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The hypotension caused by intravenous paracetamol in septic shock patients: A single center placebo controlled randomized study

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Abstract: According to the product information for parenteral paracetamol, fewer than 1% of patients will have more severe adverse effects like hypotension. However, a number of studies suggest that the prevalence of hypotension caused by parenteral paracetamol may be higher than actually thought by the drug's producers. We carried out prospective, controlled, randomized research to compare the clinical implications of intravenous paracetamol bolus versus intravenous paracetamol extended infusion. The 61 adult septic shock patients were divided into three groups by randomization: Bolus group who received paracetamol 1g/100ml infused over 15 minutes, while the extended infusion group who received paracetamol 1g/100ml infused over three hours. The control group who received normal saline 100ml infused over 15 minutes. The main outcome was the incidence and prevalence of reduced blood pressure, which was detected by a systolic blood pressure drop of ≥ 20٪ from baseline. Mean arterial pressure, vasopressor infusion flow rate, and both diastolic and systolic blood pressure did not change significantly according to statistical analysis between the three groups at baseline, one, three, or six hours after the intervention. The incidence of hypotension was 19% (4 of 21 patients) within the control or normal saline group, 50% (10 of 20 patients) within the bolus group, and 35% (7 of 20) within the extended infusion group. The prevalence of hypotensive episodes was greater in the bolus group, even though there was no clinically meaningful difference between intravenous paracetamol prolonged infusion and bolus. We do not need to administer paracetamol as a prolonged infusion to prevent the hemodynamics parameter from being negatively impacted.

. **Keywords:** intravenous, paracetamol, acetaminophen, septic shock, blood pressure, hypotension, vasopressors**.**

1. INTRODUCTION

One of the most famous analgesics and antipyretics on the market today is paracetamol, sometimes known as acetaminophen. The paracetamol mechanism of action remained unclear for many years. Among the essential mechanisms that have been implicated include cannabinoid, opioid, nitric oxide (NO) and serotonergic pathways. It is also likely that a number of linked pathways are involved[1]. Outpatient and hospital settings, notably those in critical care facilities, regularly use intravenous paracetamol. Pain is a typical sign of adult individuals in critical care facilities for trauma, medical care and surgery[2]. The addition of paracetamol would be beneficial to opioids in the Clinical Practice PADIS guidelines to lessen pain intensity and opioid consumption frequently used as part of multimodal analgesia at the critical care facilities[3]. At some time during their stay at the critical care facilities, fever is a typical indicator of infection in septic individuals[4]. Hypotension is one of the few side effects of intravenous paracetamol that the manufacturer lists with an incidence of <1%[5]. While paracetamol manufacturers previously stated that hypotension was less common after treatment investigations have shown otherwise demonstrated a higher incidence of hypotension[6-9]. The possible negative effects of intravenous paracetamol in many different populations have been the focus of investigation because of these publications[10-13]. These results need to be confirmed by sufficiently

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powered randomized trials to determine the impact of hypotension caused by paracetamol. When administering intravenous paracetamol in particular populations, additional monitoring may be necessary, particularly if there is a greater risk of fatal outcomes when the patient is hemodynamically unbalanced prior to treatment. Septic shock patients may be among the most susceptible people who need fluid and vasopressor treatment to keep their hemodynamics working. Regarding these concerns, no research has evaluated the hemodynamic consequences of intravenous paracetamol prolonged infusion in the context of critically ill adult individuals in septic shock. We conducted a controlled, prospective, randomized single-center experiment to better understand the possibilities. In individuals with hemodynamic instability (septic shock), the present study compared the incidence of hypotension brought on by an intravenous bolus of paracetamol (acetaminophen) to that produced by a prolonged intravenous infusion of paracetamol (acetaminophen).

2. METHODS

2.1. Design of study and setting:

This open-labeled, parallel, randomized, prospective, controlled clinical trial was conducted the critical care facilities (185 trauma and surgical ICU) of Emergency Department, Cairo University Hospitals (kasr alainy), Cairo, Egypt. The study started in November 2020 till January 2023. The study's protocol received the Ethical Committee in the Faculty of Pharmacy (Girls), Al-Azhar University, REC.No.277. All patients, or their representative, provided written informed permission before being allowed to participate in the research.

2.2. Study population:

All patients who were diagnosed with septic shock (hemodynamic unstable) in conducted the critical care facilities were planned to be recruited Depending on the following rules of participation and exclusion in this research.There were patients involved: (1) Age adult ≥ 18 years old. (2) The patient fulfills criteria of septic shock definition: Sepsis needs vasopressor therapy and Serum lactate level greater than 2 mmol/l[14, 15] . (3) Patient with contractility greater than 40%.The patients were excluded: (1) paracetamol hypersensitivity or allergy. (2) Acute liver injury , failure or Childs-Pugh C liver illness. (3)Heat stroke. (4) Malignant hyperthermia. (5)Neuroleptic Malignant Syndrome. (6)Continous renal replacement therapy. (7)Ventricular assist device. (8)Around-the-clock scheduled of acetaminophen-containing medications administration or non-steroidal anti-inflammatory drugs. (9)Pregnancy /lactation. Sixty-one patients who met the study's inclusion and exclusion requirements were approved to participate They were hidden by opaque, sealed and serially numbered envelopes and allocated at random using computer-generated numbers. The group assignment was maintained in a set of secret envelopes, each carrying just the case number on the outside, and the investigator was unaware of the specifics of the series. The investigator opened the correctly numbered envelopes before the trial began, and according to the flowchart. (Fig. 1) , the card on each envelope indicated the patient's allocated intervention. Three groups of patients were randomly selected; - Extended infusion adminstration group : paracetamol 1g/100ml (Medalgesic® 1g/100ml, Arab company for medical products, Obour City, Cairo, Egypt) infused over 3 hours via syringe pump by rate 30ml/hr. Bolus group : paracetamol 1g/100ml (Medalgesic® 1g/100ml, Arab company for medical products, Obour City, Cairo, Egypt) infused over 15min via infusion line. Control group: normal saline 100ml (0.9% Sodium Chloride®, Egypt Otsuka Pharmaceutical Co, S.A.E) infused over 15 min via infusion line.

2.3.Data collection:

From medical records, demographic information and baseline variables such as gender, age, comorbidity history (such as diabetes, hypertension, or stroke), APACHE IV score, and the origin of septic shock were collected. According to the intervention, all measured values were invasively and continuously recorded at baseline, as well as at 1, 3, and 6 hours later: A small-bore (18 to 22 gauge) plastic catheter is percutaneously inserted into a peripheral artery, then connected to a portable vital signs monitor (GE Dash 5000®), which records the mean arterial pressure and both diastolic and systolic blood in millimeters of mercury (mmHg). The rate of infusion of Norepinephrine expressed by mcg/min .The episodes of hypotension were recorded for six hours.

2.4. Study endpoints:

The main outcome was the incidence and prevalence of reduced blood pressure, which was detected by a systolic blood pressure drop of ≥ 20٪ from baseline. Adjustments in the mean arterial pressure, diastolic blood pressure, and vasopressor dosage were the secondary endpoints.

2.5. Statistical analysis:

The sample size was determined using MedCalc Software version 14.10.2 (MedCalc Sofware bvba, Ostend, Belgium). Data analysis was carried out using the SPSS program, version 15 for Microsoft Windows (SPSS Inc., Chicago, IL, USA).

Categorical data were evaluated using the chi-square test and shown as frequency (%). The Shapiro-Wilk test was used to determine if continuous data were normal, and the appropriate mean (standard deviation) or median (interquartile range) was provided. Unpaired t-tests or Mann Whitney analyses were used as appropriate for continuous data analysis. Analysis of variance(ANOVA) for repeated measures was used to evaluate the repeated data, and the Bonferroni test was used for post hoc pairwise comparisons. Statistical significance was defined as a P value less than 0.05.

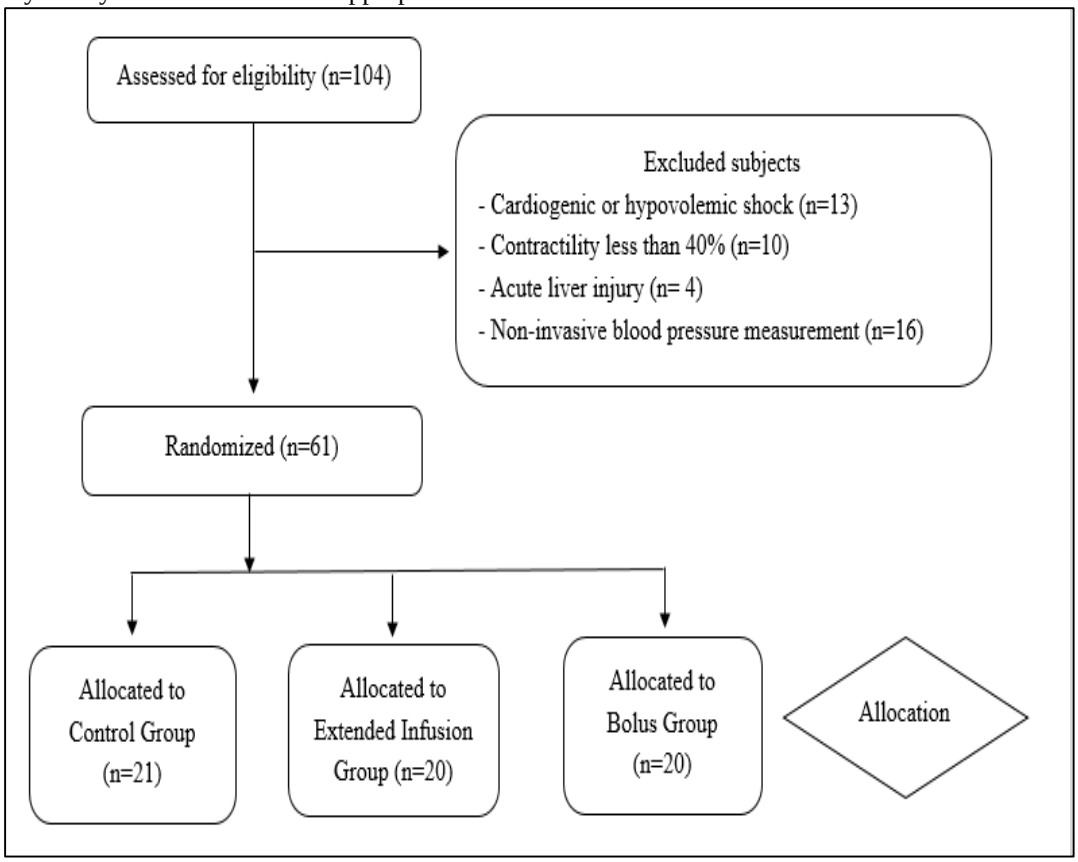

Figure 1: Flow Chart Showing the Patient Randomization

3. RESULTS

A 61 patients in the hospital's critical care section had septic shock participated in the controlled randomized trial Three groups were created out of them: Twenty patients got an extended infusion of intravenous paracetamol throughout a three-hour period in the prolonged infusion group. The bolus group's 20 patients got intravenous paracetamol during a 15-minute period. In the control group, normal saline was administered to 21 individuals during a 15-minute period. According to the study's participants' demographic information, there were no statistically significant differences between the three groups at the study's baseline: gender, age, comorbidity history (such as diabetes, hypertension and/or stroke), APACHE IV score, and the origin of septic shock (Skin and soft tissue, Pneumonia and/or Abdomen) presented as (Table. 1). Overall 40 individuals (65.6%) were male furthermore, the average age of control, bolus, and extended infusion group was 53, 61.5, and 59.5 years, respectively. In 37 individuals (60.6%), the comorbidity history was not present or different from diabetes, hypertension, and stroke. The abdomen was the site of infection and the origin of septic shock in 44 individuals (72%). Prior to the intervention (Paracetamol over 3 hours, Paracetamol over 15 minutes or Normal saline over 15 minutes) at baseline, one, three, and six hours later, the measurable data were obtained. At the beginning of the intervention, (Paracetamol over 3 hours, Paracetamol over 15 minutes or Normal saline over 15 minutes), one, three or six hours later.

There were no statistically significant differenc es between the three groups in terms of systolic, dia stolic, and mean arterial pressure (p-value > 0.05) presented as (Table. 2). As demonstrated in (Figure 2), the rate of norepinephrine infusion was not statistically different for any of the groups at baseline, one, three, or six hours (p-value > 0.05). The mean ± SD baseline of norepinephrine infusion rate expressed (mcg/min) in each group: 26.66±15.64 in the control group, 26.13±18.36 in the bolus group,

29.19±17.16 in the extended infusion group. One hour after the intervention: 26.28±16 in the control group, 26.92±19.05 in the bolus group, and 27.06±17.29 in the extended infusion group. At three hours after intervention: 24.76±15.70, 26.79±19.11, and 26.13±17.97 in the control, bolus, and extended infusion group, respectively. Six hours after the intervention: 23.62±16.65, 25.86±18.85, and 26± 18.42 in the control, bolus, and extended infusion group, respectively. The incidence of hypotension in control group 19% (4 from 21 patients), bolus group 50% (10 from 20 patients) and in extended infusion group 35% (7 from 20 patients). Despite the fact that our findings showed that the bolus group had a greater frequency of hypotensive episodes than the control and extended infusion groups, these findings were not clinically significant (p-value > 0.05), presented as (Figure 3).

Table. 1: The basic characteristics of all individuals in all groups.

		Control (Saline) Group Q=21(%)	Bolus Group Q=20(%)	Extended Infusion Group Q=20(%)	P-value
Gender	Female	9(43)	8(40)	4(20)	0.249
	Male	12(57)	12(60)	16(80)	
Age(yrs)	Median (minimum- maximum)	53(19-75)	61.5(19-76)	59.5(30-78)	0.334
APACHEIV	Mean±SD	17 ±12.46	26 ± 20.7	25±18.8	0.181
History of comorbidities	Free or others	12(57)	13(65)	12(60)	0.646
	Diabetes mellitus	2(9.5)	2(10)	5(25)	
	Hypertension	3(14.3)	2(10)	0(0)	
	Stroke	1(4.8)	0(0)	1(5)	
	Diabetes mellitus and Hypertension	3(14.3)	2(10)	1(5)	
	Diabetes mellitus, Hypertension and Stroke	0(0)	1(5)	1(5)	
Origin of septic shock	Skin and tissue	3(14.3)	3(15)	4(20)	0.384
	Pneumonia	1(4.8)	0(0)	2(10)	
	Abdomen	13(61.9)	17(85)	14(70)	
	Pneumonia and Skin and tissue	1(4.8)	0(0)	0(0)	
	Abdomen and Skin and tissue	1(4.8)	0(0)	0(0)	
	Abdomen and Pneumonia	2(9.5)	0(0)	0(0)	

Table. 2: The measured parameters of all patients in three groups at all-time points.

		Control (Saline) Group Q = 21	Bolus Group Q =20	Extended Infusion Group Q =20	P-value
Systolic blood pressure SBP (mmHg)	Baseline	125.19±10.30	123.35±11.44	125.95±10.53	0.735
	1 hour	122.05±12.71	121.05±14	127.20±13.73	0.307
	3 hours	122.71±8.80	120.35±10.57	120.25±15.33	0.752
	6 hours	121.29±10.37	124.50±12.35	122.55±11.82	0.670
Diastolic blood pressure DBP (mmHg)	Baseline	66.48±13.45	67.40±10.70	63.65±12.33	0.602
	1 hour	65.05±13.94	65±9.53	62.05±12.65	0.673
	3 hours	67.19±13.14	63.50±11.28	59.55±12.09	0.144
	6 hours	66.57±13.24	67.35±12.51	59.80±12.03	0.122
Mean arterial pressure MAP (mmHg)	Baseline	86.81±11.33	86.55±9.61	84.85±9.65	0.805
	1 hour	84.71±11.83	84.75±11.17	83.50±10	0.920
	3 hours	86.19±10.76	83.80±10.87	80.30±10.50	0.218
	6 hours	85.24±11.04	86.90±10.96	81±10.36	0.212

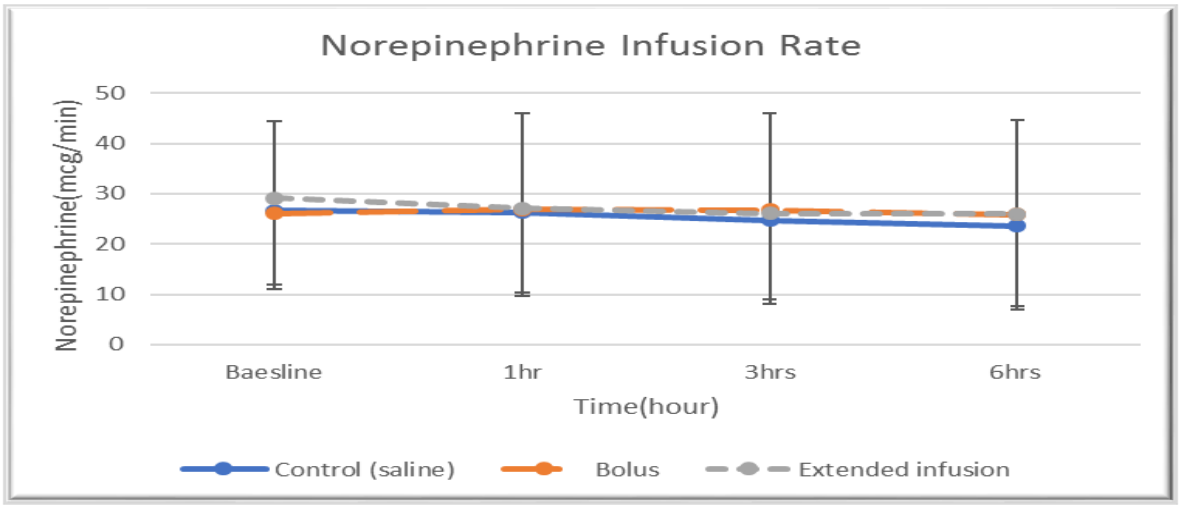

Figure 2. Norepinephrine infusion rate in three groups at all-time points.

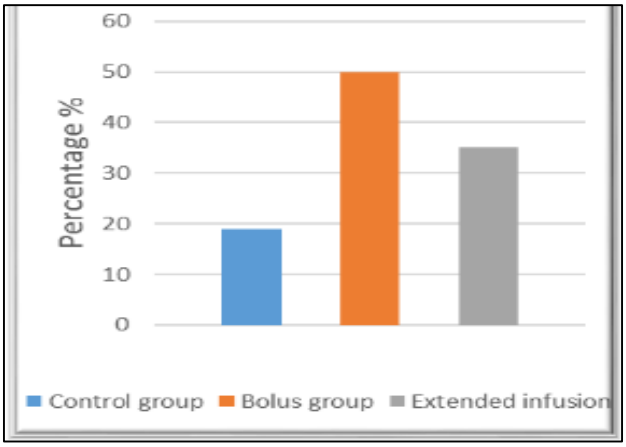

Figure 3. The prevalence of hypotension in three groups.

4. DISCUSSION

Parenteral paracetamol, sometimes referred to as acetaminophen, is a useful painkiller and antipyretic medication used to treat feverish and/or mild pain in critically ill individuals. It is a crucial component of multimodal analgesia. However, a growing body of evidence indicates that paracetamol administered intravenously may have negative side effects, including a tendency to cause hypotension. Septic shock accounts for 62% of all occurrences of shock syndromes requiring vasopressors. It is the most severe type of sepsis due to arterial hypotension, reduced tissue perfusion, and high blood lactate levels. This randomized controlled trial compares the incidence of hypotension in intravenous paracetamol prolonged infusion over 3 hours' vs intravenous paracetamol bolus over 15 minutes. All patients had their invasive levels of blood pressure (systolic, diastolic, and mean arterial pressure) measured continuously. Our findings showed that there was a 50% prevalence of hypotension in the bolus group and a 35% incidence in the prolonged infusion group, although these results were not clinically significant. Numerous research has examined the blood pressure alterations brought on by intravenous paracetamol: Chiam E et al. (2015) attempted to compile research and published a review of 50 publications that searched in evidence-based websites. The findings in this collection of literature provide evidence for the hypothesis that critically ill patients who receive IV paracetamol may be more likely to develop hypotension. Administration of IV paracetamol caused substantial reductions in either SBP or MAP when compared to baseline values[16]. Another review of the literature searches in evidence- based databases from 2002 to 2019 is given by Maxwell EN et al. (2019). A large proportion of the 19 studies reviewed in this analysis—five RCTs, six prospective open-label trials, and eight retrospective reviews—found a significantly reduction in hemodynamic variables after 500–1000 mg IV acetaminophen, as measured by changes in systolic as well as diastolic pressure, or the average arterial

pressure. Among the trials reporting the use of vasopressors, the authors found a significant increase in their requirement after IV acetaminophen treatment. The largest number of studies (14 of 19) were patients with serious illness who were admitted to the hospital's ICU or showed up at the emergency room[6]. There was also a multidisciplinary planned observational research with 160 severely ill individuals. 34.9% of the reported occurrences needed therapeutic intervention, according to Cantais A et al. (2016), while 51.9% of patients who got IV acetaminophen developed hypotension. There was no correlation between variations in mean arterial pressure and variations in body temperature[7]. Additionally, a study published in (2017) by Lee HY et al. examined hemodynamic impacts of propacetamol, a prodrug of acetaminophen that is quickly converted to its active form in the serum by plasma esterases. The study looked at 403 Korean patients who had adverse hypotension related to intravenous paracetamol or propacetamol; data were gathered from the Korea Adverse Event Reporting System. Hypotension was the most frequently reported adverse[17]. Our research has certain limitations, such as having a single-center prospective study; broadening it to include other centers will probably provide more reliable findings. The findings for other patient categories may vary since our sample (patients with septic shock) wasn't sufficiently representative of the whole population of critical care units. Further research may be required to show a relationship between blood pressure changes and the antipyretic activity of paracetamol, particularly the fact that paracetamol increases the flow of blood through the skin and vasodilation when given to febrile critical care patients.

5. CONCLUSIONS

Even though receiving an intravenous paracetamol bolus caused more hypotensive episodes than receiving an intravenous paracetamol prolonged infusion, this difference had minimal clinical significance (half of the patients receiving an intravenous paracetamol bolus experienced hypotension). To prevent the adverse effects on blood pressure levels, paracetamol does not need to be given as a prolonged infusion.

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Conflicts of Interest: The writers all claim that they, in fact, possess no potential competing interests.

Ethical Statement: This study's research was granted authorization by the Ethical Committee in the Faculty of Pharmacy (Girls), Al-Azhar University, REC.No.277.

Author Contribution: The following authors confirm their participation in the article: Zeinab AlKasaby Mahmoud Zalat, Ahmed Mohamed Mukhtar, and Ayah Mohammed Khalil Ibrahem all helped conceptualize and design the research, as well as do formal analysis and analyze the results. Zeinab AlKasaby Mahmoud Zalat guided every step of the study. The data were evaluated and interpreted by Karema Abu-Elfotuh and Ahmed Mohamed Lotfy. Ayah Mohammed Khalil Ibrahem performed the experiment, wrote the article, conducted the experimental research with the assistance of all authors, and created the written work. And the complete version of the manuscript was agreed upon by all.

List of Abbreviations: NO: nitric oxide, ICU: intensive care units, PADIS: the Prevention and Management of Pain, Agitation/Sedation, Delirium, Immobility, and Sleep Disruption guidelines, APACHE: Acute Physiology And Chronic Health Evaluation. SBP: systolic blood pressure, DBP: diastolic blood pressure, MAP: mean arterial pressure, IV: intravenous, RCT: randomized controlled trial.

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