This pdf / A file is a protocol of thesis under the title Haemodynamic Effects of Paracetamol (Acetaminophen) as Extended Intravenous Infusion Versus Intravenous Bolus in Septic Shock patients.

30/8/2020

A Thesis

Under The Title

Haemodynamic Effects of Paracetamol (Acetaminophen) as Extended Intravenous Infusion Versus Intravenous Bolus in Septic Shock patients

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Introduction:

Sepsis, inflammatory response to infection, contributes directly or indirectly to mortality in the majority of critically ill patients. An elevated cardiac index and a decreased systemic vascular resistance leading to hypotension and hypo perfusion of vital organs characterize the early stage of septic shock. The hypotensive state is often not amenable to fluid resuscitation alone and requires institution of vasoactive agents to counter the profound fall in systemic vascular resistance, which is an integral feature of septic shock [1, 2].

Acetaminophen is the antipyretic and analgesic that is most often given to hospitalized patients, including those in critical care units. The mechanism of action of acetaminophen remains incompletely understood, but the antipyretic response appears to be due to blocking cyclooxygenase-II and inhibiting prostaglandin-II synthesis in the central nervous system [3].

Intravenous (IV) acetaminophen has gained popularity for inpatient management of acute pain for its practical and clinical advantages. IV administration is associated with more predictable pharmacokinetic performance compared with rectal (30%-40% bioavailability) and oral dosage forms of acetaminophen (60%-70% bioavailability) [4-7].

Predictable kinetics as well as ease of IV administration has made it an especially attractive option in the critically ill patients who have altered gut absorption secondary to numerous pathophysiological and therapeutic influences.

IV acetaminophen has shown promise in improving patient satisfaction, managing fever, and decreasing postoperative opioid requirements. These features have made it one of the most widely ordered medications within critical care and surgical services [8].

Product information for IV acetaminophen lists mild effects such as nausea or vomiting among the most common adverse events (incidence ≥ 5%), with the estimated incidence of more serious adverse effects such as hypotension being <1%. However, there have been an increasing number of randomized controlled trials which indicated that the incidence of IV acetaminophen–induced hypotension may be higher than previously reported by manufacturers. These publications have prompted investigators to look more closely at the possible untoward effects of IV acetaminophen across a variety of populations. . None of these studies examined whether the extended infusion of IV paracetamol can minimize the degree of hypotension in critically hemodynamic unstable patients [9-10] .

Aim of the Work:

To assess the incidence of hypotension of the extended intravenous paracetamol (acetaminophen) infusion in comparing with intravenous paracetamol bolus in haemodynamically unstable patients (septic shock).

Hypothesis:

Extended intravenous paracetamol infusion will minimize the incidence of hypotension compared to intravenous bolus.

Ethical considerations:

The study protocol was approved by the Research Ethics Committee (REC), Faculty of Pharmacy (Girls), Al-Azhar University, REC.No.277.

Methodology :

- **Study design:** Open labeled, Paralled, Randomized, Controlled study.
- **Study Setting and location:** Emergency department, Intensive care units, Cairo University Hospitals (kasr alainy), Cairo, Egypt.
- **Study population:** Patients critically ill hemodynamically unstable (septic shock).
- **Eligibility Criteria:** Patients eligible for the study fulfilled the following inclusion criteria and exclusion criteria:

Inclusion criteria:

The prescribed paracetamol will be at the discretion of the treating ICU clinician for either fever or pain, were eligible for enrolment.

1- Age more than 18 years old

2- Patient fulfill criteria of septic shock definition:

- Sepsis need vasopressor therapy.
- Serum lactate level greater than 2 mmol/l (SSC 2016).

3- Patient with contractility greater than 40%

Exclusion criteria:

1-paracetamol hypersensitivity or allergy.

2- Acute liver injury or failure.

3-Childs-Pugh C liver disease.

4-Heat stroke.

5-Malignant hyperthermia.

6-Neuroleptic Malignant Syndrome.

7-Continous renal replacement therapy.

8-Around the clock scheduled of acetaminophen containing medications administration or non-steroidal anti-inflammatory drugs.

9- ventricular assist device

- **Study procedures**

1. Randomization

Randomization will be done by computer generated numbers and concealed by serially numbered, opaque and sealed envelopes.

2. Study protocol

After institutional ethical committee approval, patients with septic shock will be investigated for exclusion criteria.

The recruited patients will be allocated randomly into group ***I*** (paracetamol 1 g infused over 3 hours) , group ***II*** (paracetamol 1 g infused over 15min) or control group (normal saline 100ml infused over 15 min).

Baseline values of cardiac output, blood pressure (SBP + DBP + MAP) ,temperature and vasopressor inotropic score will collect immediately before (paracetamol or normal saline) administration and 60 ,180, 360 min after and need for inotropic support or intravenous fluid bolus during 360 min after administration.

3. Measurement tools

Temperature: electronic sensor

Cardiac output: cardiometry

- **Study outcomes:**

Primary outcome

The incidence of hypotension, defined as decrease in SBP ≥ 20٪ from baseline, by extended infusion of intravenous paracetamol.

Secondary outcome

a. Changes in mean arterial pressure, diastolic blood pressure, cardiac output and heart rate.

b. Changes in the body temperature, defined as the greatest difference in the temperature between preinfusion temperature and temperature during 60,180,360 min after
c. Changes in vasopressor dose , defined by vasopressor infusion rate (mcg/min)
d. Changes in need of fluid boluses.

❖ **Statistical analysis**

Sample size:

Sixty patients with hemodynamic instability (septic shock) will be enrolled in the study according to the inclusion and exclusion criteria.

Patients will be randomized into three groups each group includes 20 patients:

Control Group: Twenty patients will receive normal saline with their standard analgesia (15 min).

Tested Group I: Twenty patients will receive extended IV paracetamol infusion (3 hours).

Tested Group II: Twenty patients will receive IV paracetamol bolus (15 min).

Statistical Methods:

- SPSS statistical software package recent version.
- Data will be expressed as Mean ± SD for quantitative measures and both number and percentage for categorized data.
- The probability of error at 0.05 will be considered significant, while at 0.01 and 0.001 are highly significant.
- Suitable statistical tests will be used to enable the comparison between the results of the three study groups.

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