Influence of Preemptive Intravenous Ibuprofen on Post-Operative Pain and Opioid Consumption after Laparoscopic Cholecystectomy

Thesis

Submitted for Partial Fulfillment
of Master Degree in Anesthesia

By

Daoud Mahamad Hissein
M.B.B.Ch, Tripoli University 2009, Resident of Anesthesia and Intensive Care, Ministry of Health N'djamena Chad

Under Supervision of

Prof. Dr. Raafat Abdel-Azim Hammad
Professor of Anesthesia, Intensive Care and Pain Management
Faculty of Medicine – Ain Shams University

Prof. Dr. Manal M. Kamal Shams Eldin
Professor of Anesthesia, Intensive Care and Pain Management
Faculty of Medicine – Ain Shams University

Dr. Mohammad Mohammad Kamal
Lecturer of Anesthesia, Intensive Care and Pain Management
Faculty of Medicine – Ain Shams University

Faculty of Medicine - Ain Shams University
2018

سورة البقرة الآية: ٣٢

Acknowledgments

First and foremost, I feel always indebted to ***Allah*** *the Most Beneficent and Merciful.*

I wish to express my deepest thanks, gratitude and appreciation to ***Prof. Dr. Raafat Abdel-Azim Hammad****, Professor of Anesthesia, Intensive Care and Pain Management, Faculty of Medicine,. Ain Shams University, for his meticulous supervision, kind guidance, valuable instructions and generous help.*

Special thanks are due to ***Prof. Dr. Manal M. Kamal Shams Eldin****, Professor of Anesthesia, Intensive Care and Pain Management, Faculty of Medicine, Ain Shams University, for her sincere efforts, fruitful encouragement.*

I am deeply thankful to ***Dr. Mohammad Mohammad Kamal****, Lecturer of Anesthesia, Intensive Care and Pain Management, Faculty of Medicine, Ain Shams University, for his great help, outstanding support, active participation and guidance.*

Daoud Mahamad Hissein

Dedication

To:

My parents

for their endless love, support,

and continuous care

My wife

&

My Family

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List of Abbreviations

Abb.	Full term
ACU	*Area under the curve*
ASA	*American Society of Anesthesiologists*
BSA	*Bovine serum albumin*
Cmax	*Maximum concentration*
CNS	*Central nervous system*
COX-1	*Cyclo-oxygenase-1*
COX-2	*Cyclo-oxygenase-2*
CYP_2C_8	*Cytochrome P_2 C_8*
ECG	*Electrocardiogram*
ED_{50}	*Effective dose 50*
GI	*Gastrointestinal*
IV	*Intravenous*
NSAIDs	*Non steroidal anti-inflammatory drugs*
OTC	*Over the counter*
PACU	*Post anesthesia care unit*
PCA	*Patient controlled analgesia*
PD	*Parkinson's disease*
PGS	*Prostaglandins*
RA	*Rheumatoid arthritis*
SD	*Standard deviation*
SPO_2	*Peripheral oxygen saturation*
US	*United States*
USFDA	*US Food and Drug Administration*
VAS	*Visual analogue score*
WDR	*Wide Dynamic Range*

INTRODUCTION

Laparoscopic cholecystectomy is regarded as the gold standard surgical technique for gallstone diseases ***(Soper et al., 1992)***. This procedure results in less postoperative pain, a better cosmetic outcome, shorter hospitalization, faster healing, and earlier mobilization than open cholecystectomy ***(Johansson et al., 2005).***

Nonetheless, pain after laparoscopy may be moderate or even severe for some patients, and may require opioid treatment. Interestingly, the type of pain after laparoscopy differs considerably from that seen after laparotomy. Indeed, whereas laparotomy results mainly in parietal pain (abdominal wall), patients complain more of visceral pain after operative laparoscopy.

Factors involved in the development of this pain include phrenic nerve irritation resulting from the insufflation of CO_2 into the peritoneal cavity, abdominal distension, port-site incisions, trauma associated with removal of the gallbladder, sociocultural status, and individual factors ***(Protic et al., 2017).***

Postoperative pain is an acute sensation accompanied by an inflammatory process associated with surgical trauma and that decreases with tissue healing. Successful postoperative analgesia is known to prevent the majority of pain-related effects occurring in the patient, such as inability to breathe

comfortably, increased workload in the cardiovascular system, thromboembolic events with delayed mobilization, and increased stress response with neuroendocrine and sympathetic nervous system activation ***(Kehlet and Holte, 2001; American Society of Anesthesiologists, 2012).***

Analgesic administration before surgical trauma has been shown in experimental and clinical studies to be capable of reducing posttraumatic sensitivity in the spinal cord and secondary hyperalgesia ***(Woolf, 1995).*** If analgesic treatment is started after a painful stimulus then difficulties may be experienced in the treatment of postoperative pain in such cases because peripheral hypersensitivity and central nervous system hyperexcitability may occur ***(Woolf and Chong, 1993).***

Ibuprofen is a propionic acid derivative with anti-inflammatory, antipyretic, and analgesic effects, like other non-steroidal anti-inflammatory drugs (NSAIDs). The oral form has for long been safely used, and it is one of the most commonly employed NSAIDs. The intravenous (IV) form of ibuprofen has been used in the treatment of mild and moderate pains and to treat severe pain in combination with opioids. Although there are still insufficient studies concerning IV ibuprofen, it has been shown to be capable of use in the treatment of postoperative pain ***(Kroll et al., 2011; Moss et al., 2014; Gago et al., 2016).***

Aim of the Work

The purpose of this study is to investigate the effects of a single preemptive dose of IV ibuprofen on postoperative pain and opioid consumption in patients undergoing laparoscopic cholecystectomy.

PHARMACOLOGY

Ibuprofen is (2RS)-1[4-(2-methyl propyl) phenyl] propionic acid (BP. 2004). Ibuprofen was the first member of propionic acid derivatives to be introduced in 1969 as a better alternative to Aspirin. Gastric discomfort, nausea and vomiting, though less than aspirin or indomethacin, are still the most common side effects ***(Tripathi et al., 2003).***

Ibuprofen is the most commonly used worldwide and most frequently prescribed NSAID ***(Bradbury, 2004; Abrahm et al., 2005).*** It is a non-selective inhibitor of cyclooxygenase- 1 (COX-1) and Cyclooxygenase-2 (COX-2) ***(Chavez and DeKorte, 2003).***

Although its anti-inflammatory properties may be weaker than those of some other NSAIDs, it has a prominent analgesic and antipyretic role. Its effects are due to the inhibitory actions on cyclooxygenases, which are involved in the synthesis of prostaglandins. Prostaglandins have an important role in the production of pain, inflammation and fever ***(Wahbi et al., 2005).***

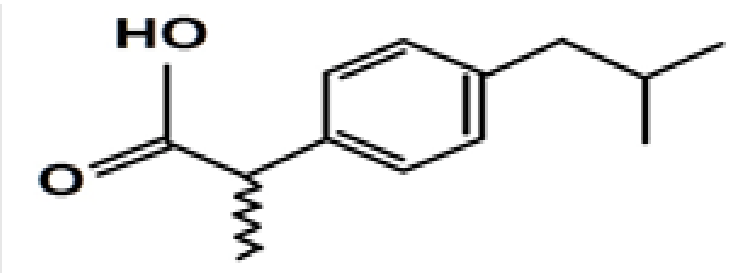

Figure 1: Structural formula of ibuprofen ***(Chavez and DeKorte, 2003).***

Intravenous Ibuprofen

In June 2009, the USFDA approved intravenous ibuprofen (Caldolor , Cumberland Pharmaceuticals Inc.) for the treatment of mild to moderate pain, moderate to severe pain as an adjunct to opioids and fever in adult patients ***(Smith and Voss, 2012).***

Pharmacodynamic Properties:

Ibuprofen is a propionic acid derivative that, like other NSAIDs, has analgesic, anti-inflammatory and antipyretic effects ***(Vane and Botting, 1998).*** Although the mechanisms of action of ibuprofen are not fully understood***, (US prescribing information. Nashville (TN), 2009)***. Its effects may be related to inhibition of cyclo-oxygenase isoenzymes (COX-1, the constitutively expressed isoform, and COX-2, the inducible isoform), leading to inhibition of prostaglandin synthesis (mediators of pain and inflammation) ***(Vane and Botting, 1998).***

Ibuprofen causes rapid, reversible, competitive inhibition of both COX-1 and COX-2 isoenzymes ***(Cashman, 1996; Van Hecken et al., 2000).*** In healthy adult volunteers, oral ibuprofen 800 mg three times daily inhibited COX-1 activity by 88.7% and COX-2 activity by 71.4% ***(Van Hecken et al., 2000).***

The selectivity of individual NSAIDs for the COX isoenzymes differs and may determine the likelihood of adverse effects. NSAIDs that have a COX-1: COX-2 inhibition ratio higher than 1 are more likely to be associated with adverse

events than NSAIDs that have a ratio of less than 1 ***(Vane and Botting, 1998; Van Hecken et al., 2000).***

Inhibition of the COX-1 isoenzyme is generally associated with toxicological effects of NSAIDs, whilst inhibition of the COX-2 iso enzyme is generally associated with the beneficial effects ***(Vane and Botting, 1998; Van Hecken et al., 2000).***

Ibuprofen, like many NSAIDs, is a racemic mixture, with in vivo and in vitro studies indicating that the S-enantiomer is responsible for clinical activity ***(US prescribing information. Nashville (TN), 2009; Hayball et al., 1996).*** The R-enantiomer is thought to be pharmacologically inactive and is slowly and incompletely interconverted to the S-enantiomer in adults; thus, the R-enantiomer acts as a circulating reservoir to maintain levels of active drug ***(US prescribing information. Nashville (TN), 2009).***

In addition to exerting effects via central and peripheral inhibition of COX isoenzymes, ibuprofen may modulate COX-independent signal transduction pathways, including inhibiting the activation of nuclear factor kappa B (a transcription factor that acts as a central mediator of the immune response), inhibiting neutrophil activity and actions on leukocytes to prevent inflammatory edema ***(Cashman et al., 1996; Tegeder et al., 2001).***