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RESEARCH

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Role of Montelukast in modulation of response to sepsis in preterm infants: a randomized-controlled trial

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Abstract

Background Since inflammatory mediators play a crucial role in the pathophysiology of neonatal sepsis. Montelukast, as an anti-inflammatory drug, could be a beneficial therapy. In searching the literature, no previous research addressed the role of Montelukast in neonatal sepsis; hence, 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.

Methods An open-label, randomized controlled intervention trial conducted on 40 late preterm newborn infants (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 clinical and laboratory outcomes were reported along hospital admission.

Results 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 ± 50.25 versus 119.54 ± 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.

Conclusions 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.

Trial registration The study was approved by Mansoura Faculty of Medicine institutional research board (IRB) (MS/17.06.95) and it was registered in clinical trials database (clinicaltrials.gov, ID: NCT04474327; registered July 16, 2020).

Keywords Anti-inflammatory, Montelukast sodium, Premature infants, Sepsis, Tumor necrosis factor alpha

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Background

Sepsis is a syndrome resulting 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 is evidence 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 reactions through the induction of microvascular permeability and leukocyte 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 inflammatory reaction and also reduces fibrosis and oxidative damage in the lungs in experimental work [9, 10] and could prevent bronchopulmonary dysplasia (BPD) in preterm infants [11, 12]. The pharmacokinetics and safety of Montelukast were studied in preterm infants [12] and infants younger than 3 months old [13] that reported safe use of Montelukast.

Multiple previous experimental studies investigated the effect of Montelukast in sepsis showed that Montelukast had anti-inflammatory properties via decreasing pro-inflammatory cytokines levels (serum TNF alpha [14, 15], lactate dehydrogenase [14], and IL-6 [15]) and increasing antioxidant enzymes on sepsis-induced organ dysfunctions [14–17].

To our knowledge, all studies addressed Montelukast in preterm infants were directed to prevent BPD while the effect of Montelukast in neonatal sepsis has never been investigated. The current work was conducted to discover 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

An open-label, randomized controlled parallel intervention trial was conducted on 40 late preterm newborn infants. The study was carried out at the neonatology units of Mansoura University Children's Hospital and Mansoura Insurance Hospital over 10 months from July 2020 to April 2021. Mansoura Faculty of Medicine institutional research board (IRB) approved the study and fully informed written consent was obtained from the neonate's parents or guardian before enrolment in the study. The study was registered in the clinical trials database (clinicaltrials.gov, ID: NCT04474327).

Study participants

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 (white blood cells count (WBCs) < 5000 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 ≤ 7 mmol/L); with (culture-confirmed) or without (culture-negative) a positive blood culture result [18, 19]. Infants presented initially with septic shock, multi-organ dysfunction syndrome (MODS), disseminated intravascular coagulopathy, or feeding intolerance requiring to be nil by mouth were excluded from the study. Besides, we did not include infants with major congenital malformations, chromosomal aberrations, or postoperative patients.

Intervention

Infants were divided into the Montelukast group and the routine care group. Both groups received the same protocol for the 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 h combined with Aminoglycoside (Gentamycin) at a dose of 4.5 mg/kg/36 h for infants with suspected early-onset sepsis while for late-onset sepsis, Cloxacillin (50 mg/kg/dose, every 8 h) 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 drug 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 and Dohme Corp.) for 10 days in a dose guided by the infant's birth weight as follows (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/1 ml.

Infants were discharged from the neonatal intensive care unit (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 from infection determined as normal WBCs count with negative blood culture results and declining CRP reaching < 10 mg/L.

For the 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 (Power of the hydrogen ion (PH) more than 7.25, Partial pressure of carbon dioxide (pCO2) less than 60 mmHg, and base deficit less than 8 meq/L) on a mean airway pressure less than 8 cmH_2O and frequency less than 30 breath /minute and saturation more than 88% on a fraction of inspired oxygen (FiO_2) less than 30% in the preceding 24 h 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 h, FiO_2 less than 30% to keep target saturation in the preceding 24 h, respiratory rate less than 60 breath/minute, no single apnea requiring bagging in the preceding 24 h, no more than 6 apneas requiring stimulation in the preceding 24 h, satisfactory blood gases (PH > 7.25, pCO_2 < 60 mmHg, and base deficit < 8 meq/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 h or the infant could tolerate a trial of discontinuing oxygen therapy to 21% FiO_2 for 1 h.

Outcome measures

The primary outcome was serum TNF Alpha level, an inflammatory marker, at day 10 after receiving therapy. Serum TNF alpha level was measured by the double-antibody sandwich Enzyme-linked immunosorbent assay (ELISA) technique (TNFa ELISA kits, Sunred PeloBiotech GmbH, Germany) [20]. 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 and serum CRP level at day 10 after receiving therapy. Pediatric Logistic Organ Dysfunction (PELOD) score was performed by the treating physician on admission and on day 10 in order to follow the 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 [21]. The score assesses cardiovascular function (heart rate and systolic blood pressure), neurologic function (Glasgow coma scale and pupillary reaction), hepatic function (aspartate aminotransferase (AST) and international normalized ratio (INR)), pulmonary function (partial pressure of oxygen in arterial blood (PaO2)/FiO2, PCO2 and whether the patient is on mechanical ventilation), hematologic function (WBCs and platelet count), and renal function (serum creatinine). Patient survival was recorded during 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) [22] were observed during hospital admission.

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, and use of inotropes were registered. A venous sample was withdrawn for a 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. A lumbar puncture was performed when meningitis was suspected.

Randomization and allocation

Infants were assigned randomly to treatment groups using an internet-based random table technique with a block size of four. Cards in sequentially numbered, opaque, sealed envelopes were kept in 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 the mean TNF level between the studied groups (routine care group and Montelukast group). A pilot study was carried out on 10 cases (5 in each group) to calculate sample size. During this stage of the clinical trial, none of the participants was withdrawn; moreover, none had intolerable adverse events. Using the 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 a power = 80%, mean ± standard deviation (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

Statistical Package for the Social Sciences (SPSS) for Windows (SPSS, Inc, an IBM Company, Chicago, IL, USA), version 20 was used for statistical analysis of the collected data. Shapiro–Wilk test was used to check the normality of data distribution. Quantitative variables were expressed as mean ± SD or median (minimum–maximum) as appropriate while categorical variables were expressed as frequency and percentage. Independent sample *t* test and Mann–Whitney *U* 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. Probability (p value) < 0.05 was considered statistically significant.

Results

Between July 2020 and April 2021, 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 17 newborn infants were excluded due to a variety of causes (Fig. 1). Baseline characteristics, clinical data and laboratory data at the time of allocation were non-significantly different between the studied groups (Table 1).

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).

The TNF alpha level was significantly lower in the Montelukast group compared to the routine care group. Moreover, Delta TNF alpha (difference between TNF alpha level on the 10th day and its level on admission) was compared between the studied groups, significant decrement in TNF alpha level was observed in the Montelukast 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 show non-significant differences between the Montelukast and routine care groups (Fig. 2).

There were no statistically significant differences between both groups as regards 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 (on day 16 and day 20 of admission) while in the Montelukast group, one patient died (on day 14) without statistical significance between both groups. 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 (difference between PELOD score on the 10th day and on admission) did not significantly differ between both groups (p value 0.617 and 0.547; respectively). During the follow-up period, non-significant differences in Montelukast-related possible adverse events were reported and the drug was tolerated in the studied patients as summarized in Table 4.

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 (such as patient survival, duration of NICU admission, duration of antibiotics, and oxygen support) and other outcome measures (such 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 needed to achieve its effects.

To the best of our knowledge, the effect of Montelukast on neonatal sepsis has never been addressed before in original articles. Previous studies that reported its anti-inflammatory and antioxidant effects in the diminution of sepsis-induced organ failure were experimental. Sener and coauthors [14] 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

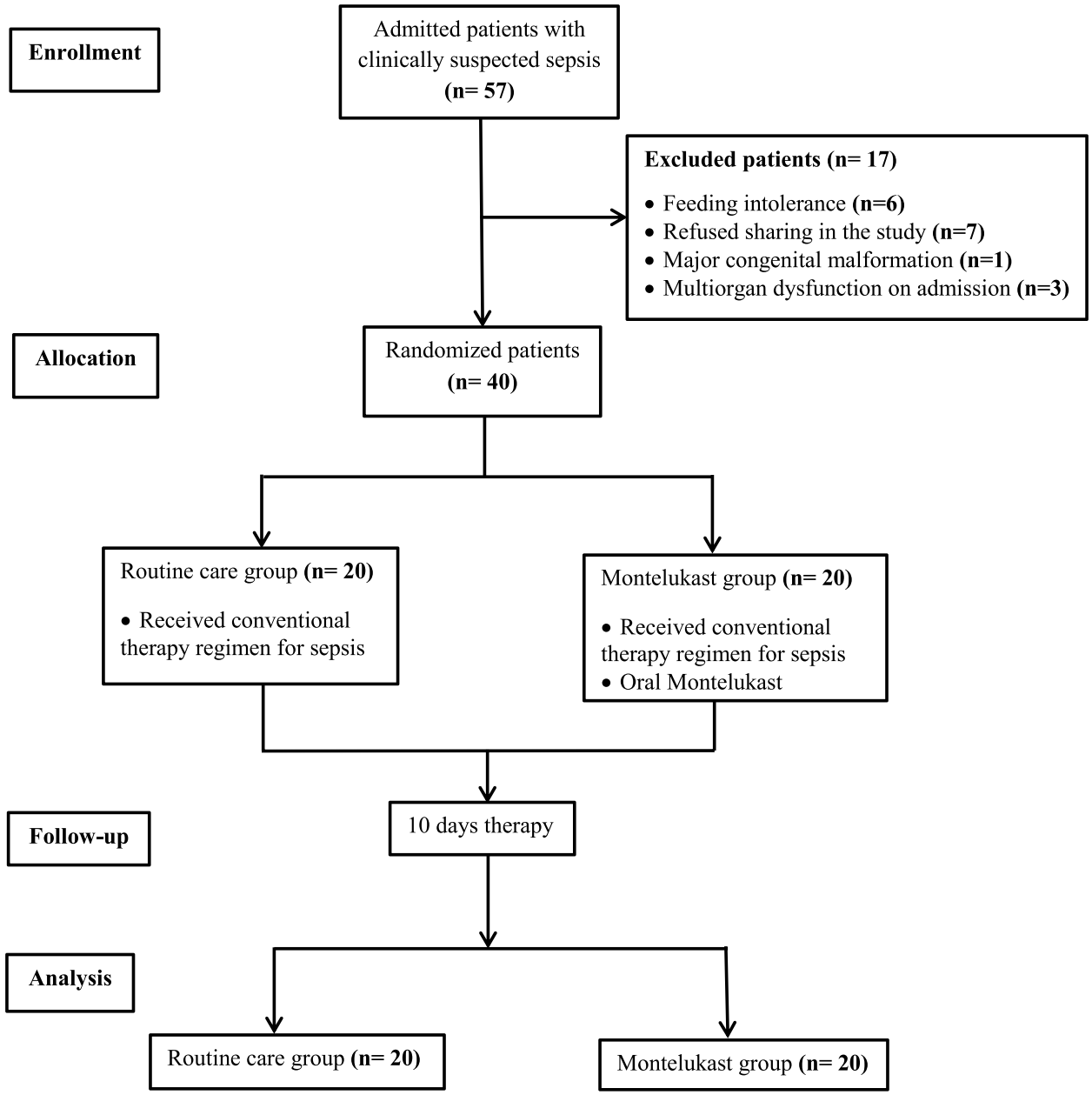

Fig. 1 CONSORT Flow diagram of participants in the study

increase in the TNF alpha level was reduced in the Montelukast group. Another study [15] 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 decreases pro-inflammatory (TNF alpha, IL-6) cytokine levels. Moreover, in 2011 Mohamadin [23] reported that Montelukast significantly suppresses liver injury (assessed by serum level of liver enzymes and bilirubin) and inflammatory mediators (TNF-alpha, Interleukin-1β (IL-1β)), after lipopolysaccharides (LPS)-induced sepsis challenge in rats.

Additionally, in 2014, Khodir and coauthors´ study [16] 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

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)[b]	34.85 ± 1.14	34.55 ± 0.95	0.370
Birth weight (grams)[b]	1655.5 ± 77.77	1688.5 ± 104.74	0.258
Male (sex)[a]	12 (60%)	8 (40%)	0.343
Postnatal age (days)[b]	5.30 ± 2.60	5.20 ± 2.51	0.902
Site of infection[a]			0.694
Bacteremia	11	10	
Pneumonia	7	8	
Meningitis	2	1	
Septic arthritis	0	1	
Respiratory distress[a]	9 (45%)	7 (35%)	0.748
Temperature instability[a]	8 (40%)	14 (70%)	0.11
Poor activity[a]	14 (70%)	12 (60%)	0.74
WBCs (10^9/l)[b]	12.13 ± 5.26	10.19 ± 5.13	0.244
Platelet (10^9/l)[b]	110.75 ± 44.13	112.45 ± 42.24	0.902
Serum C-reactive protein (mg/L)[c]	96 (24–96)	96 (24–96)	0.599
INR[b]	1.14 ± 0.26	1.08 ± 0.14	0.426
Blood glucose (mg/dL)[b]	136.65 ± 44.82	127.15 ± 58.71	0.569
TNF alpha (pg/dL)[b]	153.05 ± 50.47	167.57 ± 41.78	0.328
Serum Creatinine (mg/dL)[b]	0.53 ± 0.36	0.41 ± 0.23	0.233
AST (IU/L)[b]	18.51 ± 7.43	22.34 ± 12.23	0.240
ALT (IU/L)[b]	16.60 ± 7.68	20.18 ± 11.66	0.257
PELOD score on admission[c]	0 (0–10)	0 (0–11)	0.513

Data expressed as number (percent)[a], mean ± SD[b], or median (minimum–maximum)[c] and analyzed by Fisher's exact test[a], Student's *t* test[b], and Mann–Whitney test[c] respectively

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

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 pneumoniae	1	1	
Proteus species	1	0	
Pseudomonas aeruginosa	1	0	

Data expressed as number and analyzed by Fisher's exact test

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 [17].

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 [24]. There is good proof that pulmonary overproduction of TNF alpha is included in the development of experimentally induced acute lung [25] and renal [26] injuries. In 2011, an experimental study [15] reported that early elaboration of serum pro-inflammatory cytokines (including TNF alpha) is essential in the pathogenesis of septic

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

Characteristics	Routine care group ($n=20$)	Montelukast group ($n=20$)	*P* value
Duration of NICU admission (days)[b]	15.4 ± 4.08	14.6 ± 2.48	0.46
Patients survival survivors/died[a]	18/2	19/1	0.999
Antibiotics duration (days)[b]	14.80 ± 3.99	14.55 ± 2.46	0.81
Patients on nasal oxygen[a]	14 (70%)	13 (65%)	0.999
Nasal oxygen duration (days)[b]	2.79 ± 1.25	2.31 ± 0.75	0.245
Patients on CPAP[a]	7 (35%)	8 (40%)	0.999
CPAP duration (days)[b]	3.0 ± 1.16	2.38 ± 0.74	0.248
Patients on mechanical ventilation[a]	2 (10%)	1 (5%)	0.999
Inotropes[a]	10 (50%)	12 (60%)	0.999
Inotropes duration (days)[b]	5.8 ± 2.2	5.0 ± 1.86	0.366
WBCs (10^9/l)[b]	8.07 ± 2.48	8.19 ± 4.74	0.922
Platelet (10^9/l)[b]	232.35 ± 74.70	257.10 ± 68.79	0.283
Serum C-reactive protein (mg/L)[c]	24 (6–96)	12 (6–96)	0.256
INR[b]	1.08 ± 0.24	1.06 ± 0.21	0.781
Blood glucose (mg/dL)[b]	126.70 ± 22.87	136.75 ± 33.91	0.279
TNF alpha (pg/dL)[b]	119.54 ± 58.46	80.73 ± 50.25	**0.030**
Delta TNF alpha (pg/dL) (level on 10th day–score on admission)[c]	−33.51 (−113.23: 56.12)	−86.84 (−181.11: 13.40)	**0.001**
Serum creatinine (mg/dL)[b]	0.47 ± 0.25	0.52 ± 0.32	0.547
AST (IU/L) [b]	17.08 ± 5.47	19.49 ± 8.40	0.288
ALT (IU/L) [b]	17.83 ± 7.18	18.56 ± 9.96	0.790
PELOD score at 10 days[c]	0 (0–11)	0 (0–10)	0.617
Delta PELOD score (score on 10th day–score on admission)	0 [(−10)–(10)]	0 [(−9)–(0)]	0.547
Acute kidney injury[a]	3 (15%)	3 (15%)	0.999
Acute lung injury[a]	2 (10%)	1 (5%)	0.999
Disseminated intravascular coagulopathy[a]	0	0	
Thrombocytopenia[a]	2 (10%)	2 (10%)	0.999
Anemia required blood transfusion[a]	5 (25%)	4 (20%)	0.999

Data expressed as number (percent)[a], mean ± SD[b] or median (minimum–maximum)[c], and analyzed by Fisher's exact test [a], Student's *t* test[b], and Mann–Whitney test[c] respectively

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

shock. In addition, the role of TNF alpha in sepsis pathogenesis is recommended by many researches performed on humans [27, 28]. Moreover, in an experimental study, the measurement of TNF alpha concentration is a helpful predictor for sepsis prognosis [29].

In reviewing the literature, few studies were conducted on the effect of Montelukast in neonates, these studies searched the role of Montelukast in the prevention of BPD in preterm infants [11, 12, 30]. The recruited infants received different doses of Montelukast. Kim and coworkers [12] gave Montelukast once daily 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 2 kg: 2 mg) while in Ruprecht et al., [11] the dose was 1 mg/kg once daily in the first week of therapy then 1.5 mg/kg in the second week and increased to 2 mg/kg in the third week). Whereas In 2009, Kim and coauthors [30] 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 applying these results. Until then, we cannot recommend the use of Montelukast as a routine treatment in neonatal sepsis.

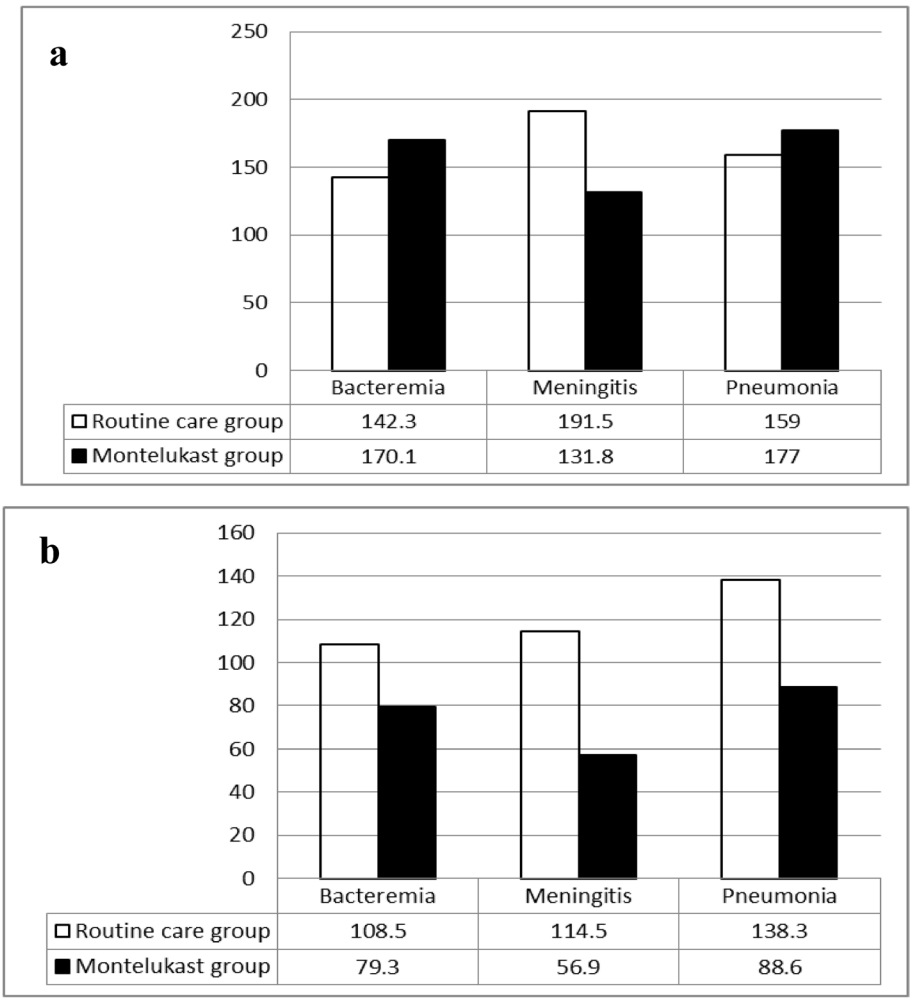

Fig. 2 Comparison of tumor necrosis factor (TNF) alpha levels (pg/dL) in patients categories presented with different sources of infection in the studies groups **a** at the start of the study and **b** on the 10th day of therapy

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	

Data expressed as number and analyzed by Fisher's exact test

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 treated neonates. 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
IL-1β	Interleukin-1β
IL-6	Interleukin-6
INR	Institutional Research Board
Kg	Kilogram
LPS	Lipopolysaccharides
MODS	Multi-organ dysfunction syndrome
NICU	Neonatal intensive care unit
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
SPSS	Statistical Package for the Social Sciences
TNF	Tumor necrosis factor
TNFa	Tumor necrosis factor alpha
WBCs	White Blood cells

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None.

Authors' contributions
NE shared in the research protocol, collected patients' blood samples and clinical data, and wrote the manuscript. HAE shared in research protocol, performed all biochemical tests for all patients, and wrote the manuscript. NN shared in research hypothesis and research protocol, supervised the provided medical care to all patients, and wrote the manuscript. SE participated in formulating the research hypothesis and plan, supervised the provided medical care to all patients and wrote the manuscript. HE 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. All authors read and approved the final manuscript.

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Availability of data and materials
Data and material are available upon request.

Declarations

Ethics approval and consent to participate
This study was performed in accordance with the principles of the Declaration of Helsinki, and was approved by Mansoura Faculty of Medicine Institutional Research Board (MS/17.06.95) and was registered in clinical trials database (clinicaltrials.gov, ID: NCT04474327; registered July 16, 2020; https://clinicaltrials.gov/ct2/show/NCT04474327). Written informed consent was obtained from parents and/or legal guardians of the study participants.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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