Intravenous infusion of Acetaminophen versus Nalbuphine as a post-operative pain relief after lower abdominal surgery

Thesis

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Presented by

Mohamed Ahmed Abdel Aziz Ahmed

B.SC. Pharmaceutical sciences (2003)

Under Supervision of

Prof. Dr. Manal Hamed El-Hamamsy

Professor of Clinical Pharmacy
Faculty of Pharmacy
Ain Shams University

Prof. Dr. Helmy Mahmoud El-sayed El-Kawaly

Professor of Anesthesia and Intensive Care

Faculty of Medicine , Al-Azhar University

Faculty of Pharmacy
Ain Shams University
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List of Abbreviations

AA	**Arachidonic acid.**
ALF	**Acute liver failure.**
APAP	**Acetaminophen.**
APS	**Acute Pain Service.**
ASA I	**Normal healthy patient.**
ASA II	**Patient with mild systemic disease.**
BMS	**Bristol-Myers Squibb Pharmaceuticals.**
COX	**Cyclo oxygenase enzyme.**
CR	**Controlled release.**
CYP	**Cytochrome P450.**
DILI	**Drug induced liver injury.**
DBP	**Diastolic Blood Pressure.**
DDS	**The Descriptor Differential Scale.**
EA	**Epidural Analgesia.**
ED	**Emergency department.**
ER	**Extended Release.**
FDA	**Food and Drug Administration.**
GI	**Gastrointestinal.**
GTN	**Glyceryl trinitrate.**
HR	**Heart rate.**
INR	**International normalized ratio.**
IR	**Immediate release.**
LANSS	**Leeds Assessment of Neuropathic Symptoms and Signs.**
LMPLA	**Liposomes Containing Mono phosphoryl Lipid A.**
MAOIs	**Monoamine Oxidase Inhibitors.**
MAP	**Mean Arterial Pressure.**
MPLA	**Mono phosphoryl Lipid A.**

MPQ	**The Mcgill Pain Questionnaire.**
NAC	**N-acetyl cysteine.**
NAPQI	**N-acetyl para benzoquinoneimine.**
NCA	**Nurse Controlled Analgesia.**
NMDA	**N-methyl d–aspartate.**
NO	**Nitric Oxide.**
NRS	**Numeric Rating Scale.**
NSAIDs	**Non-Steroidal Anti-inflammatory Drugs.**
OIH	**Opioid-induced hyperalgesia.**
POCU	**Postoperative care unit.**
PCA	**Patient Controlled Analgesia.**
PGH_2	**Prostaglandin H.**
PGHS	**Prostaglandin H Synthase.**
PO	**Per Os.**
PONV	**Post-operative nausea and vomiting.**
POX	**Peroxidase enzyme.**
PQAS	**The Pain Quality Assessment Scale.**
QID	**To be taken 4 times a day.**
SBP	**Systolic Blood Pressure.**
SkBF	**Skin Blood Flow.**
SSRIs	**Selective Serotonin Reuptake Inhibitor.**
StEP	**the Standardized Evaluation of Pain.**
SULT	**sulfonyl transferase.**
TCA	**Tricyclic Antidepressant.**
UGT	**UDP-glucoronyl transferase.**
VAS	**Visual Analogue Scale.**
VRS	**Verbal Rating Scale.**
WHO	**World Health Organization.**

ABSTRACT

Background: Pain after surgery is common, often severe and largely unnecessary. Effective relief of post-operative pain is vital and not just humanitarian reasons, this study was concerning in comparing the effect and safety of an agonist-antagonist opioid analgesic drug (Nalbuphine) to the non-opioid IV infusion of Acetaminophen in the assessment of post-operative pain developed after lower abdominal surgery.

Objective: Assessment of pain relief and safety after administering a single dose of Acetaminophen intravenous infusion against a single dose of Nalbuphine intravenous injection after lower abdominal surgery.

Methods: One hundred male patients were divided in to two groups; each group of 50 patients subjected to lower abdominal surgery, first group was given 1g Acetaminophen intravenous infusion while the other group was given 10 mg Nalbuphine intravenous injection. The patients were educated to express their pain feelings in the form of marks on the visual analogue scale (VAS) sheet.

VAS readings were taken before giving both drugs (baseline), then after 15 min, 1hr, 2h, 3h and 4h from giving the drugs of study. The difference between both groups regarding VAS and the difference inside each group (to baseline) were statistically analyzed.

Blood glucose level was measured before giving drugs (baseline), then after 1h, 2h, 3h and 4h from giving the drugs of study. The difference between both groups regarding blood glucose level and the difference inside each group (to baseline) were statistically analyzed.

Heart rate and blood pressure were measured before giving both drugs, then after 1h, 2h, 3h and 4h from giving the drugs of study. The differences between both groups were statistically analyzed.

The need for any additional analgesia was recorded in both groups and statistically analyzed.

Finally, any side effects appeared as a result of the drugs of study were noticed and recorded.

Results: After 15 min and 1h from giving both drugs, there were no significant differences between Acetaminophen group and Nalbuphine group in lowering VAS recorded.

After 2h, 3h and 4h Nalbuphine lowered VAS readings in a significant way more than Acetaminophen.

While there were no significant difference regarding blood glucose level, heart rate and arterial blood pressure between both groups at all times of study.

Both groups needed additional analgesia, although the difference between both groups was statistically insignificant.

Both drugs almost showed no adverse effects.

Conclusion: This study concludes that both Acetaminophen IV infusion and Nalbuphine IV injection were effective and safe in relieving post-operative pain in male patients suspected to lower abdominal surgeries. However, Nalbuphine IV injection is more preferable than Acetaminophen IV infusion in relieving pain after lower abdominal surgeries as it's efficacy in lowering VAS maintained until the end of the study time.

Review of literature

Pain

Pain: the good, the bad, and the ugly (Woolf, 2004).

1- Definitions

An acceptable definition of pain remains an enigma. Once thought to be a punishment from the God, the word is derived from the Latin ***peone*** and the Greek ***poine***, meaning "penalty" or "punishment". Aristotle considered pain a feeling and classified it as a passion of the soul, where the heart was the source or processing center of pain. This Aristotelian concept predominated for 2,000 years, although Descartes, Galen, and Vesalius postulated that pain was a sensation in which the brain played an important role. In the 19th century, Mueller, Van Frey, and Goldscheider hypothesized the concepts of neuroreceptors, nociceptors, and sensory input **(Stimmel, 1983).**

These theories developed into the current definition of pain by The International Association for the Study of Pain: **"an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage" (Steven and Srinivasa, 2016).**

Pain management or pain medicine is a branch of medicine which employs a multidisciplinary approach for easing the suffering and improving the quality of life of those patients living with pain **(Paul, 1997).**

Pain is often so subjective, however, that many clinicians define pain as whatever the patient says it is **(Story, 2012)**. The patient's report of pain is the most reliable indicator of pain and should be believed, even when observed behaviors do not seem to correspond **(Jane et al, 2015).** The best care is achieved when the patient comes first. This means that pain requires consciousness, so describing pain as an experience separates pain from nociception **(Huether and McCance, 2004).**

Because pain is a private, personal experience, it is impossible for us to know precisely what someone else's pain feels like. No man can possibly know what it is like to have menstrual cramps or labor pain nor can a psychologically healthy person know what psychotic patients are feeling when they say they have excruciating pain **(Veilleux and Melzack 1976).**

Pain is often referred to as the fifth vital sign because of its association with tissue damage, the pathophysiologic effect of pain on body systems and the patient's emotional response **(Jane et al, 2015).**

Response to pain is individualized because it is a physiologic, behavioral, and emotional phenomenon. Individuals have different thresholds at which pain is perceived and different pain tolerance levels. Emotions, cultural background, sleep deprivation, previous pain experience, and age are some factors that have an impact on a person's perception and interpretation of pain **(Jane et al, 2015).**

Post-operative pain is common, often severe and largely unnecessary. Effective relief of post – operative pain is vital and not just humanitarian reasons Such pain probably prolongs hospital stay, as it can affect all organ systems, including: respiratory (e.g. reduced cough, sputum retention, hypoxaemia), cardiovascular (e.g. increased myocardial oxygen consumption, ischaemia), gastrointestinal (e.g. decreased gastric emptying, reduced gut motility, constipation), genitourinary (e.g. urinary retention), neuroendocrine (e.g. hyperglycemia, protein catabolism, sodium retention), musculoskeletal (e.g. reduced mobility, pressure sores, increased risk of DVT), and psychological (e.g. anxiety, fatigue). There is now evidence that post-operative pain relief has significant physiological benefit **(Fowler and Spiess, 2013).**

The World Health Organization (WHO) estimated that approximately 80 percent of the world population has either no or insufficient access to treatment for moderate to severe pain. Every year tens of millions of people around the world suffer from such pain without treatment. Yet the medications to treat pain are cheap, safe, effective, and generally straightforward to administer **(Lohman et al, 2010).**

In 2011, institute of Medicine declared that over 116 million patients suffer with chronic pain, and this annually costs of 560–635 billion dollars in direct treatment costs and lost productivity **(Pradeep, 2016).**

2- Classifications of pain

Multiple classifications have been used to describe pain states on the basis of etiology, anatomic source and duration **(Steven and Srinivasa, 2016).**

a) Pain is classified according to etiology to:

i-Nociceptive pain: Nociceptive pain typically is classified as either somatic (arising from skin, bone, joint, muscle, or connective tissue) or visceral (arising from internal organs such as the large intestine or pancreas) **(Hall, 2011).**

ii-Neuropathic pain / functional pain: Neuropathic and functional pain is distinctly different from nociceptive pain in that it becomes disengaged from noxious stimuli or healing and often is described in terms of chronic pain. Neuropathic pain is a result of nerve damage, whereas functional pain can be thought of as abnormal operation of the nervous system ranged from deficits perceived (e.g numbness) to hypersensitivity (e.g hyperalgesia) to paresthesias (e.g tingling).

Examples of neuropathic pain as in diabetic neuropathy, post herpetic neuralgia, spinal cord injury pain, phantom limb pain and post stroke central pain also examples for functional pain syndrome are fibromyalgia, irritable bowel syndrome, sympathetic induced pain, tension-type headaches, and some non-cardiac chest pain) **(Woolf, 2004).**

iii-Inflammatory pain: where various mediators released at a site of tissue inflammation causing activation and sensitization of the pain pathway as in appendicitis, rheumatoid arthritis, Examples for these mediators are:

Proinflammatory cytokines as IL-1-alpha, IL-1-beta, IL-6 and TNF-alpha, chemokines, reactive oxygen species, vasoactive amines, lipids, ATP and other factors released by tissue resident mast cells, vascular endothelial cells and leukocytes **(Joseph et al, 2008).**

b) Pain is classified according to anatomic source to:

i- **Somatic pain** that is typically well localized and generally results from injury or disease of the skin, musculoskeletal structures, and joints. Different types of stimulation can evoke pain

by binding to distinct receptors (also known as nociceptors), which can be broadly categorized as chemosensitive, thermosensitive, mechanosensitive, or polymodal.

ii- **Visceral pain** it is arises from internal organ dysfunction and can result from inflammation, ischemia, occlusion of flow resulting in capsular or organ distention (e.g., renal stones, bowel obstruction, cholecystitis), or functional disease (e.g., irritable bowel syndrome). In contrast to somatic pain, visceral pain is usually diffuse and poorly localized, is often referred to somatic regions (e.g., myocardial ischemia radiating into the arm), and tends to be associated with exaggerated autonomic reflexes and greater emotional features **(Steven and Srinivasa, 2016).**

c) Pain is classified according to duration to:

i-Acute pain:

Acute pain can be a useful physiologic process warning individuals of disease states and potentially harmful situations. severe, unremitting, undertreated, acute pain, can produce many deleterious effects (e.g., psychological problems). Acute pain duration less than 3 to 6 months and usually is nociceptive, although it can be neuropathic in nature, Common causes of acute pain include surgery, acute illness, trauma, labor, and medical procedures. Usually it disappears when the underlying cause has been treated or has healed **(Joseph et al, 2014).**

Acute pain assessment both at rest (important for comfort) and during movement (important for function and risk of postoperative complications), with one dimensional tools such as numeric rating scales or visual analogue scales **(Breivik H et al, 2008).**

ii-Chronic pain:

When pain persists for months to years, more than 6 months, leading to a chronic pain state with features quite different from those of acute pain. This type of pain can be nociceptive, neuropathic/ functional, or both. Chronic pain can be itself classified to: pain that persists beyond the normal healing time for an acute injury (e.g., complex regional pain syndrome), pain related to a chronic disease (e.g., pain secondary to osteoarthritis), pain without an identifiable organic cause (e.g., fibromyalgia) (**Honorio et al, 2011**). Chronic pain is perhaps best construed as a "disease" that serves no useful purpose **(Steven and Srinivasa, 2016).**

Chronic pain assessment and its impact on physical, emotional, and social functions require multidimensional qualitative tools and health-related quality of life instruments **(Breivik H et al, 2008).**

iii-Cancer pain:

Pain associated with potentially life-threatening conditions is often called malignant pain or simply cancer pain. This type of pain includes both chronic and acute components and often has multiple etiologies. It is pain caused by the disease itself (e.g., tumor invasion, organ obstruction), treatment (e.g., chemotherapy, radiation, surgical incisions), or diagnostic procedures (e.g., biopsy) **(Joseph et al, 2008).**

d) Pain is essentially divided into two broad categories:

i- **Adaptive pain** that contributes to survival by protecting the organism from injury or promoting healing when injury has occurred.

ii- **Maladaptive pain** is an expression of the pathologic operation of the nervous system; it is pain as disease **(Clifford, 2004).** Also it is called dysfunctional Pain, which is a group of pain syndromes that have been characterized by amplification of pain signaling in the absence of either inflammation or injury (as in nociceptive pain) or damage to the nervous system (as in neuropathic pain). These conditions include pain states such as fibromyalgia, irritable bowel syndrome and interstitial cystitis. The precise pathophysiologic mechanisms of pain in these disorders are still being elucidated, although they share some features of neuropathic pain such as augmented sensory perception and altered central neurotransmission **(Steven and Srinivasa, 2016).**

3- Pain regulators:

Chemical substances that modulate the transmission of pain are released in to the extracellular tissue when tissue damage occurs, these mediators irritate nerve endings and stimulate it. Examples for these mediators are histamine, leukotrienes, bradykinin, prostaglandins and substance P. Although body has its own mechanism to manage pain, this step takes place by releasing certain substances inhibit the action of neurons in transmitting pain impulses, these substances known as endogenous opioids (β-endorphins and dynorphins) and is released by fibers in the dorsal horn, brain stem and peripheral tissues. Endorphins levels vary from person to another, so different persons experience different levels of pain **(Hall, 2011).**