Original Research Article

Efficacy of Budesonide, Epinephrine and Salbutamol Inhalation for Treatment of Transient Tachypnea of Newborn: Prospective Controlled Study

Abstract

Background: Transient tachypnea of the newborn (TTN) is a neonatal lung disease which has a picture of lung edema due to delayed resorption of lung fluids. It is commonly seen in full-term or late-preterm infants with an occurrence rate of 5.7 in 1,000 infants. The aim of this work was to compare the efficacy of inhaled budesonide, epinephrine and salbutamol for treatment of TTN.

Methods: This prospective controlled study was conducted on a100 full term neonates with presumed diagnosis of TTN. They were randomly assigned into four groups equally. Group I received nebulized budesonide, Group I received nebulized epinephrine, Group III received nebulized salbutamol and Group IV received nebulized normal saline.

Results: Salbutamol significantly decreased respiratory rate and TTN clinical score, duration of respiratory support along with hospitalization time and helped with reaching full feeding earlier compared to other groups.

Conclusions: Inhaled salbutamol significantly decreased TTN clinical score, shorter duration of respiratory support, hospitalization and earlier initiation of enteral feeding compared to placebo. Inhaled budesonide and epinephrine did not significantly reduce the duration of oxygen treatment, with no other significant effect on TTN.

Keywords: Budesonide, epinephrine, salbutamol, transient tachypnea of newborn.

Introduction

Transient tachypnea of the newborn (TTN) is a neonatal lung disease which has a picture of lung edema due to delayed resorption of lung fluids[1, 2]. It is commonly seen in full-term or late-preterm infants with an occurrence rate of 5.7 in 1,000 infants. The disorder is more prevalent among infants who are male, premature, born via cesarean section without labor, or born to a mother with diabetes or asthma, and among infants who have perinatal asphyxia[3, 4].

During late gestation, as a result of increased secretion of epinephrine and other hormones, the neonatal mature lung switches from secreting fluid into the air spaces to starting reabsorbing it[5]. Delayed resorption of lung fluid in the fetus is the main cause of TTN where the fluid fills the air spaces and moves into the interstitial tissue, perivascular tissues and interlobar fissures until it is drained by the lymphatics or capillaries[6, 7].

Lung liquid clearance at birth is associated with the surge in fetal catecholamines acting via b-adrenergic receptors located in alveolar type II cells and driven by active Na+ absorption by increased epithelial Na+-channels (ENaC) and Na+-K+-ATPase activity [8]. The inability of the fetal lung to switch from fluid secretion to fluid absorption and an immaturity in the expression of the ENaC may play an important role in the development of TTN[9].Stimulation of b-adrenergic receptors with up-regulates alveolar epithelial Na+ transport by increasing the activity of ENaC and Na+-K+-ATPase and protein abundance at the plasma membrane[9, 10].

The importance of catecholamines in improving absorption of fetal lung fluid, it explains why a relative catecholamine deficiency may play a role in the development of TTN. So, administration of exogenous catecholamines may be an effective treatment[11, 12].Levels of circulating catecholamines are higher in newborns delivered vaginally than in newborns delivered by cesarean section may be due to the stimulation of catecholamine release by the

stress of labor[13]**.** Catecholamine levels are lower in infants with TTN than in infants without TTN[14]**.**

Infusion of epinephrine leads to reduction of secretion and promote the absorption of fetal lung fluid[15]**.**

Because TTN is self-limiting and relatively mild symptoms, the risk of systemic epinephrine therapy is not warranted. Inhaled epinephrine, however, is theoretically ideal for reaching the lung while minimizing systemic effects. The only commercially available inhaled epinephrine is racemic epinephrine and it is considered safe[16].

Both animal and human studies suggest lower expression of ENaC subunits, indirectly reflected lower nasal potential differences, as one of possible mechanisms for late preterm and term infants suffering from TTN. Inhaled budesonide was shown to promote transcription of ENAC in lung epithelia as well as reducing the rate of degradation and increasing the activity of the existing channels[17]. This led to clinical trials that explored the role of steroids in preventing TTN. The administration of a single dose of inhaled B2 agonists effectively reduced respiratory morbidity in late preterm and term infants with TTN[18]and glucocorticoids may improve that effect[19]**.**

This study aimed to compare the efficacy of inhaled budesonide, epinephrine and salbutamol for treatment of transient tachypnea of newborns at the neonatal intensive care unit (NICU) of Tanta University hospital.

Patients and Methods

This prospective controlled study was conducted at neonatal intensive care unit of Tanta University hospital. 100 full term neonates with presumed diagnosis of transient tachypnea of newborn (TTN) were enrolled in this study from December 2018 to June 2020.

Written informed consent was obtained from the guardians of every patient. The study was approved by Ethics Committee of Faculty of Medicine, Tanta University.

The inclusion criteria were full term neonates diagnosed with TTN according to clinical parameters [20] (tachypnea> 60 breaths /minute within 24 hrs after delivery, mild to moderate respiratory distress with nasal flaring and rib retractions[intercostal & subcostal], auscultation reveals good air entry with or without crackles, manifestations usually persist for 12- 24 hours. up to 72 hrs and spontaneous improvement is an important marker of TTN), chest x-ray findings[21] (prominent perihilar streakings, fluid in the minor fissure, prominent pulmonary vascular markings, lung hyperinflation with depression of diaphragm and chest x-ray usually shows evidence of clearing by 12- 18 hrs with complete resolution by 48- 72 hrs), TTN clinical score to determine the degree of severity [19].

While neonates presented with tachypnea presented within more than 24 hrs. after delivery, severe respiratory distress with cyanosis, congenital heart diseases, evidence of sepsis, inborn error of metabolism., congenital lung malformations and chromosomal disorders were excluded.

The recruited cases were randomly assigned into four groups equally.

Group I (budesonide group) received nebulized budesonide (Pulmicort “0, 25 mg/ml” a product of AstraZeneca, Sweden) at dose of 0.5 mg in 2ml 0.9% normal saline every 8 hours till clinical resolution.

Group II (epinephrine group) received nebulized epinephrine (Adrenaline “1 mg/ml” a product of Chemical Industries Development (CID), Egypt) at dose of 0.5 ml/kg of 1:1,000 solution diluted in 2 ml 0.9% normal saline every 8 hours till clinical resolution.

Group III (salbutamol group received nebulized salbutamol (Farcolin Respirator solution “0.121 gm/ 20 ml” a product of Pharco, Egypt) at dose of 0.15 ml/kg in 2 ml 0.9% normal saline every 8 hours till clinical resolution.

Group IV (control group) received nebulized normal saline 0.9% at dose of 2 ml 0.9% normal saline every 8 hours till clinical resolution.

Statistical analysis:

Statistical presentation and analysis of the present study was conducted, using the mean, standard deviation and chi-square test by SPSS V.20. Quantitative data were reported as mean± standard deviation (SD). Qualitative data were stated as percentage and frequency. These next tests were held: A one-way analysis of variance (ANOVA) when there is a comparison between over two means with Post Hoc test: Least Significant Difference (LSD) was utilized for numerous comparisons between different variables. Chi-square (x^2) significance test was utilized for comparing proportions among qualitative parameters. The confidence interval was set to 95% and the error margin accepted was set to 5%. P-value $\leq$0.05 was considered significant.

Results

In **Table 1**therewere no significant differences among studied groups at time of enrollment as regards to sex, age, gestational age, birth weight or Apgar score at 1, 5 minutes as ($p > 0.05$). It also showed that 82% of the neonates were delivered via Caesarian section while 18% were delivered by normal vaginal delivery. As regards to mother common morbidities, 10% had hypertension, 11% had diabetes mellitus and 5% had bronchial asthma, so there was predominance of Caesarian section as risk factor.

Table 1: Demographic data and maternal characteristics of the studied groups

	GI **Budesonide (n = 25)**	GII **Epinephrine (n = 25)**	GIII **Salbutamol (n = 25)**	GIV **Control (n = 25)**	**P value**
Sex					
Male	14 (56.0 %)	14 (56.0 %)	16 (64.0 %)	17 (68.0 %)	0.769
Female	11 (44.0 %)	11 (44.0 %)	9 (36.0 %)	8 (32.0 %)	
Age at enrollment (hours)					
Mean ± SD.	3.88 ±3.55	4.44 ± 1.08	5.88 ±4.48	5.36 ±3.20	0.168
Gestational age (Weeks)					
Mean ± SD.	37.68 ± 0.99	38.08 ± 1.04	37.48 ± 0.65	37.68± 0.99	0.146
Birth weight (Kg)					

Mean ± SD.	3.66 ± 0.74	3.69 ± 0.58	3.62 ± 0.60	3.55 ± 0.67	0.896
Apgar score 1min					
Mean ± SD.	7.40 ± 0.50	7.32 ± 0.48	7.60 ± 0.50	7.40 ± 0.50	0.230
Apgar score 5 min					
Mean ± SD.	9.0 ± 0.0	9.0 ± 0.0	8.92 ± 0.28	8.88 ± 0.33	0.130
Mode of delivery					
CS	20 (80 %)	21 (84%)	19 (76%)	22 (88%)	0.816
Vaginal	5 (20%)	4 (16%)	6 (24%)	3 (12%)	
Maternal characteristics					
Maternal hypertension	3 (12%)	2 (8%)	1 (4%)	4 (16%)	0.682
Maternal asthma	1 (4%)	2 (8%)	0 (0%)	2 (8%)	0.752
Maternal diabetes	2 (8%)	2 (8%)	3 (12%)	4 (16%)	0.895
Maternal age (**years**)	31.8 ±4.9	32.7 ±5.9	31.7 ± 5.4	30.6 ± 4.5	0.564

CS: Cesarean section.

In **Table 2** there was insignificant difference among groups as $p > 0.05$ as regards grade of respiratory distress. Most cases 64% were manifested with tachypnea, 25% were manifested with retractions and 11% were manifested with grunting.

As regards to the method of respiratory support, there was insignificant difference among groups as $p > 0.05$. Most cases 62 % received LFNC as supplemental O_2 at time of enrollment, 20 % of cases received incubator O_2 and 18 % of cases received CPAP.

Table 2: Grades and methods of support of respiratory distress in the studied groups

Grade of RD	G1 **Budesonide (n = 25)**		G2 **Epinephrine (n = 25)**		G3 **Salbutamol (n = 25)**		G4 **Control (n = 25)**		**P value**
	No.	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**	
RD I (**tachypnea**)	17	68.0	16	64.0	16	64.0	15	60.0	0.985
RD II (**retractions**)	6	24.0	6	24.0	7	28.0	6	24.0	
RD III (**grunting**)	2	8.0	3	12.0	2	8.0	4	16.0	
RD IV (**cyanosis**)	0	0	0	0	0	0	0	0	
Methods of support									
CPAP	5	20.0	3	12.0	4	16.0	6	24.0	0.910
LFNC	14	56	18	72	16	64	14	56	
Incubator O_2	6	24.0	4	16.0	5	20.0	5	20.0	

RD: respiratory distress, MC: Monte Carlo, CPAP: continuous positive airway pressure, LFNC: low flow nasal cannula.

In **Table 3** and **Table 4**there was insignificant difference in heart rate at time of enrollment and after 48 hrs among the studied groups as $p > 0.05$. As regards respiratory rate , there was no statistically significant difference at time of enrollment. After 48 hrs there was

decrease in both budesonide and epinephrine groups but was statistically insignificant versus control group as $p > 0.05$. The decrease was more in salbutamol group with statistically significant difference versus other groups as $p < 0.05$.

Table 3: Heart and respiratory rate at enrollment (0), 12, 24, 48 hrs of the studied groups

Time	G1 **Budesonide (n = 25)**	G2 **Epinephrine (n = 25)**	G3 **Salbutamol (n = 25)**	G4 **Control (n = 25)**	**P value**
0 h (at enrollment) **(b/m)**	125.96 ± 7.21	124.32 ± 7.40	123.0 ± 6.26	128.36 ± 7.30	0.051
12 h **(b/m)**	136.60 ± 5.93	136.24 ± 6.22	138.64 ± 3.43	133.64 ± 6.95	0.029
24 h **(b/m)**	129.48 ± 6.11	130.84 ± 6.20	128.36 ± 6.74	128.12 ± 7.80	0.470
48 h **(b/m)**	125.44 ± 5.27	127.40 ± 5.85	123.28 ± 5.0	124.32 ± 7.66	0.101
Respiratory rate					
0 h (at enrollment) **(cycle/min)**	72.56 ± 4.74	72.96 ± 5.26	72.92 ± 5.11	73.56 ± 4.64	0.912
12 h **(cycle/min)**	60.64 ± 4.84	60.76 ± 5.55	58.40 ± 5.21	61.48 ± 4.42	0.160
24 h **(cycle/min)**	50.88 ± 3.89	51.60 ± 4.69	46.60 ± 4.78	52.24 ± 4.36	<0.001
48 h **(cycle/min)**	45.48 ± 5.11	46.24 ± 5.39	41.88 ± 4.70	48.0 ± 3.14	<0.001

h: hour, statistically significant p value: ≤ 0.05

Table 4: Respiratory rate changes of the studied groups

	G1 vs. Control	G2 vs. Control	G3 vs. Control	G1 vs. G2	G1 vs. G3	G2 vs. G3
At enrollment (0 H)	0.891	0.973	0.968	0.992	0.994	1.000
After 48 H	0.231	0.544	<0.001	0.939	0.037	0.007

H (hour) , statistically significant p value: ≤ 0.05, G1: Budesonide G 2: Epinephrine G 3: Salbutamol G 4: normal saline.

In **Table 5** at time of enrollment there was no statistically significant difference among groups, but after 48 hrs there were statistically significant differences among them. There was decrease in both budesonide and epinephrine groups but was statistically insignificant versus

control group as $p > 0.05$. The decrease was more in salbutamol group with statistically significant difference versus other groups as $p < 0.05$.

Table 5: TTN clinical score changes at enrollment (0), 12, 24, 48 hrs of the studied groups

Time	G1 **Budesonide (n = 25)**	G2 **Epinephrine (n = 25)**	G3 **Salbutamol (n = 25)**	G4 **Control (n = 25)**	P
0 h (at enrollment)	2.64 ± 0.70	2.76 ± 0.83	2.52 ± 0.71	2.92 ± 1.04	0.445
12 h	1.68 ± 0.69	1.76 ± 0.78	1.68 ± 0.69	2.08 ± 0.70	0.114
24 h	0.92 ± 0.64	0.96 ± 0.68	0.36 ± 0.57	1.20 ± 0.50	<0.001
48 h	0.32 ± 0.48	0.36 ± 0.49	0.04 ± 0.20	0.40 ± 0.50	0.020
TTN clinical score changes					
At enrollment (0 H)	0.131	0.154	0.79	0.689	0.505	0.286
After 48 H	0.531	0.754	0.005	0.754	0.028	0.012

H (hour), TTN: transient tachypnea of newborn, pairwise comparison bet. each 2 groups were done using Post Hoc test (Dunn's for multiple comparisons test), Statistically significant at $p \leq 0.05$, G1: Budesonide G 2: Epinephrine G 3: Salbutamol G 4: normal saline

Table 6 showed that PH, PaO_2 and HCO_3 increased after treatment, while PCO_2 decreased, but there was **insignificant** difference among groups as $P > 0.05$.

Table 6: Capillary blood gases of the studied groups

	G1 **Budesonide (n = 25)**	G2 **Epinephrine (n = 25)**	G3 **Salbutamol (n = 25)**	G4 **Control (n = 25)**	P
PH:					
Before treatment	7.29 ± 1.2	7.31 ± 0.88	7.30 ± 1.0	7.30 ± 0.6	1.000
After treatment	7.36 ± 0.92	7.44 ± 0.53	7.42 ± 0.6	7.35± 0.85	0.936
$PaCO_2$: **(mmHg)**					
Before treatment	50.52 ± 9.23	47.85 ± 7.64	49.32 ± 8.15	53.22 ± 10.34	0.185
After treatment	45.91 ± 6.89	44.33 ± 5.32	44.35 ± 6.12	44.15 ± 7.12	0.756
PaO_2: **(mmHg)**					
Before treatment	53.13 ±10.23	56.1 ± 8.99	55.2 ± 8.20	56.2 ± 8.99	0.612
After treatment	72.39 ± 8.12	73.22 ± 6.12	72.2 ± 5.77	71.4 ± 6.32	0.463
HCO_3: **(mmol/l)**					
Before treatment	20.33 ± 6.45	22.35 ± 5.44	20.12 ± 6.32	21.33 ± 6.01	0.377
After treatment	22.35± 5.15	23.45 ± 4.32	23.48 ± 4.22	23.53±4.19	0.425

In **Table 7**, as regards O_2 saturation there was insignificant difference at enrollment and after 48 hrs among all groups as $P > 0.05$.

Table 7: O_2 saturation at enrollment (0), 12, 24, 48 hrs of the studied groups.

	G1 **Budesonide (n = 25)**	G2 **Epinephrine (n = 25)**	G3 **Salbutamol (n = 25)**	G4 **Control (n = 25)**	P
0 h (at enrollment) (%)	90.52 ± 1.05	90.20 ± 1.47	90.24 ± 1.20	89.84 ± 1.31	0.310
12 h (%)	94.04 ± 1.37	94.28 ± 1.62	93.52± 1.76	93.44 ± 1.29	0.156
24 h (%)	95.80 ± 1.08	95.64 ± 1.22	95.08± 1.71	95.08 ± 0.95	0.096
48 h (%)	95.88 ± 2.20	95.56 ± 1.08	95.72± 2.69	94.72 ± 1.10	0.144

H: hour

In **Table 8**, as regards the duration of respiratory support and the duration of hospitalization after 48 hrs there were insignificant differences between budesonide and epinephrine groups versus control group as $p > 0.05$. The both durations were less in salbutamol group but were statistically significant versus other groups as $p < 0.05$.

Table 8: Duration of respiratory support and duration of hospitalization of the studied groups

	G1 **Budesonide (n = 25)**	G2 **Epinephrine (n = 25)**	G3 **Salbutamol (n = 25)**	G4 **Control (n = 25)**	P
Duration of respiratory support **(hours)**					
Mean ± SD.	32.75 ± 13.20	30.32 ± 10.39	21.52 ± 8.17	38.12 ± 14.32	<0.001
Duration of hospitalization **(days)**					
Mean ± SD.	2.42 ± 0.48	2.36 ± 0.40	2.0 ± 0.38	2.56±0.46	<0.001

Statistically significant at $p \leq 0.05$.

In **Figure (1),** as regards time till full feeding, there was statistically significant difference among groups asp <0.05, but when comparing budesonide and epinephrine groups versus control group, there was no statistically difference as $p > 0.05$. Salbutamol group reached full feeding earlier with **significant** difference versus other groups as $p < 0.05$.

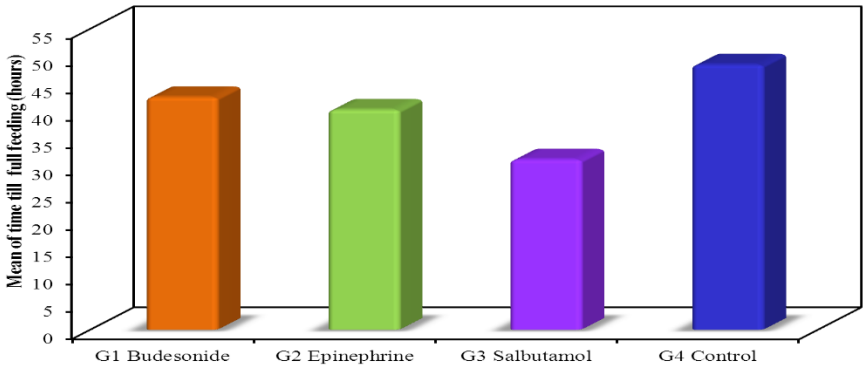

Figure 1: Time till full feeding in hours of the studied and control groups

Discussion

In the neonatal period, transient tachypnea of the newborn (TTN) is the most frequent cause of early respiratory distress because of delayed resorption of the fetal lung fluid, which fills the fetal airways (Keleş et al., 2016)[22].

In utero the lungs are filled with a liquid that is secreted by the lung epithelium. Pulmonary alveolar epithelium actively secretes cl into developing air space, promoting fluid secretion, which in turn modulates lung growth. Na absorption is relatively low. Alveolar fluid continuously passes to amniotic fluid by breathing movements via broncho-tracheal route. In late gestation and shortly before birth, fetal lungs convert from fluid secretion to fluid re-absorption (van Vonderen et al., 2015)[23].The inability of the fetal lung to switch from fluid secretion to fluid absorption and an immaturity in the expression of the ENaC may play an important role in the development of TTN (Davies, 2004)[9].

Our study showed insignificant differences among groups as regards grades of respiratory distress at time of enrollment. That was in agreement with(Malakian et al., 2018)[24].

There were insignificant differences among groups as regards methods of respiratory support as $p > 0.05$. That was in agreement with (Babaei et al., 2019)[25].

As regards to heart rate , the current study showed that there were insignificant differences before and after inhalation and that was in agreement with(Nawar et al., 2016) and (Talaat et al., 2020)[26, 27].

In this study, at time of enrollment, mean respiratory rate and mean of TTN score were relatively higher. However, after 48 hours there was a noticeable decrease in budesonide, epinephrine, and salbutamol groups.

As regards to respiratory rate and TTN clinical score after 48 hrs, the comparison of budesonide and epinephrine to control group showed insignificant differences as $p > 0.05$ and that was in agreement with (Vaisbourd et al., 2017)[28]and(Moresco et al., 2016)[29] respectively.

The decrease was **significant** in salbutamol group in comparison to other groups. That was in agreement with (Salama et al., 2020)[30] as both respiratory rate and TTN score significantly decreased in salbutamol group (treatment group) when compared to normal saline group (control group) at half hour after treatment and continued till 8 hours after treatment.

Regarding capillary blood gases before and after nebulization, there were insignificant differences between groups in pH, PaO_2, $PaCO_2$ and HCO_3 and that was is disagreement with (Nawar et al., 2016) and (Malakian et al., 2018)[24, 26]**.** In [26], the studied neonates were divided into three groups: group 1 received one dose of inhaled epinephrine, group 2 received one dose of inhaled salbutamol and group 3 (control group) received saline 0.45% and there were significant differences between groups in pH, PaO_2, $PaCO_2$ after nebulization. Saline group recorded the lowest readings of pH and PaO_2 in comparison to the other groups, but the highest reading in $PaCO_2$. In salbutamol group, there was significant increase in PH, PaO_2 and significant decrease in $PaCO_2$ after nebulization.

In our study as regards O_2 saturation, there were insignificant differences at enrollment and after 48 hrs as $p > 0.05$ and that was not in agreement with(Babaei et al., 2019)[25] where there was significant difference between salbutamol and control groups after 4 hours.

As regards the duration of respiratory support and the duration of hospitalization, all were shorter than control group. They were **significantly** shorter with salbutamol group than other groups and that was in agreement with (Talaat et al., 2020)[27] which investigated 100 neonates with TTN to receive nebulized normal saline solution or salbutamol in saline solution. This study reported that the duration of respiratory support and duration of hospitalization were significantly shorter in salbutamol group than control group.

While the comparison of budesonide and epinephrine to control group showed insignificant differences as $p > 0.05$ and that was in in agreement with (Vaisbourd et al., 2017) and (Moresco et al., 2016)[28] and [29].

The mean time till full feeding in hours in budesonide group was shorter than in control group, but salbutamol group reached full feeding earlier with **significant** differences in comparison to other groups and that was in agreement with(Mohammadzadeh et al., 2017)[31], where neonates were assigned to receive either salbutamol inhalation or normal saline inhalation as placebo group , where salbutamol group reached full feeding earlier with significant differences.

Also, budesonide and epinephrine reached full feeding earlier than control group, but with insignificant differences and that was in agreement with (Vaisbourd et al., 2017)and (Moresco et al., 2016)[28][29].

Conclusions

Inhaled salbutamol significantly decreased TTN clinical score, shorter duration of respiratory support, hospitalization and earlier initiation of enteral feeding compared to

placebo. Inhaled budesonide and epinephrine did not significantly reduce the duration of oxygen treatment, with no other significant effect on TTN.

Strengths & Limitations

One of the strengths of the present study was its prospective controlled approach which facilitated investigating and examining the hypothesis of the researcher.

On the other hand, the main limitations of the study was the small sample size and the time limit required for completion of our investigation.

COMPETING INTERESTS DISCLAIMER:
Authors have declared that no competing interests exist. The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

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