Comparison between subcutaneous ketamine with intramuscular pethidine versus intramuscular pethidine for post-operative analgesia after cesarean section

Thesis

Submitted For Partial Fulfillment of Master Degree in Anesthesia

By

Hesham Mohamed Mahmoud Sultan
M.B, B.CH
Faculty of Medicine –Zagazig University

Supervised by

Prof. Dr. Bassel Mohamed Essam Noureldin
Professor of Anesthesia and Surgical Intensive Care
Faculty of Medicine – Ain Shams University

Dr. Mohamed Mohamed Kamal
Lecturer of Anesthesia and Surgical Intensive Care
Faculty of Medicine- Ain Shams University

Dr. Ahmed Abd Elmohsen Ali Bedewy
Lecturer of Anesthesia and Surgical intensive care
Faculty of Medicine- Helwan University

Faculty of Medicine
Ain Shams University
2018

سورة البقرة الآية: ٣٢

Acknowledgment

First and foremost, I feel always indebted to **ALLAH,** *the Most Kind and Most Merciful.*

I'd like to express my respectful thanks and profound gratitude to **Prof. Dr. Bassel Mohamed Essam Noureldin,** *Professor of Anesthesia and Surgical Intensive Care Faculty of Medicine – Ain Shams University for his keen guidance, kind supervision, valuable advice and continuous encouragement, which made possible the completion of this work.*

I am deeply thankful to **Dr. Mohamed Mohamed Kamal,** *Lecturer of Anesthesia and Surgical Intensive Care Faculty of Medicine- Ain Shams University, for his great help, active participation and guidance.*

I wish to introduce my deep respect and thanks to **Dr. Ahmed Abd Elmohsen Ali Bedewy,** *Lecturer of Anesthesia and Surgical intensive care Faculty of Medicine- Helwan University, Ain Shams University, for his kindness, supervision and cooperation in this work.*

Hesham Mohamed Mahmoud Sultan

List of Contents

List of Tables

List of Figures

List of Abbreviations

Abb.	Full term
CNS	Central nervous system
COX-2	Cyclooxygenase-2
CS	Caesarean section
CSF	Cerebrospinal fluid
NMDA	N-methyl-D-aspartate
NSAIDs	Non-steroidal anti-inflammatory analgesics
PACU	Post operative care unit
PCA	Patient controlled analgesia
RCTs	Randomized controlled trials
TAP	Transversus abdominis plane

INTRODUCTION

Cesarean section is one of the most common operations. Women undergoing cesarean delivery should achieve adequate postoperative pain relief because of different factors related to the operation complications as well as maternal and neonatal well-being. Immobility due to inadequate pain control could result in thrombo-embolic events, inappropriate neonatal care and delay in discharge which consequently increase the cost of this common procedure both for patients and health care system ***(Shahraki et al., 2012)***.

Surgical trauma and nerve injury induce N-methyl-D-aspartate (NMDA) receptors activation which facilitates nitric oxide production, resulting to dorsal horn stimulation. Central sensitization may cause increased postoperative pain ***(Simin et al., 2011)***.

Although opioids remain the strongest analgesics for pain management, one must consider that they may also paradoxically facilitate postoperative pain in humans. Opioid-induced hyperalgesia and allodynia have also been observed in human volunteers after analgesia produced by various opioid injections. To optimize pain management and outcome, there is a continuous search for new analgesics and alternative routes of delivery ***(Zakine et al., 2008)***.

Ketamine is a well-known short acting general anesthetic in use for almost three decades. Experimental pain research of the NMDA receptor revealed that ketamine is a potential anti-hyperalgesic agent that may inhibit C fiber activity. There are various routes of ketamine administration in the treatment of postoperative pain: topical, intramuscular, intravenous, intra-thecal, and subcutaneous administration**.** Some studies have shown the reduction of postoperative opioid consumption, prevention of the adverse effects of opioids, and improvement in analgesic quality via subcutaneous ketamine alone or by combining ketamine and opioids. Therefore, subcutaneous injection of ketamine may be an alternative for pain control in patients with contraindication to neuroaxial blockade. This study will explore the role of repeated subcutaneous injections of ketamine in diminishing postoperative pain and decreasing the overall opioid consumption ***(Tan et al., 2007)***.

Aim of the Study

The aim of the study is to investigate the efficacy of adding subcutaneous ketamine for postoperative analgesia in cesarean section and comparing it to using intramuscular pethidine only regarding opioid requirements and pain level.

Chapter 1
METHODS OF POST-OPERATIVE ANALGESIA AFTER CESARIAN SECTIONS

Caesarean section results in both direct surgery induced somatic pain and visceral pain, mediated by tissue injury induced inflammation. Pain is ranked highest among undesirable clinical outcomes associated with caesarean section (CS). Adequate post-operative analgesia in the obstetric patients is crucial as they have different surgical recovery needs which include breastfeeding and care of the newborn; these can be impaired if analgesia is unsatisfactory. The ideal post-CS analgesic regime should be efficacious without impacting the ability of mother to take care of the neonate and with minimal drug transfer through breast milk. However, observational data from developing as well as developed countries have shown that we are far from achieving these goals. In developing countries, limited availability of drugs, equipment and expertise are the major issues in providing adequate post-CS analgesia ***(Ismail et al., 2012)***.

Perioperative medicine now promotes ERAS (enhanced recovery after surgery), a multidisciplinary focus on evidence-based practices to enhance postoperative recovery not only for humanistic but also for economic reasons. Postpartum women are willing to recover rapidly and ERAS programs are being developed specifically for cesarean section ***(Corso et al., 2017)***.

Postoperative pain control is a major component of ERAS programs because pain negatively affects recovery. It is worth noting that, as for other surgical procedures, pain on movement remains under-evaluated after cesarean section, although it is more severe than pain at rest and may require different analgesics ***(Benhamou and Kfoury, 2016)***.

Implementation of ERAS programs after cesarean section implies a better understanding and objective assessment of post cesarean pain and its impact on womens` recovery. Pain significantly affects different dimensions of recovery. Pain also interferes with mother–child bonding by limiting breastfeeding ***(Marcus et al., 2015)***.

These are some of the most commonly used methods for post-operative analgesia after CS.

1. Opioids

Opioids have been the cornerstone of postoperative analgesia; they are effective but often accompanied by unwanted side-effects. They still have a significant role in multimodal postoperative analgesia, but the use of different drugs and delivery routes has made it possible to reduce the amount of opioids used and their adverse effects. Less opioid use has a positive effect on perioperative nutrition, improves early ambulation and facilitates earlier discharge. These elements are essential parts of enhanced recovery programs,

which are being considered and introduced into obstetrics ***(Aluri and Wrench, 2014)***.

Opioids are used via different routes to provide analgesia after cesarean delivery, depending on available techniques and resources. Systemic opioids have shown to have less efficacy and more side effects than neuraxial administration ***(McDonnell et al., 2009)***.

I. Neuraxial opioids:

To this day, neuraxial opioids, especially morphine and diamorphine, are considered to be the 'gold standard' for post cesarean pain relief. The analgesia, depending on the type of opioid used, or the route of administration, can last from 12 till 24 h after cesarean section.

a) Intrathecal opioids

Opioids, especially morphine, are central to many intrathecal-based analgesic regimens and act principally on mu-opioid receptors in the substantia gelatinosa of the dorsal horn. While intrathecal fentanyl and sulfentanil are both widely given for their intraoperative analgesic effect, unless used in high doses (e.g. fentanyl 40 to 60 μg) their effects are too short-lived to be of benefit postoperatively and they do not alter 24-hour opioid consumption. Their short analgesic duration of action contrasts with the long duration from morphine which is due to the latter's low lipid solubility, such that it takes longer to

penetrate neural tissues. The comparatively lower lipid solubility of morphine delays its onset of action and prolongs its duration of action. Moreover, the longer residence time of morphine in the cerebrospinal fluid allows it to spread rostrally, from which complications such as respiratory depression may arise ***(Dahl et al., 1999)***.

Intrathecal morphine

Many doses of intrathecal morphine have been investigated and at doses above 100 μg no clear dose-response relationship has been demonstrated. Most studies have favored doses between 25 to 50 μg maximum 100 μg to avoid the unwanted side effects of intrathecal morphine. The side effects include pruritus the most common side-effect and others which include nausea, vomiting, reactivation of oral herpes simplex, urinary retention and delayed respiratory depression ***(McDonnell et al., 2009).***

One of the most severe adverse events associated with the use of neuraxial opioids is respiratory depression. Obstetric patients with high BMIs, prior use of opioids, magnesium sulfate infusion, and respiratory comorbidities are at higher risk of developing respiratory depression under these conditions. Likewise, high progesterone concentrations during pregnancy offer some protection against respiratory depression, since progesterone is a respiratory stimulant ***(Gómez and Garzón, 2015)***.

Intrathecal diamorphine

Diamorphine, in a dose of between 250 to 375 μg, is a suitable alternative to intrathecal morphine. It is particularly popular in the United Kingdom, where it is more commonly used than intrathecal morphine for post-caesarean analgesia ***(Giovannelli et al., 2008)***.

Being more lipophilic, diamorphine has a faster onset of action and despite a short half-life in Cerebrospinal fluid, once it has diffused into neural tissues it is metabolized into its active components, 6-acetylmorphine and morphine, thus increasing its duration of action. Consequently diamorphine is attractive in providing both intra- and prolonged postoperative analgesia, its intraoperative analgesia being of similar quality to intrathecal fentanyl. Side-effects are dose-dependent, with pruritus and nausea common, occurring in 90% and 30 to 50% of women respectively after a 200 μg dose at caesarean delivery ***(Giovannelli et al., 2008).***

b) Epidural opioids

There are several approaches to epidural opioid delivery for post-cesarean analgesia. Morphine's low lipid solubility and prolonged duration of action means that a single bolus dose is often satisfactory for the first 24 hours. Fentanyl and pethidine are more lipid soluble and thus have a short duration of action, making them better suited to patient- or nurse-controlled