods for measurement of pain intensity. The VAS consists of a 10cm line anchored by two extremes of pain, usually "no pain" and "unbearable pain" (or a similar verbal descriptor representing the upper pole). The patient is asked to make a vertical mark through the line corresponding to the intensity of pain .the scale is scored by measuring the distance in mm from (no pain) to the

patient's mark simple and reproducible ***(Rawer and Alvin, 1998)***.

The visual analogue scale (VAS) is easy to use, provides reproducible results and is applicable to a variety of practice settings It is also sensitive to treatment effects and the data derived can be analyzed using parametric statistical techniques ***(Todd, 1996).***

AIM OF THE WORK

The aim of this study is to compare the efficacy of intravenous infusion of paracetamol in comparison with meperidine (pethidine) as post cesarean section analgesia, as demonstrated by the degree of pain relief.

Chapter I

PHYSIOLOGY OF PAIN

Pain is a universal human experience and the most common reason people seek medical care. Pain tells us something is wrong in the structure or function of our body and that we need to do something about it. Because pain is such a strong motivator for action, it is considered one of the body's most important protective mechanisms ***(Watkins et al., 2008)***.

Definition of pain

The International Association for the Study of Pain (IASP) defines pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" ***(Merskey, 2008)***.

There are two different approaches to pain: the sensory-discriminative (perception of the intensity, location, duration, temporal pattern, and quality of noxious stimuli) and motivational-affective (relationship between pain and mood, attention, coping, tolerance, and rationalization) ***(Lin, 2009)***.

The Purpose of pain

A withdrawal reflex response to an acute noxious stimulus is an understandable and necessary reaction that has an obvious protective function even in the absence of conscious

perception. More importantly, the experience of pain may lead to the avoidance of potentially harmful situations and possible injury. Immobility and withdrawal due to pain may serve to provide an environment in which healing and restoration of function can occur ***(Hudspith et al., 2006)***.

Classification of pain

IASP classification system describes pain according to five categories: duration and severity, anatomical location, body system involved, cause, and temporal characteristics (intermittent, constant, etc) ***(Pace et al., 2006)***.

a) According to the clinical status:

Acute pain is "the normal, predicted physiological response to an adverse chemical, thermal or mechanical stimulus associated with surgery, trauma and acute illness". Generally, acute pain resolves within 1 month ***(Macres et al., 2009)***.

The most important type of acute pain is the postoperative pain.

Chronic pain is defined as pain without apparent biological value that has persisted beyond the normal tissue healing time usually taken to be 3 months."The presence or extent of chronic pain often does not correlate with the