SAFTY AND EFFICACY OF TRANSDERMALFENTANYL VERSUS ORAL MORPHINE IN PEDIATRIC CANCER PAIN

Thesis

Submitted for Partial Fulfillment of M. D. Degree in Anesthesia and Pain Relieve

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فاعلية وامان لاصقات الفنتانيل مقارنة بالمورفين عن طريق الفم فى الام سرطان الاطفال

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DR; FAWZY

List of Abbreviations

5HT= 5- HydroxyTryptamine

ATC=Around The Clock

cAMP= Cyclic Adenosine Mono Phosphate

CNS= Central Nervous System

CSF= Cerobrospinal Fluid

E= Embryonic day

EMLA= Eutectic Mixture of Local Anesthetic

G- Protein= Guanine nucleotide Binding Protein

G= glutamate

GABA= Gaba Amino Putyric Acid

GDP= Guanosine Diphosphate

GIT= Gastrointestinal tract

GRP= Calcitonin Gen Related Peptide

GTP= Guanosine Triphosphate

h= hour

IV= Intravenous

IM= Intramuscular

kg= kilogram

mcg= Micro Gram

mg= milligram

MP= mixed Pain

NGF= Nerve Growth Factor

NK1= neurokinin 1

NK2= neurokinin 2

NMDA= N-methyl D-aspartat

NP= nucleus proprius

NcP= Nociceptive Pain

OP= Opioid Receptor

P= post natal

PAG= PeriAquiductal Grey

PCA= Patient Controlled Analgesia

prn= Per request Need

q= Every

SG= Substentia Gelatinosa

SP= Substance P

TTS= Transdermal Therapeutic System

VAS= Visual Analog Scale

VIP= Vasoactive Intestinal Peptide

VP= Visceral Pain

VRPS = Verbal Rating Pain Scale

Introduction

Pain in infants and children is still not properly treated. This is attributed to the lack of knowledge about the anatomical and physiological properties of pain perception in infants and children. Also, there is no sufficient pharmacological products or studies to categorize management of pain in pediatrics, we are usually using preparations and equipments designed for adults. Added to that, the difficulty of communication with the children, to assess properly the painful condition and the outcome of our management [1,2].

Children with cancer don't need to suffer unrelieved pain; effective pain management for all children must have the major priority. Families, nurses and specialists play an important role through training programs to support, understand and share in the treatment of critically-ill children [2].

Morphine is the corner stone drug for controlling severe pain for most children and is the standard against which the analgesic properties of other drugs are measured. Oral morphine (Tablets) vary in strength 5 - 100 mg, crushing tablets eliminates the sustained release properties. The recommended dose for children is based on 0.3 mg/kg 4 hourly. Using sustained formula we have to give 0.6 mg/kg every 8 hours or 0.9 mg/kg every 12 hours [2].

It is common knowledge among specialists that sustained release oral formulae especially strong opioids play a major role in cancer pain management over the last few years. Apart from pain there are many

other symptoms presenting in cancer patients (such as anorexia, nausea, vomiting, dysphagia and other GIT symptoms). Although the great majority of these symptoms are cancer related, oral analgesics and especially opioids can however further aggravate the situation. Looking for a simpler and less invasive mode of administration for these patients, the transdermal application was found to offer interesting novel alternative, with a better profile of side effects [3].

The transdermal delivery route allows the release and absorption of drug in sustained manner without the need for intravenous access. This results in relatively constant serum concentration that may decrease adverse effects associated with fluctuations in drug concentrations. Fentanyl is the first narcotic analgesic available in a transdermal drug delivery system [2].

Fentanyl an opioid with pure μ-agonist activity is 75 – 100 times more potent than morphine on a molar basis. Parenteral fentanyl is a short acting analgesic at non-steady state conditions, when half-life time is primarily determined by redistribution. Due to low molecular weight and high lipid solubility fentanyl can be administrated transdermaly. The cutaneous uptake from a transdermal therapeutic system (fentanyl TTS) is proportional to the application area. After application of a patch, peak serum levels are approached within 8-12 hours. The transdemal therapeutic system delivers fentanyl continuously for up to 72 hours.

Aim of the work:

To assess the safety, tolerability, feasibility and efficacy of transdermal fentanyl in comparison with oral morphine in pediatric cancer pain in a trial to obtain an alternative novel route for oral opioids in pediatric cancer pain.

Patients and Methods

Patients:

This study enrolled 30 children with cancer pain 4 - 15 years of age. Patients were randomly divided into two equal groups (**G I** & **G II**).

Exclusion criteria:

Patients excluded from the study, who had:

1-History of hypersensitivity to narcotic analgesic.

2-History of chronic obstructive pulmonary disease.

3-Acute respiratory distress, severe hepatic or renal insufficiency, severe cardiac or central nervous system disease or active skin disease.

4-If they still receiving opioid treatment (must be opioid naive).

Methods:

After obtaining a written informed consent from patients and full clinical examination, each group was 15 in number. Group I (G I) received oral morphine tablets (MST) in a dose of 0.9 mg/kg /12 hours (30-40 mg/day) for 2 weeks (phase I), then received oral tramal 2 mg/kg /12 hours with non opioid analgesics such as acetaminophen 10-15mg/kg orally every 6 hours and/or NSAIDs such as ibuprofen 10 mg/kg every 8 hours or naproxin 5mg/kg orally every 12 hours, for 1 week (1 week wash out) (phase II), then received fentanyl transdermal patch of 25 u/h applied to normal skin of upper chest, upper back or upper arm which changed every 72 hours, skin sites rotated with each application to reduce the

possibility of skin irritation, for 2 weeks(phase III). Group II (G II) received fentanyl transdermal patch of 25 u/h applied to normal skin of upper chest, upper back or upper arm which changed every 72 hours, skin sites rotated with each application to reduce the possibility of skin irritation (phase I), then received oral tramal 2 mg/kg/12h with non opioid analgesics such as acetaminophen 10-15mg/kg orally every 6 hours and/or NSAIDs such as ibuprofen 10 mg/kg every 8 hours or naproxin 5mg/kg orally every 12hours for 1 week (1 week wash out) (phase II), then received oral morphine tablets (MST) in a dose of 0.9 mg/kg /12 hours (30-40 mg/day) for 2 weeks(phase III). At the end of the study patients decided the type of the treatment they continued and the cause of the choice recorded.

Clinical assessment of patients:

* Patients were monitored daily during the study (for respiratory rate, blood pressure, O_2 saturation).

* Demographic and disease related data collected: patient age in years, weight in kgms, type of pain (noceceptive, visceral, neuropathic or combined), type of cancer, and type of the treatment they continued and the cause of the choice for each patient.

* Side effects were recorded:

1-**Nausea,** either:

- No nausea.

- Mild nausea needs no treatment.

-Moderate nausea needs occasional treatment, such as metclopramid 0.1 – 0.2 mg/kg orally every 6 hours.

-Severe nausea needs persistent treatment, such as metclopramid 0.1 –0.2 mg/kg orally every 6 hours with maximum 15 mg/day.

2-**Vomiting**, either:

- No vomiting.

- Mild vomiting needs no treatment.

-Moderate vomiting needs persistent treatment, such as metclopramid 0.1 –0.2 mg/kg orally

-Severe vomiting needs persistent treatment, such as metclopramid 0.1 – 0.2 mg/kg orally every 6 hours with maximum 15 mg/day.

3-**Constipation**, either:

- No constipation.

- Mild constipation needs no treatment.

-Moderate constipation needs occasional treatment, such as increase fluids and bulk and stool softeners as decussate in combination with stimulant (senna).

-Severe constipation needs persistent treatment, such as increase fluids and bulk and stool softeners as decussate in combination with stimulant (senna).

4-Sedation, either:

-No drowsiness: wide awake.

- Mild : drowsy needs no treatment.

-Moderate : dozing intermittently needs occasional treatment, such as psychostimulants (dextroamphetamine or methylphenidate 0.05 -0.1 mg/kg, twice daily in the morning and mid-day.)

-Severe : mostly sleeping needs persistent treatment, such as psychostimulants (dextroamphetamine or methylphenidate 0.05 -0.1 mg/kg, twice daily in the morning and mid-day, maximum dose 0.5 mg/kg/day).

* Other side effects as respiratory depression (respiratory rate < 8c/m or O_2 saturation < 90%), dermatological reactions, urine retention, hallucination and myoclonus, recorded and treated.

* Pain measurement: Verbal rating pain score (VRPS) from the patient. Children asked to indicate how much pain they have with 5 verbal anchors where 0= no pain, 1= mild pain, 2= moderate pain, 3= severe pain, 4= worse pain and 5= worst possible pain.

Statistical analysis:

All clinical data tabulated, summarized, and expressed as mean values ± standard deviation and using analysis of variance with repeated measures, a P value of ≤ 0.05 will be considered statistically significant.

Equipments and Drugs

Duragesic patch 25 u/h (Jensen)

MST (10-15-30mg)

Tramal (50mg), non opioid analgesics and Adjuvant drugs.

Review of Literature

Pain development and perception in children

Pain in children is often disregarded, denied or underestimated, for two main reasons: First, some adults feel helpless when a child has pain, especially chronic pain, so that they may prefer to ignore things they can not fix. Second, the intensity of pain is conditioned by physiological, psychological, behavioral, and environmental factors that make the measurement and assessment of pain difficult, especially in small children who cannot adequately express themselves [1].

Interest in the management of all forms of pain in children has been escalated in exponential fashion over the past 15-20 years. This interest stemmed from the realization that pain management in children was an area neglected, received almost no research attention, and clinically appeared to be sub-optimal.

The publication of several significant studies led to the realization that much could be done to improve the agony of children. The recent development of suitable pain measurement and assessment tools has improved the ability to conduct such research. Unique to infants and children is the immaturity of their nervous system. The developing nervous system is particularly vulnerable to, and can be permanently altered by tissue insult at critical stages of development.

Pain in infancy, through surgery, intensive care or chronic diseases must be adequately understood and well treated. The efficacy of support and palliative care in chronic illness depends upon the quality of pain relief achieved and there is evidence that adequate pain relief may aid recovery and repair following acute tissue trauma [2].