Role of Montelukast in Modulation of Response to Sepsis in Preterm Infants: A Randomized-controlled Trial

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Abstract

Inflammatory mediators play a crucial role in the pathophysiology of neonatal sepsis. Montelukast, as an anti-inflammatory drug, could be a beneficial therapy. This study aimed to explore the adjuvant role of Montelukast in regulating the inflammatory response associated with neonatal sepsis and its associated effect on the clinical outcomes. An open-label, randomized controlled intervention trial conducted on 40 late preterm newborn (gestational age $34^{0/7}$ to $36^{6/7}$ weeks) admitted to NICU, with clinical evidence of sepsis. In the Montelukast group (n=20), infants received oral Montelukast once daily for 10 days (infant's weight <2 kg received 1.5 mg whereas >2 kg received 2 mg) with antibiotics plus routine supportive care. In the routine care group (n=20), infants received antibiotics plus routine supportive care. Primary outcome was the serum level of tumor necrosis factor (TNF) alpha at day 10 of therapy. Secondary outcomes included the clinical outcomes along hospital admission. Baseline characteristics were non-significantly different between both groups. After 10 days of therapy, TNF alpha level was significantly lower in the Montelukast group (80.73$\pm$50.25 versus 119.54$\pm$58.46; *p=* 0.03). There were non-significant differences between both groups regarding duration of NICU admission, antibiotics duration or modalities and duration of respiratory support. C-reactive protein didn't differ between both groups (*p= 0.256*). No documented significant adverse effects of Montelukast during the study period. *Conclusion:* in late preterm neonates with sepsis, 10 days of Montelukast therapy as an adjuvant to antibiotics lowered TNF alpha level without any impact on clinical outcomes.

Summary

What is known?

- Multiple experimental studies investigated the effect of Montelukast in sepsis showed that Montelukast had anti-inflammatory effects through decreasing inflammatory cytokines levels while this was not investigated in neonates
- Montelukast was administered in neonates to prevent bronchopulmonary dysplasia

What this subject adds?

- In late preterm neonates with sepsis, 10 days of Montelukast therapy as an adjuvant to antibiotics lowered TNF alpha level without any impact on clinical outcome
- No documented harmful adverse effects of Montelukast when administered in preterm neonates

Introduction

Sepsis is a syndrome results from dysregulation of systemic inflammatory response to infection which results in injury to the tissues and subsequent organ failure [1]. Neonatal sepsis remains a principal etiology of morbidity and mortality in neonates [2]. The frequency of sepsis in hospitalized neonates varies inversely with the birth gestational age and may reach up to 60% in preterm infants [3].

Although the pathophysiology is not well clear, monocytes seem to organize the innate immune response to bacteria by regulating a variety of inflammatory cytokines, particularly tumor necrosis factor (TNF) alpha and interleukin-6 (IL-6) [4; 5], which provoke the inflammatory cascade of systemic inflammatory response syndrome, multiple organ failure which may lead to death. There are evidences that TNF alpha is present free in plasma parallel with the appearance of manifestations of bacterial infection and can be used as a marker of sepsis [5]. Since inflammation and inflammatory mediators have an important role in the pathophysiological aspects of sepsis, anti-inflammatory medications have become a major line of therapy [6].

Leukotrienes are end products of arachidonic acid metabolism and play a role in inflammatory reaction through induction of microvascular permeability and leukocytes chemotaxis [7]. Montelukast is a cysteinyl leukotriene receptor 1 (CysLT1) antagonist; it blocks Leukotriene D4 action on CysLT1 within lungs and airway [8]. This decreases bronchoconstriction and inflammatory reaction and also reduces fibrosis and oxidative damage in the lungs in experimental work [9].

Montelukast was evaluated in the prevention of bronchopulmonary dysplasia (BPD) after induced lung injury in mouse where it was found to be beneficial through inhibiting inflammation, oxidative stress and lung injury and apoptosis [10]. During the neonatal period, limited studies investigated the efficacy and safety of Montelukast to prevent BPD in premature infants [11; 12]. Although contradicting results for the efficacy were observed, both studies proved safety with no documented harmful effects.

Multiple previous experimental studies investigated the effect of Montelukast in sepsis showed that Montelukast exerted anti-inflammatory effects through decreasing pro-inflammatory cytokines levels and increasing antioxidant enzymes on sepsis-induced organ dysfunctions [13–16].

To our knowledge, this is the first study to investigate the effect of Montelukast on neonatal sepsis. The current work was conducted to explore the role of Montelukast sodium, as an adjuvant therapy to antibiotics and routine supportive care, in modulating the inflammatory process associated with neonatal sepsis (assessed by TNF alpha level) and the subsequent impact on the infants´ clinical outcome.

Methods

Study locality and duration

This study was carried out at neonatology units of Mansoura University Children's Hospital and of Mansoura Insurance Hospital over one year. IRB approved the study and fully informed written consents were obtained from the neonates' parents or guardians before enrolment in the study. The study was registered in clinical trials database (clinicaltrials.gov, ID: NCT04474327).

Study design

An open-label, randomized controlled parallel intervention trial

Population

The study was conducted on late preterm infants at a gestational age between $34^{0/7}$ weeks and $36^{6/7}$ weeks with a birth weight of more than 1.5 Kg with clinical evidence of neonatal sepsis. Neonatal sepsis was defined in the presence of one of the following signs; fever (> 38°C, rectal), hypothermia (< 36°C, rectal), tachycardia (heart rate (HR) > 180 beats/min) or bradycardia (HR < 100 beats/min), apnea, lethargy, feeding problems, mottled skin, convulsions, hypotonia plus at least 2 of the following laboratory findings; leukopenia (WBCs < 5,000 mm^3), leukocytosis (WBCs > 20,000 mm^3), thrombocytopenia (< 100,000 mm^3), serum C-reactive protein (CRP) > 15 mg/L, fibrinogen > 150 mg/dL, or metabolic acidosis (base excess of $\leq$7 mmol/L); with (culture-confirmed) or without (culture-negative) a positive blood culture result [17; 18]. Infants presented initially with septic shock, multi-organ dysfunction syndrome (MODS), disseminated intravascular coagulopathy, or feeding intolerance requiring to be null per mouth or infants with major congenital malformations, chromosomal aberrations or postoperative patients were excluded from the study.

Intervention

Infants were divided into Montelukast group and routine care group. Both groups received the same protocol of treatment of sepsis including antibiotics and supportive measures according to the policy of neonatal units and patients' needs. Infants in both groups were started on empirical antibiotics with Ampicillin at a dose of 50 mg /kg/12 hours combined with Aminoglycoside (Gentamycin) with a dose 4.5 mg/kg/36 hours for infants with suspected early-onset sepsis while for late-onset sepsis, Cloxacillin (50 mg/kg/dose) was used instead of Ampicillin. After that, antibiotics were changed as appropriate according to the results of culture and antibiotic sensitivity. The use of positive pressure ventilation and its duration, inotropic drugs usage and other supportive measures were guided and monitored by the treating physicians according to the policy of the neonatal units and patients' needs.

The Montelukast group received, in addition to the routine care, Montelukast sodium (Singulair, Merck sharp & Dohme Corp.) for ten days in a dose guided by the infant's birth weight as follow (infant's weight 1.5 to 2 kg received 1.5 mg once daily whereas greater than 2 kg received 2 mg). The given dose was calculated according to Kim and coauthors [12]. Montelukast was given by oral route by dissolving one sachet containing four mg of the Montelukast sodium in four ml milk to get a concentration of 1 mg/1ml.

Infants were discharged from NICU if they fulfilled the following criteria: adequate oral feeding sufficient to support appropriate growth and gaining weight, the ability to maintain normal body temperature in a home environment and sufficient mature respiratory control that allow safe discharge in addition to acceptable bilirubin level and free of infection.

For policy of discontinuation of respiratory support; infants were weaned off mechanical ventilation if they fulfilled the following NICU guidelines: Spontaneous respiratory effort, Gag or cough with suctioning, Satisfactory blood gases (PH more than 7.25, Partial pressure of carbon dioxide (pCO2) less than 60 mmHg, and base deficit less than 8meq/L) on a mean airway pressure less than 8 cm H_2O and frequency

less than 30 breath /minute and saturation more than 88% on fraction of inspired oxygen (FiO_2) less than 30% in the preceding 24 hours besides approval of the attending physician.

Infants were weaned off continuous positive airway pressure (CPAP) if they fulfilled the following NICU guidelines: Pressure of 3 to 6 cm H_2O for 24 hours, FiO_2 less than 30% to keep target saturation in the preceding 24 hours, respiratory rate less than 60 breath/minute, no single apnea requiring bagging in the preceding 24 hours, no more than 6 apneas requiring stimulation in the preceding 24 hours, satisfactory blood gases (PH > 7.25, pCO_2 < 60 mmHg, and base deficit < 8meq/L) and infant tolerates time off CPAP during nursing care in addition to approval of attending physician.

Infants were weaned off oxygen therapy if they fulfilled the following NICU guidelines: Infant's saturation remained above 91% in less than 30% FiO_2 for 24 to 48 hours or infant could tolerate a trial of discontinuing oxygen therapy to 21% FiO_2 for 1 hour.

Outcome measures

Primary outcome was serum TNF Alpha level, an inflammatory marker, at day 10 after receiving therapy. Serum TNF alpha level (TNFa ELISA kits, Sunred PeloBiotech GmbH, Germany) was measured by double-antibody sandwich ELISA technique [19]. Secondary outcome measures included; needs and duration for invasive mechanical ventilation, needs and duration of non-invasive ventilation, needs and duration of inotropic support, the total duration of NICU admission, serum CRP level at day 10 after receiving therapy. Pediatric Logistic Organ Dysfunction (PELOD) score was performed by the treating physician on admission and at day 10 in order to follow improvement or deterioration of the studied patients in both groups. Furthermore, delta PELOD (score at day 10 – score on admission) was calculated. PELOD score is used in neonates to calculate sepsis-induced organ dysfunction [20]. The score assesses cardiovascular function (heart rate and systolic blood pressure), neurologic function (Glasgow coma scale and pupillary reaction), hepatic function (AST and INR), pulmonary function (PaO2/FiO2, PaCO2 and whether the patient is on mechanical ventilation), hematologic function (WBCs and platelet count) and renal function (serum creatinine). Patient survival was recorded along the duration of NICU admission. In our research, adverse effects of Montelukast therapy such as diarrhea, vomiting, fever, cough, conjunctivitis and skin signs (rash, eczema, bruises and erythematous lesions) were observed [21].

Clinical data such as demographic data, cause of admission, site of infection (bacteremia, pneumonia, meningitis or septic arthritis), vital signs, activity, feeding tolerance, respiratory symptoms, duration of respiratory support, use of inotropes and a venous sample was withdrawn for complete blood picture, serum CRP, TNF alpha, creatinine, liver enzymes, INR and blood culture. Blood sampling in the studied groups was performed twice: First, at the start of the study, once sepsis was suspected, and the second sample was after 10 days of treatment. Lumbar puncture was performed when meningitis was suspected.

Randomization and allocation

Infants were assigned randomly to treatment groups using internet-based random table technique with a block size of four. Cards in sequentially numbered, opaque, sealed envelopes kept in the NICU. A designated nurse who was not involved in the study was responsible for the randomization of selected infants.

Sample size calculation

Sample size calculation was based on mean TNF level between the studied groups (Routine care group & Montelukast group). Pilot study was carried out on 10 cases (5 in each group) to calculate sample size. Using G power calculator to calculate the difference between 2 means using t-test with an effect size of 0.894, 2-tailed, with α error = 0.05 and power = 80%, mean ± SD of mean TNF level (110±30 and 90.73±10), the total calculated sample size was 40 infants (20 in each group).

Statistical analysis

IBM's SPSS statistics (Statistical Package for the Social Sciences) for Windows, version 20 was used for statistical analysis of the collected data. Shapiro-Wilk test was used to check the normality of the data distribution. Quantitative variables were expressed as mean ± standard deviation or median (minimum-maximum) as appropriate while categorical variables were expressed as frequency and percentage. Independent sample t-test and Mann Whitney tests were used for inter-group comparison of parametric and non-parametric continuous data. Chi-square /Fisher´s Exact tests were used for inter-group comparison of nominal data using the crosstabs function. P (probability) value < 0.05 was considered statistically significant.

Results

During the study period a total of 57 late preterm infants were eligible for the study. Of those, 40 infants were allocated to randomization either in the Montelukast group (n = 20) or the routine care group (n = 20) and seventeen infants were excluded due to different causes (Fig. 1). Baseline characteristics, clinical data and laboratory data were equal between the studied groups (Table 1).

Table 1
Clinical and laboratory characteristics of the studied groups at the start of the study

Characteristics	Routine care group (n= 20)	Montelukast group (n= 20)	*P* value
Gestational age (weeks)	34.85 ± 1.14	34.55 ± 0.95	0.370
Birth weight (grams)	1655.5 ± 77.77	1688.5 ± 104.74	0.258
Male Sex	12 (60%)	8 (40%)	0.343
Postnatal age (days)	5.30 ± 2.60	5.20 ± 2.51	0.902
Site of infection			
Bacteremia	11	10	
Pneumonia	7	8	0.694
Meningitis	2	1	
Septic arthritis	0	1	
Respiratory distress	9 (45%)	7 (35%)	0.748
Temperature instability	8 (40%)	14 (70%)	0.11
Poor activity	14 (70%)	12 (60%)	0.74
WBCs (10^9/l)	12.13 ± 5.26	10.19 ± 5.13	0.244
Platelet (10^9/l)	110.75 ± 44.13	112.45 ± 42.24	0.902
Serum C-reactive protein (mg/L)	96 (24–96)	96 (24–96)	0.455
INR	1.14 ± 0.26	1.08 ± 0.14	0.426
Blood glucose (mg/dL)	136.65 ± 44.82	127.15 ± 58.71	0.569
TNF alpha (pg/dL)	153.05 ± 50.47	167.57 ± 41.78	0.328
Serum Creatinine (mg/dL)	0.53 ± 0.36	0.41 ± 0.23	0.233
AST (IU/L)	18.51 ± 7.43	22.34 ± 12.23	0.240
ALT (IU/L)	16.60 ± 7.68	20.18 ± 11.66	0.257
PELOD score on admission	0 (0–10)	0 (0–11)	0.513

Data expressed as number (%), mean ± SD or median (minimum – maximum) as appropriate.

WBCs: white blood cells; INR: international normalization ratio; TNF: tumor necrosis factor; AST: aspartate aminotransferase test; ALT: alanine aminotransferase test; PELOD: Pediatric Logistic Organ Dysfunction

In the Montelukast group; 18 (90%) infants had culture-positive sepsis (11 infants with gram-positive bacteria and 7 infants with gram-negative bacteria) and 2 (10%) infants were culture-negative (clinically suspected) sepsis (Table 2). In the routine care group; 17 (85%) infants had culture-positive sepsis (9 infants with gram-positive and 8 infants with gram-negative bacteria) and 3 (15%) infants were culture-negative (clinically suspected) sepsis (Table 2).

Table 2
Results of Blood culture of the studied groups drawn at the start of the study

Type of organism	Routine care group (n= 20)	Montelukast group (n= 20)	*P* value
Culture positive/negative	17/3	18/2	0.633
Gram stain positive/negative	9/8	11/7	0.625
Gram positive bacteremia			
Streptococcal pneumonia	3	5	0.648
Staphylococcus aureus	2	1	
Coagulase negative staph	4	4	
Enterococci	0	1	
Gram negative bacteremia			
Escherichia coli	5	6	0.566
klebsiella	1	1	
Proteus	1	0	
Pseudomonas aeruginosa	1	0	

TNF alpha level was significantly lower in the Montelukast group compared to the routine care group (Table 3). Comparisons of TNF alpha level between both groups according to localization of infection at the start of the study and at the 10th day of therapy shows no significant differences between the Montelukast and routine care groups (Fig. 2).

Table 3
Clinical and laboratory characteristics of the studied groups after 10 days of therapy

Characteristics	Routine care group (n= 20)	Montelukast group (n= 20)	*P* value
Duration of NICU admission (days)	15.4 ± 4.08	14.6 ± 2.48	0.46
Patients survival survivors/died	18/2	19/1	0.999
Antibiotics duration (days)	14.80 ± 3.99	14.55 ± 2.46	0.81
Patients on Nasal oxygen	14 (70%)	13 (65%)	0.999
Nasal oxygen duration (days)	2.79 ± 1.25	2.31 ± 0.75	0.245
Patients on CPAP	7 (35%)	8 (40%)	0.999
CPAP duration (days)	3.0 ± 1.16	2.38 ± 0.74	0.248
Patients on Mechanical ventilation	2 (10%)	1 (5%)	0.999
Inotropes	10 (50%)	12 (60%)	0.999
Inotropes duration (days)	5.8 ± 2.2	5.0 ± 1.86	0.366
WBCs (10^9/l)	8.07 ± 2.48	8.19 ± 4.74	0.922
Platelet (10^9/l)	232.35 ± 74.70	257.10 ± 68.79	0.283
Serum C-reactive protein (mg/L)	24 (6–96)	12 (6–96)	0.256
INR	1.08 ± 0.24	1.06 ± 0.21	0.781
Blood glucose (mg/dL)	126.70 ± 22.87	136.75 ± 33.91	0.279
TNF alpha (pg/dL)	119.54 ± 58.46	80.73 ± 50.25	**0.030**
Serum Creatinine (mg/dL)	0.47 ± 0.25	0.52 ± 0.32	0.547
AST (IU/L)	17.08 ± 5.47	19.49 ± 8.40	0.288
ALT (IU/L)	17.83 ± 7.18	18.56 ± 9.96	0.790
PELOD score at 10 days	0 (0–11)	0 (0–10)	0.617
Delta PELOD score	0 (-10) – (10)	0 (-9) – (0)	0.547
Acute kidney injury	3 (15%)	3 (15%)	0.999

Data expressed as number (%), mean ± SD or median (minimum – maximum) as appropriate.

CPAP: continuous positive airway pressure; NICU: neonatal intensive care unit; WBCs: white blood cells; INR: international normalization ratio; TNF: tumor necrosis factor; AST: aspartate aminotransferase test; ALT: alanine aminotransferase test; PELOD: Pediatric Logistic Organ Dysfunction

Characteristics	Routine care group (n= 20)	Montelukast group (n= 20)	*P* value
Acute lung injury	2 (10%)	1 (5%)	0.999
Disseminated intravascular coagulopathy	0	0	
Thrombocytopenia	2 (10%)	2 (10%)	0.999
Anemia required blood transfusion	5 (25%)	4 (20%)	0.999
Data expressed as number (%), mean ± SD or median (minimum – maximum) as appropriate.			
CPAP: continuous positive airway pressure; NICU: neonatal intensive care unit; WBCs: white blood cells; INR: international normalization ratio; TNF: tumor necrosis factor; AST: aspartate aminotransferase test; ALT: alanine aminotransferase test; PELOD: Pediatric Logistic Organ Dysfunction			

There were no statistically significant differences between both groups as regard duration of NICU admission, antibiotic usage, respiratory support and inotropes administration (Table 3). Moreover, there was no statistically significant difference between the two studied groups concerning the clinical outcome. Among the routine care group, 2 infants died while in the Montelukast group, one patient died without statistical significance. Furthermore, none of the laboratory data or organ injury showed statistically significant differences between the routine care and Montelukast groups. PELOD score on day 10 and delta PELOD score did not significantly differ between both groups (p-value 0.617 and 0.547; respectively). During the follow-up period, non-significant differences of Montelukast-related possible adverse events were reported and the drug was tolerated in the studied patients (Table 4).

Table 4
Adverse events that may be related to Montelukast in the studied patients

Characteristics	Routine care group (n= 20)	Montelukast group (n= 20)	*P* value
Diarrhea	1	0	0.999
Vomiting	1	1	0.999
Fever	8	7	0.999
Cough	3	4	0.999
Conjunctivitis	1	0	0.999
Liver injury	0	0	
Skin signs (rash, eczema, bruises, erythematous lesions)	0	0	

Discussion

Sepsis is characterized by a generalized inflammatory cascade, which might induce extensive tissue injury. In the existing work, when Montelukast was added to antibiotics for 10 days in neonates with clinical or culture-proven sepsis, the level of TNF alpha decreased significantly. Although this may indicate the efficacy of Montelukast as an adjuvant anti-inflammatory drug, the clinical parameters (as patient survival, duration of NICU admission, duration of antibiotics and oxygen support) and other outcome measures (as WBCs count, serum CRP, organ dysfunction/injury) did not differ between the Montelukast and routine care groups. These findings may be explained by a relatively small sample size or by higher Montelukast doses are needed to achieve its effects.

To the best of our knowledge, this is the first work that searches the effect of Montelukast on neonatal sepsis. Previous studies that reported its anti-inflammatory and antioxidant effects in diminution of sepsis-induced organ failure were experimental. Sener and coauthors [13] in a study done on albino rats, aiming to investigate the possible protective effect of Montelukast against cecal ligation and perforation-induced oxidative injury and sepsis, revealed that sepsis-induced increase in the TNF alpha level was reduced in the Montelukast group. Another study [14] done on rats to investigate the potential protective effects of Montelukast after cecal ligation and puncture-induced sepsis and tissue injury in different organs (liver, heart, kidneys and lungs) found that Montelukast treatment significantly decrease pro-inflammatory (TNF alpha, IL-6) cytokine levels. Moreover, in 2011 Mohamadin [22] reported that Montelukast significantly suppress liver injury (assessed by serum level of AST, ALT and bilirubin) and inflammatory mediators (TNF-alpha, IL-1β), after lipopolysaccharides (LPS)-induced sepsis challenge in rats.

Additionally, in 2014, Khodir and coauthors´ study [15] was carried out to detect the effects of Montelukast on endotoxin-induced organ injury (lung and kidney) in rats. The study showed that, oral administration of Montelukast (20 mg/kg) for one week resulted in a marked decrease in pro-inflammatory cytokine (TNF alpha) expression in lung and renal tissues. These data recommended that the capability of Montelukast to produce less inflammatory cytokines in response to sepsis might, partially, account for a reduction in cytokine-related lung and kidney injury. In 2016, the same authors´ group demonstrated that Montelukast may have a protective effect on the cardiac tissues against LPS-induced cardiac injury in rats owing to the increase in glutathione enzyme and the significant decrease in the previously sepsis-induced increase in TNF alpha [16].

In the present research, TNF alpha was chosen during group comparison as it is considered an essential mediator for sepsis. It activates the inflammatory cascade by the provocation of production of cytokines and chemokines; it regulates the secretion of IL-1β. High levels of TNF alpha appear to be associated with the severity of sepsis [23]. There is a good proof that pulmonary overproduction of TNF alpha is included in the development of experimentally-induced acute lung [24] and renal injuries [25]. In 2011, an experimental study [14] reported that early elaboration of serum pro-inflammatory cytokines (including TNF alpha) is essential in the pathogenesis of septic shock. In addition, the role of TNF alpha in sepsis

pathogenesis is recommended by many researches performed on humans [26; 27]. Moreover, the measurement of TNF alpha concentration is a helpful predictor for sepsis prognosis [28].

To our knowledge, no previous studies were conducted on the effect of Montelukast in neonates apart from some studies that searched for the role of Montelukast in the prevention of BPD in preterm infants [11; 12; 29]. The recruited infants received different doses of Montelukast. Kim and coworkers [12] gave Montelukast according to body weight (< 1 kg body weight: 0.5 mg, 1-1.5 kg: 1 mg, 1.5-2 kg: 1.5 mg and more than 2kg: 2 mg) while in Rupprecht et al., [11] the dose was once daily 1 mg/kg in the first week of therapy then 1.5 mg/kg in the second week and increased to 2 mg/kg in the third) whereas In 2009, Kim and coauthors [29] prescribed Montelukast (Once daily 1 mg/kg). All reported that Montelukast is safe to be used in neonates with no documented significant side effects.

As far as we know, this is the first randomized controlled intervention clinical trial to investigate the adjuvant role of Montelukast in neonatal sepsis. All previous studies were experimental challenges. Out of the limitations faced during the current study is being open-label non-blinded but this design was preferred to allow early anticipation of any complications that might occur from Montelukast use in septic infants. Another is a relatively small sample size of the studied infants. A larger number of recruited neonates for evaluation of the efficacy and safety of Montelukast in neonatal sepsis is critically needed before universally apply these results. Until then, we cannot recommend the use of Montelukast as a routine treatment in neonatal sepsis.

Conclusion

In late preterm neonates with sepsis, Montelukast did not avail with antibiotics in helping patients´ clinical and laboratory improvement but may have an adjuvant anti-inflammatory role in modulation of the response to sepsis as indicated by a significantly lower TNF alpha level in Montelukast group. No documented significant adverse effects of Montelukast during the study period.

Abbreviations

ALT: Alanine aminotransferase

AST: Aspartate aminotransferase

BPD: Bronchopulmonary dysplasia

CPAP: Continuous positive airway pressure

CRP: C-reactive protein

CysLT1: Cysteinyl leukotriene receptor

ELISA: Enzyme-linked immunosorbent assay

FiO_2: Fraction of inspired oxygen

HR: Heart rate

IBM´s SPSS: Statistical Package for the Social Sciences

IL-1β: Interleukin-1β

IL-6: Interleukin-6

INR: International normalized ratio

Kg: Kilogram

LPS: Lipopolysaccharides

MODS: Multi-organ dysfunction syndrome

NICU: Neonatal intensive care unit

PaCO2: Partial pressure of carbon dioxide in arterial blood

PaO2: Partial pressure of oxygen in arterial blood

pCO2: Partial pressure of carbon dioxide

PELOD: Pediatric Logistic Organ Dysfunction

PH: Power of the hydrogen ion

P-value: probability value

SD: Standard deviation

TNF: Tumor necrosis factor

TNFa: Tumor necrosis factor alpha

WBCs: White Blood cells

Declarations

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no funding was received

Conflict of interest:

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Availability of data and material:

data and material are available upon request.

Informed consent:

Informed consent was obtained from all individual participants included in the study.

Code availability:

N/A.

Ethical Approval:

This study was reviewed and approved by Mansoura Faculty of Medicine Institutional Research Board **(MS/17.06.95).** The study was registered in clinical trials database (clinicaltrials.gov, ID: NCT04474327).

Authors' contributions:

Nouran El-Shehaby shared in the research protocol, collected patients' blood samples and clinical data and writing the manuscript. Heba El-Shahawy shared in research hypothesis and research protocol, performed all biochemical tests for all patients and the manuscript writing. Nehad Nasef shared in research hypothesis and research protocol, supervised the provided medical care to all patients and the manuscript writing. Shadia El-Sallab participated in formulating the research hypothesis and plan, supervised the provided medical care to all patients and manuscript writing. Hanan El-Halaby shared in research hypothesis, research protocol, data collection and interpretation, did the statistical analysis of the data and wrote the first draft of the manuscript.

Consent to participate:

All the authors approved the final manuscript as submitted and are responsible for all aspects of the study.

Consent for publication:

The Authors transfer to Springer the publication rights and warrant that the contribution is original.

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Figures

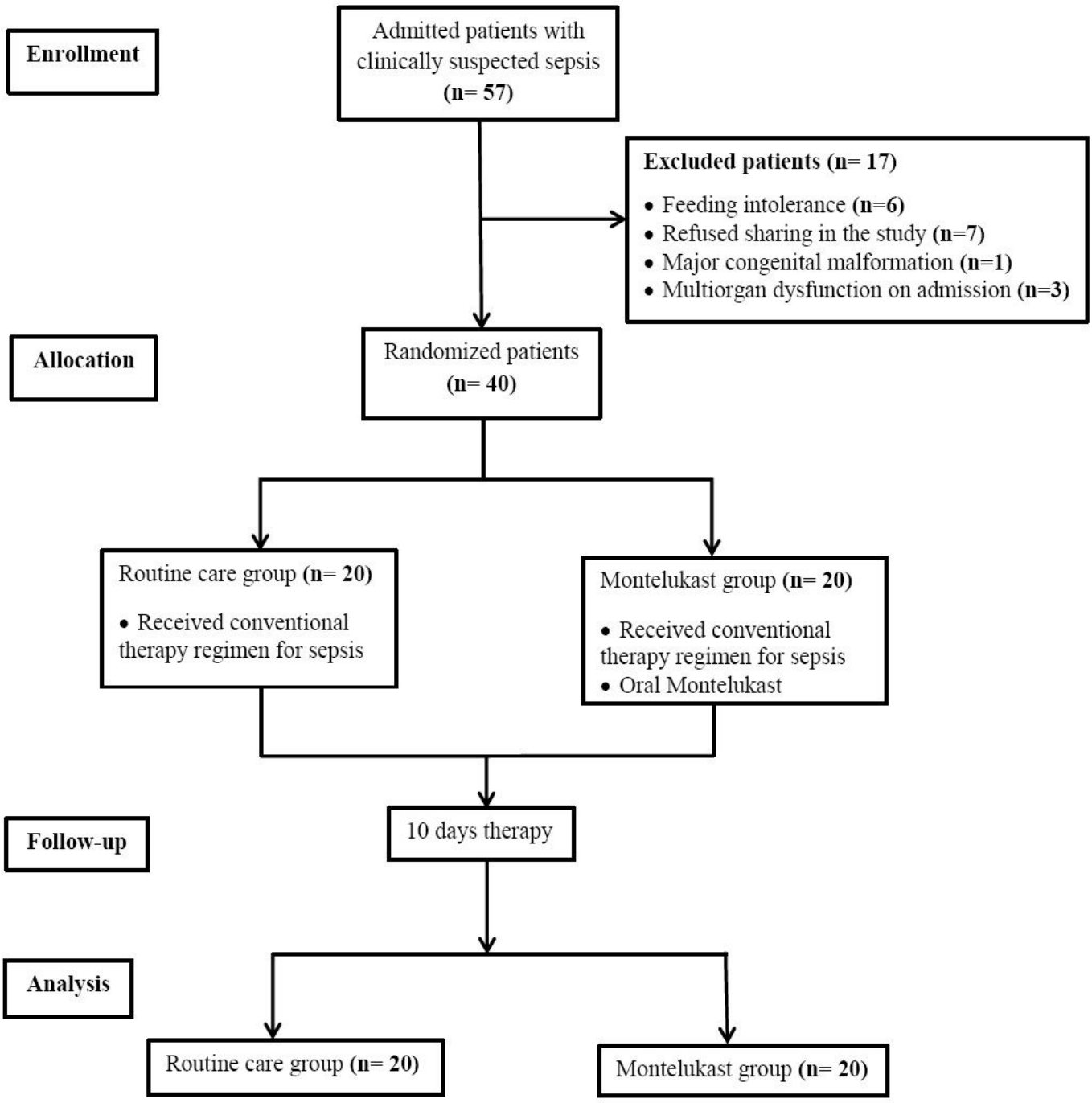

Figure 1

Flow diagram of participants in the study

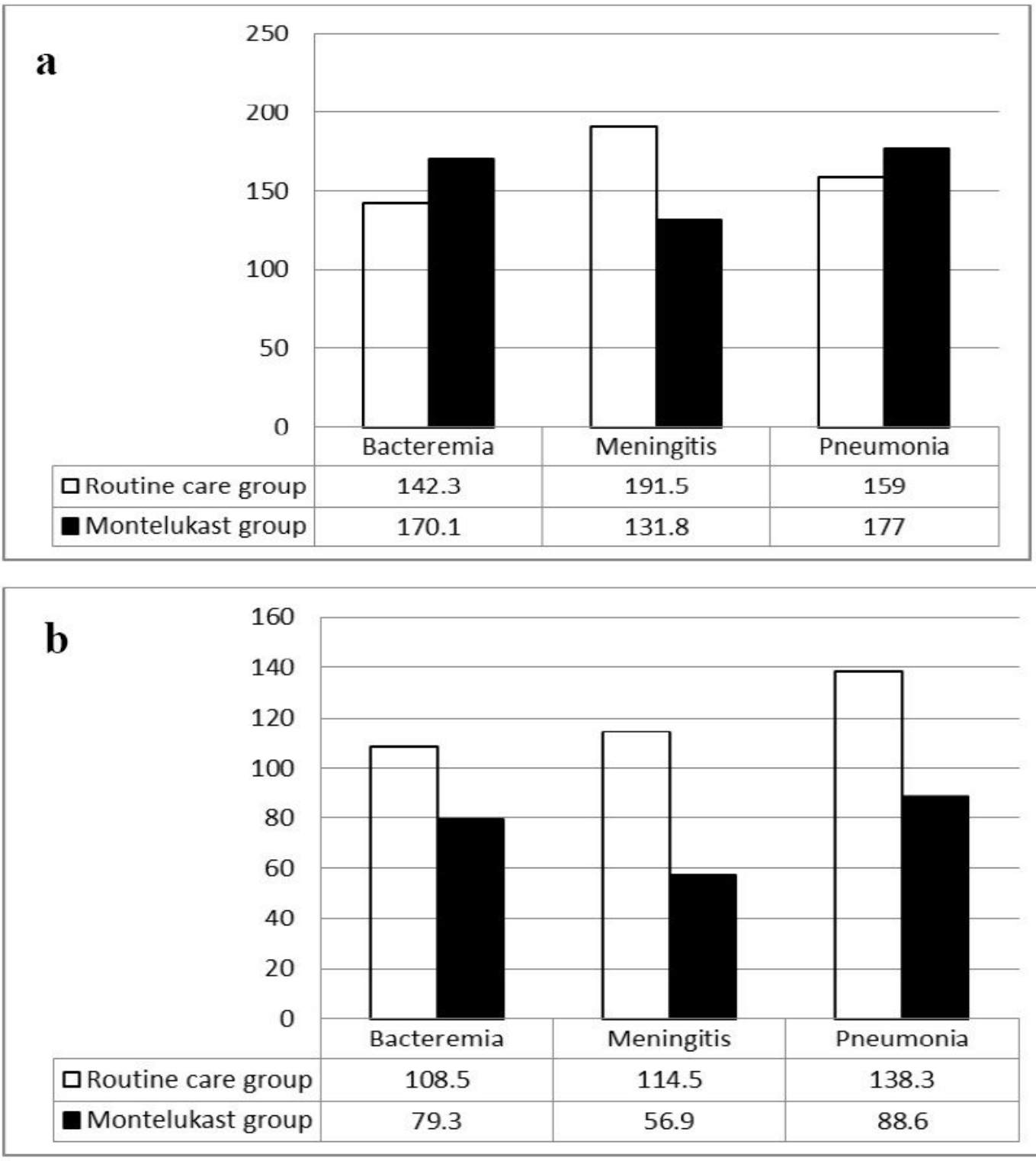

Figure 2

Comparison of tumor necrosis factor (TNF) alpha levels (pg/dL) in patients categories presented with different sources of infection in the studies groups a) at the start of the study b) at the 10th day of therapy