CLINICAL AND EXPERIMENTAL EVALUATION OF DICLOFENAC SODIUM FOR POSTOPERATIVE PAIN RELIEF

THESIS

Submitted in Partial Fulfilment of the M.D.. Degree in Anaesthesiology

By

AIMAN ADEL ABD RABO DESSOUKI

M.B.,B.Ch., M.Sc. Anaesthesiology

SUPERVISED BY

PROF. Dr.
INAS KAMEL
PROFESSOR OF ANAESTHESIA
FACULTY OF MEDICINE
CAIRO UNIVERSITY

PROF. Dr.
OMAYMA GOUHAR
PROFESSOR OF CLINICAL PATHOLOGY
FACULTY OF MEDICINE
CAIRO UNIVERSITY

PROF. Dr.
NAHED MOUSA
PROFESSOR OF PHARMACOLOGY
FACULTY OF MEDICINE
CAIRO UNIVERSITY

FACULTY OF MEDICINE
CAIRO UNIVERSITY
1994

ACKNOWLEDGEMENT

I wish to express my deepest obligation and everlasting gratitude to **Prof. Dr. Inas Kamel**, Professor of Anaesthesiology, Cairo University, to whom no words of thanks and feelings are sufficient. Her continous encouragement, advise, support and guidance helped me through the rough times.

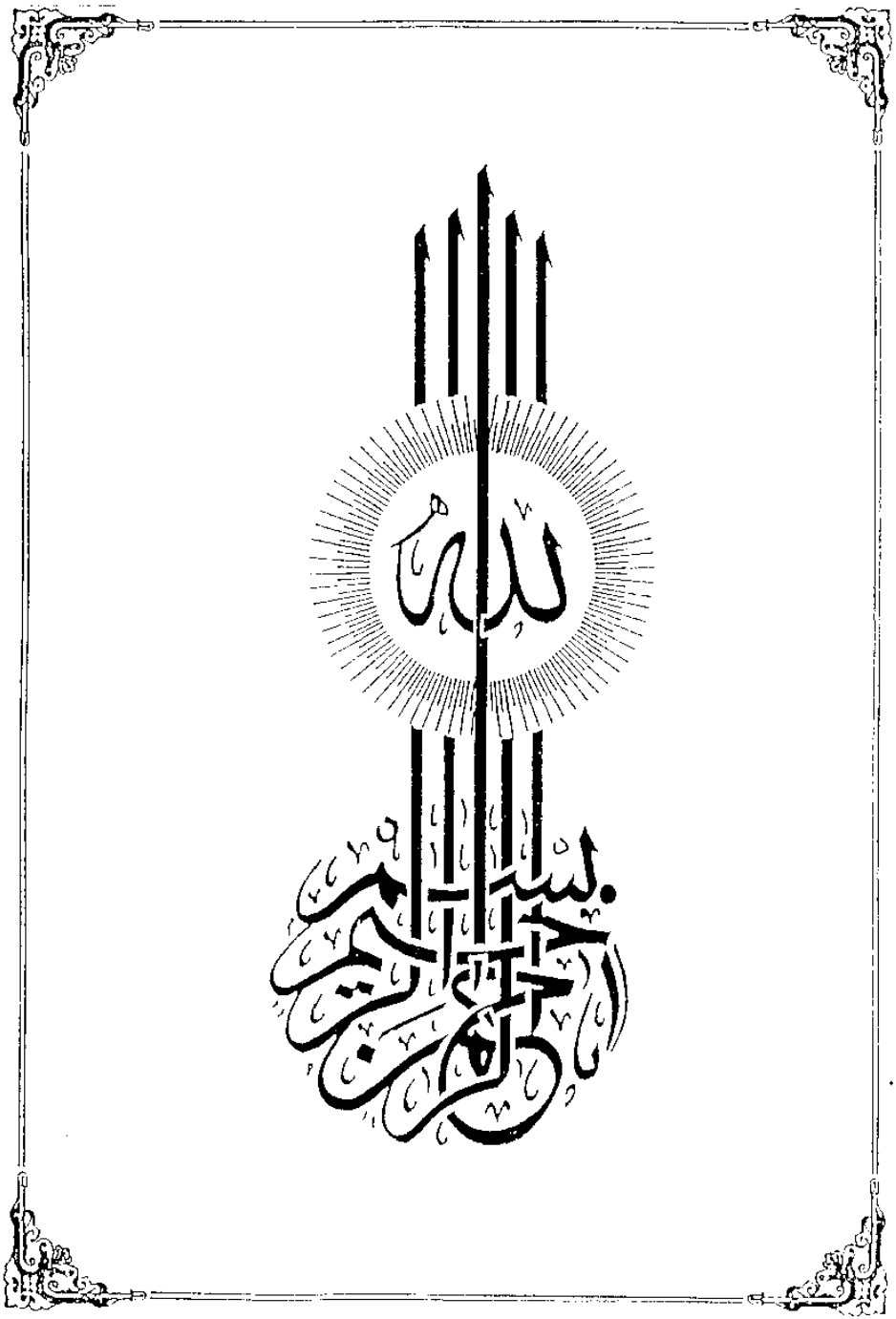
I am greatly indebted and grateful to **Prof. Dr. Nahed Moussa**, Proessor of Pharmacology, Cairo University. As A Supervisor, she made many suggestions, revised the results and followed the work step by step.

A special appreciation is heartly paid to **Prof. Dr. Omayma Gohar**, Professor of Clinical Pathology, Cairo University, for her valuble time, and advise.

I would also like to express my appreciation to **Dr. Ibtessam Abd El Gaffar,** Lecturer of Pharmacology, for her continous, close supervision, valuble help and assistance.

My cordial thanks are due to **Prof. Dr. Kadry Madkour** who carried out the pharmacolocical statistical analysis.

Finally, I have to thank all my colleagues in the Cardio-Thoracic Department, **Prof. Dr. Fawzeya Abu El-Futuh**, Professor of Anaesthesiology, **Prof. Dr. Hoda Abd El Kader**, Professor of Anaesthesiology, **Prof. Dr. Ahmad Helmy**, Assistant Professor of Anaesthesiology, **Dr. Tarek Kadah**, Lecturer of Anaesthesiology, **Dr. Hoda Okasha**, Lecturer of Anaesthesiology, for their great help, time and encouragement althrough the preparation of this work.



CONTENTS

INTRODUCTION

- **AIM OF THE WORK**
- **FACTORS THAT MODIFY POSTOPERATIVE PAIN**

بسم الله الرحمن الرحيم

INTRODUCTION

INTRODUCTION

The problem of inadequate relief of postoperative pain has been recognised for many years and has been the subject of considerable research. Millions of patients world-wide undergo surgery each year and would benefit from effective postoperative pain relief. Although effective pain control is essential for optimal care of surgical patients, many patients continue to experience considerable discomfort [1,2,3,].

It should be stressed on, that total postoperative pain relief cannot be achieved by a single agent or method, without major expenditure on equipment and surveillance systems, or without significant side effects and therefore, combined analgesic regimens (balanced analgesia) are recommended. The 3 L system (Lowest dose; Least side effects; Least problematic) should be always considered when analgesic drugs are prescribed.

After major abdominal or thoracic surgery, it has been reported that more than 50% of patients suffer severe pain, and administration of opioids may result in respiratory depression[4].

Non steroidal anti-inflammatory drugs (NSAID's) produce analgesia by inhibiting the arachidonic acid cascade at the peripheral

site of the nociceptive process. Prostaglandin's alone induce pain, only in concentrations that are unlikely to occur physiologically, they rather seem to enhance the potency of algesic (pain inducing) substances, such as bradykinin, that stimulate nerve endings of unmyelinated C fibres and small-diameter A-fibres to elicit noxious afferent input. Hence they work mainly peripherally and this is different from the working of the opioids, whose action is central, within the nervous system. For postoperative use, NSAID's have traditionally been restricted for providing pain relief after minor, usually body surface surgeries[(5)].

However recent studies have also indicated that they may be useful adjuvants to opioids in major surgeries[(6)], and that the combination of drugs, acting by different mechanisms, can result in additive or synergistic analgesia[(7)].

The reduction in the overall dose of opioids will decrease the risk of opioid-induced side effects, in particular respiratory depression and nausea.

AIM OF THE STUDY

Since NSAID's act by interfering with the initiation of the nociceptive process, it would seem logical to start NSAID treatment before the initiation of the nociceptive insult, so that activation and sensitisation of peripheral nociceptors is minimized[(6)].

McQuay (1988) has demonstrated that an effective reduction in postoperative pain can be achieved if an analgesic is given before surgery[(5)].

In the absence of regional analgesia or opioids, surgery results in an afferent bombardment of the CNS with resultant hyperexcitability of the spinal cord. The administration of analgesics before the operation reduces this CNS barrage and prolonged cord hyperexcitability, so that activation and sensitisation of peripheral nociceptors are minimised. Only few studies have compared pre versus postoperative treatment with NSAID's for analgesic efficacy.

The aim of the study is to compare, in a single blind investigation, the analgesia obtained by DICLOFENAC given both pre and postoperatively, or only postoperatively, in patients after major surgery under general anaesthesia. The efficiency of analgesia will be assessed by consumption of morphine given. A third group of patients who will be given only morphine, will act as a control group.

This study is designed to assess clinically and pharmacologically the analgesic efficacy and safety of diclofenac compared with morphine. The effect of diclofenac on operative blood loss, skin bleeding and platelet aggregation will be also evaluated (Hematological analysis).

FACTORS THAT MODIFY POSTOPERATIVE PAIN

The main role of the anaesthetist, is to enable patients to undergo surgical and other painful or uncomfortable procedures without pain or distress. Although this is almost invariably achieved during the procedure, the pain and discomfort which are present after surgery are usually less effectively relieved.

Postoperative pain is an acute pain which starts with the surgical trauma, unless a painful state exists such as a fractured bone or trauma patients; and usually ends with tissue healing.

When the patient first awakes after surgery, the period of the first **"fast"** pain is over (intra-operative), and the pain of which the patient initially becomes aware is the poorly localised "second" pain[(8)].

A number of factors may influence the intensity, quality and duration of postoperative pain[(9)]. The most important of these are:

1. The site, nature, and duration of surgery.
   The results for the different nature of operations result in different postoperative pain perception.

2. The type and extent of the incision.
   Whether a cholecystectomy incision, is a Kocher incision or a right paramedian incision, as it varies in postoperative pain (TABLE -I-).

- TABLE -I-

% of patients who require various numbers of analgesic injections

OPERATION	NO ANALGESIC	1 OR MORE INJECTION
Minor chest wall	81.7 %	0 %
Inguinal Hernia	52.4 %	2 %
Appendicectomy	22.5 %	8.8 %
Lower abdominal surgery	17.6 %	40 %
Upper abdominal surgery	4 %	45-65 %

From Parkhouse, Lambrechts and Simpson[10] 1961

3. The physiological makeup of the patient.

The behavioural external response to postoperative pain is modified because patients tend to behave in ways expected of them. For example, men are expected to be more tough and stoical and may therefore ask for fewer injections of analgesic drugs even when experiencing severe pain. Patients of particular social and racial groups may also respond to pain to a greater or lesser extent[11].

4. Attitudes of Staff

Medical and nursing staff will often have their own ideas about which analgesics should be given, how often and to which patients.

-Nurses may attribute the distress of patients to psychological factors rather than pain.

-Even when medication is written up, many nurses will not give an injection unless THEY think it is needed.

-Medication for pain is often not given unless the patients asks for it.

-There is a trend to give more analgesics to women than to men and to adults than to children.

-Patients who complain excessively may have doses of drugs withheld, or be given a placebo.

-Fear of respiratory depression or hypotension or even vomiting may result in withholding of opioid analgesia.

-Some staff consider that pain should be borne stoically as it will help to build character.

-Some are concerned about the possibility of addiction[16].

5. The preoperative psychological, physiological information about the postoperative period may have been acquired by patients from their own experience, or from what others have described. This information will affect the experience after surgery, and the perception of, and response to, pain can be increased or decreased by such information.

Egbert and Colleagues (1964)[14] carried out an important study in which they provided some patients who were about to undergo surgery with detailed information about postoperative pain and instructed them on how to ease the pain by muscle relaxation and how to move with the minimum of pain. These are termed ***"coping strategies"***. All this information was given in an atmosphere of enthusiasm and confidence and was reinforced on the day after the operation. These patients were compared with a group who were not given this ***"special care "***. It was found that the ***"special care"*** patients required less analgesia and left the hospital 2,7 days earlier[14].

6. Premedication

The objectives of premedication were defined by Mushin (1960)[15] as:

1) To prevent undesirable side effects.

2) To assist anaesthesia.

3) To prevent autonomic reflexes.

4) To lessen preoperative anxiety.[15]

7. Attitudes of other patients

Experimental pain studies have demonstrated that pain perception can be altered when subjects experiencing a painful stimulus can observe another subject, a ***"model"*** being apparently subjected to the same stimulus. When the model is tolerant the subject's response to pain is reduced; and vice versa, if the model is intolerant[16].

8. The psychological makeup of the patient (personality of the patient).

This has been quite extensively investigated, psychometric techniques providing a means of measuring anxiety, neuroticism and extroversion. High preoperative neuroticism scores have been found to be associated with several aspects of postoperative pain. Greater degree of postoperative pain will need larger postoperative morphine requirements leading to a greater degree of impairment of vital capacity, and higher incidence of postoperative chest infections[12].

ANXIETY:

Preoperative anxiety can be measured as A-trait (i.e. anxiety proneness) and A-state (i.e. anxiety in response to circumstances). Higher A-state scores correlated with higher postoperative pain scores, and higher A-trait scores correlated with increased morphine requirements[13].

Anxiety is provoked by surgery and will be present during the postoperative period, especially on first recovery from anaesthesia. At this time , the patient feels, and is very helpless in contrast to his/her autonomy only a few hours before. Experimental pain studies have shown that subjects ***"overestimate"*** the severity of a painful stimulus when it is applied in an atmosphere of anxiety, but in a relaxed atmosphere, the intensity of the stimulus is ***"underestimated".***

The patient's feeling of anxiety and helplessness may contribute to the severe pain which often occurs during the postoperative period and can be difficult to relieve. A few hours later, when the patient is fully awake and oriented and can better understand the situation the pain will seem less severe and can be easier to relive[13].