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RESEARCH ARTICLE

EFFICACY OF INHALED BUDESONIDE IN TRANSIENTTACHYPNEA OF NEWBORN ": A RANDOMISED CONTROL STUDY

Dr. Shrishail A.J[1] and Dr. Varsha S.A[2]

1. Resident of Department of Paediatrics MVJ Medical College and Research Hospital Bengaluru.
2. Professor of Paediatrics,- MVJ Medical College And Research Hospital Bengaluru.

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Abstract

Background And Objectives: Corticosteroids have a role in increasingthe reabsorption of lung fluids. Hence, this study wasconductedto assess efficacyandsafetyofinhaledBudesonideinreducingtheneedforrespiratorysupport,clinicalimprovement, time to reach full feeds and duration of hospital stay in neonates withTTN.

Materials And Methods: 100 Neonates(>35weeks), diagnosed as TTNwere included in study andrandomized into 2 groups-study and control groups. Allthe neonates were managed as per existing NICU protocol. Along with standardsupportivemanagementincludingrespiratorysupport,theyreceivedfollowingnebulizationwith6hoursand12hoursafterthat.

Intervention:

Studygroup:Budesonidenebulization(2ml=1000ug)

Controlgroup: Placebo(0.9%Normalsalinesolution2ml)

Baselinedemographicandclinicalprofile,clinicalparametersat4,12,24and48hoursafter intervention, requirement of respiratory support, duration of hospital stay andadverseeventswererecorded,comparedandanalyzedinbothgroups.

Results: Improvement in Budesonide group was significantly better in regard torespiratoryrate,Downescore(P<0.000),andoxygensaturation(P<0.000)at4hours,12 hours, 24 hours and 48hour. The total duration of mean respiratory support instudygroup(13.8hours)wassignificantlylowerthanplacebogroup(32.52hours)andwasstatisticallysignificant(p<0.000).Therewassignificantdifferenceindurationof NICUstay(2.50±1.055vs3.86±1.088days,p<0.05) andoccurrenceofnosocomialinfection among study and control group. No significant adverse events related tosteroidinhalationwereobserved.

Conclusion: The early inhaled corticosteroid (budesonide) in TTN improved theclinicalcourseofTTN,withreducedduration of respiratorysupportand hospitalstay,withoutanysignificantsideeffects.

InconclusioninhaledbudesonidecanbeusedasaoptioninmanagementofTTNinlatepretermandtermneonates.

Corresponding Author:- Dr. Shrishail A.J
Address:- Resident of Department of Paediatrics.

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Introduction:-

Newborns are considered as a vulnerable group because of the sudden transition from the intrauterine to extrauterine life. For this transition to be smooth, the foetus undergoes several changes inside the uterus. One of such changes is to establish lung as the organ of gas exchange. For this to occur five major events take place at birth which include: clearance of foetal lung fluid, establishment of spontaneous breathing, decrease in pulmonary vascular resistance, release of surfactant, and cessation of the right-to-left shunting of venous blood returning to the heart(1). During the foetal life, to maintain the normal growth and function, fluid is secreted into the alveoli and this fluid is cleared before air breathing is initiated(2,3). When there is a delay in the clearance or resorption doesn't happen, there will be ineffective gas exchange, respiratory distress and transient tachypnea of newborn ensues.

Transient tachypnea of the newborn (TTN) is a benign, self-limited condition that can present in infants of any gestational age shortly after birth. In mild cases TTN is considered a self-limiting disease, while in severe cases it can lead to acute manifestation of respiratory distress such as tachypnea, severe retraction, audible grunting, and cyanosis. Sometimes in severe cases, this can result in fatigue and exhaustion of respiratory muscles and impending respiratory failure unless respiratory support is provided through nasal cannula, or mechanical ventilation(4,5). Few cases of persistent pulmonary hypertension and pulmonary air leak has also been reported following in TTN(6,7). In term and late preterm newborns, TTN is the most common cause of respiratory distress(8). Thus, TTN can cause maternal-infant separation, the need for respiratory support, extended unnecessary exposure to antibiotics and prolonged hospital stays. TTN may also be associated with wheezing syndromes later in childhood(9). TTN is also called as foetal lung liquid syndrome.

Epithelial Na+ channel (ENaC) is susceptible to the level of corticosteroids and is believed to be one of the most crucial pathways through which absorption of lung fluids takes place(10). Corticosteroids had a vital role in improving the functions of these specific Na+ channels in the lung by enhancing the effectiveness of ENaC, resulting in the functional maximization of these receptors in the absorption of lung fluids(10). Steroids have the capacity to increase the transcription of ENaC in lung epithelia as well as decreasing the rate of degradation and increasing the activity of the existing channels(10,11). Corticosteroid inhalation by the lungs in preterms with respiratory distress syndrome decreases the prevalence of respiratory complications, such as bronchopulmonarydysplasia, pneumonia, andother disorders, without causing any major systemic adverse side effects in neonates(12).

The availability of a therapy to improve the natural course of TTN would reduce the need for respiratory support, intensive care and result in early establishment of breastfeeds and early discharge. It is possible that exogenous administration of corticosteroids might partly compensate for the impaired hormonal changes which occur when infants are delivered late preterm, or at term before the onset of spontaneous labour (elective caesarean section)(13). Administration of inhaled glucocorticoids may have favourable effects on the pulmonary system, with a insignificant risk of adverse effects(14). Despite their widespread use, inhaled glucocorticoids have been evaluated in only a few small, short-term studies(15). There is a lack of data and studies on the use of inhaled corticosteroids in TTN, and hence this study was conducted to evaluate the efficacy of inhaled budesonide in TTN.

Aims & Obectives:-

1. To determine whether Early Inhaled corticosteroids(budesonide) would reduce the duration of respiratory support in late preterm and term neonates.
2. To determine the safety profile of inhaled budesonide.

Research Methodology:-

Study Design:

Randomized controlled trial

Study Area

This study was conducted in the rural tertiary care hospital of MVJ Medical College and Research Hospital, Hoskote.

Study Population
All neonates born in MVJ Medical College and Research Hospital, meeting the inclusion criteria.

Inclusion criteria:
All neonates, who were born after 35 weeks of gestation and diagnosed with TTN as defined by Armangil et al., andRiskin et al, with the following criteria were included in the study

Criteria:
1. Tachypnea (respiratory rate [RR] ≥ 60 breaths/min) within 6hours after delivery with arequired FiO2 >0.30.
2. Chest X-ray showing one of the following:

I. Evident pulmonary vascular markings,
II. Increased interlobar fissures with evident fluid,or
III. Symmetrical congested perihilar tissues

3. Exclusion of other causes of respiratory distress in them(pneumonia, congenital heart disease, perinatal asphyxia, early onset sepsis)

Exclusion criteria:
1. Neonates with exposure to prenatal steroids.
2. Neonates who have undergone any other medical intervention which could influence the outcome.
3. Major congenital malformations.

Outcome:
1.Primary outcome variable would be duration of respiratory support.
2.Secondary outcome variable would be change in downe'sscore,duration of hospital stay and complication associated with inhalation of corticosteroids.

Method of Data Collection:-

They were randomised into two groups (group A and group B) using a table of random numbers
1. Group A were given inhaled corticosteroids (budesonide 2ml = 1000µg) by nebulization. The first dose of budesonide was given within 6 hours of age and the second dose was given after 12 hours.
2. Group B were given placebo in the form of 0.9% normal saline solution of 2ml as nebulization.

Respiratory management was done as per NICU protocol in both the groups. Clinical assessment was done every second hourly, during the first 48 hours or until the resolution of respiratory distress. Respiratory distress was assessed byDowne's score. Assessment in terms of Downe's score was compared before and after the intervention.

The following information was collected as a part of the study:

Socio-demographic details, birth weight, gestational age, mode of delivery, Apgar score at 5 minutes, total duration of illness, heart rate, respiratory rate, spO_2, RDS/Downe's score, need and duration of respiratory support, time of enteral feeding initiation, duration of hospital stay, side effects and outcome.

Statistical Methods:-

Data was collected and entered into Microsoft excel data sheet and analysed using SPSS (Statistical Package for the Social Sciences) version 22.0 software. All study variables were analysed using descriptive statistical methods like frequencies and percentage for categorical variables and mean with standard deviation or median with interquartile range for continuous variables. Intention to treat analysis for RCT was used in this study. Chi -square test, student's t test and non-parametric tests were used whenever appropriate. A p value of <0.05 was considered statistically significant in this study.

Results:-

This study was conducted in neonatal intensive care unit of rural tertiary care hospital from January 2021 and was continued till the intended sample size of 100.

Changes in the clinical parameters in the both groups after intervention is shown in the following table.

Variable (mean ± SD)		Budesonide group	Placebo group	F value	P value
At 4hrs					
	Heart rate	145.52 ± 8.844 (142.02 – 147.02)	144.50 ± 8.814 (142.02 – 147.02)	0.140	0.609
	Respiratory rate	62.28 ± 9.536 (59.57 – 64.99)	67.16 ± 10.413 (64.20 – 70.12)	5.973	0.016*
	Spo2	94.24 ± 1.533 (93.80 – 94.68)	92.10 ± 1.418 (91.70 – 92.50)	52.523	0.000*
	Downe's score	2.56 ± 1.128 (2.24 – 2.88)	3.40 ± 0.948 (3.13 – 3.67)	16.260	0.000*
At 12hrs					
	Heart rate	135.84 ±8.269 (133.49 – 138.19)	135.96 ± 8.519 (133.54 – 138.38)	0.005	0.943
	Respiratory rate	54.60 ± 8.910 (52.07 – 57.13)	63.08 ± 9.750 (60.31 – 65.85)	20.611	0.000*
	Spo2	95.90 ± 1.298 (95.53 – 96.27)	93.32 ± 1.332 (92.94 – 93.70)	96.282	0.000*
	Downe's score	0.90 ± 1.055 (0.60 – 1.20)	2.59 ± 0.832 (2.34 – 2.83)	74.826	0.000*
At 24hrs					
	Heart rate	134.16 ± 8.397 (131.77 – 136.55)	133.52 ± 8.365 (131.14 – 135.90)	0.146	0.703
	Respiratory rate	51.96 ± 3.625 (50.93 – 52.99)	59.64 ± 4.579 (58.34 – 60.94)	86.457	0.000*
	Spo2	96.86 ± 1.010 (96.57 – 97.15)	94.52 ± 1.313 (94.15 – 94.89)	99.741	0.000*
	Downe's score	0.20 ± 0.571 (0.04 – 0.36)	1.46 ± 0.994 (1.18 – 1.74)	60.379	0.000*
At 48hrs					
	Heart rate	134.28 ± 6.224 (132.51 – 136.05)	134.38 ± 6.050 (132.66 – 136.10)	0.023	0.935
	Respiratory rate	50.12 ± 4.214 (48.83 – 51.41)	53.72 ± 4.815 (52.35 – 55.09)	14.842	0.000*
	Spo2	97.28 ± 0.730 (97.07 – 97.49)	95.82 ± 1.424 (95.42 – 96.22)	99.741	0.000*
	Downe's score	0.00 ± 0.000 (0.00 – 0.00)	0.38 ± 0.725 (0.17 – 0.59)	13.723	0.000*

Comparision of Mean duration of NICU stayin study and control group

Variable	Budesonide group	Placebo group	t test	P value
Mean duration of NICU stay	2.50 ± 1.055	3.86 ± 1.088	-6.346	0.000*

Adverse Events Following Intervention

Variable	Categories	Budesonide group	Placebo group	Chi-square test	P value
Hyperglycaemia	Yes	2 (4.0)	3 (6.0)	0.211	0.646
	No	48 (96.0)	47 (94.0)		

Hypertension	Yes	0 (0.0)	1 (2.0)	1.010	0.315
	No	50 (100.0)	49 (98.0)		
Nosocomial infection	Yes	5 (10.0)	14 (28.0)	5.263	0.022*
	No	45 (90.0)	36 (72.0)		

Duration of required respiratory support after intervention:

Variable (mean duration) (hours)		**Budesonide group**	**Placebo group**	**t test**	**P value**
O2 support		1.08 ± 2.221 (0.45 – 1.71)	4.80 ± 9.390 (2.13 – 7.47)	-2.726	0.008*
Non – invasive ventilation	CPAP	6.00 ± 8.806 (3.50 – 8.50)	12.84 ± 16.971 (8.02 – 17.66)	-2.530	0.013*
	NIV	5.04 ± 8.771 (2.55 – 7.53)	10.96 ± 19.659 (5.37 – 16.55)	-1.945	0.055
	HHFNC	1.68 ± 6.419 (-0.14 – 3.50)	3.12 ± 11.059 (-0.02 – 6.26)	-0.796	0.428
	Total	13.8 ± 8.54 (11.37 –16.22)	32.52 ± 12.367 (29.00-36.03)	-8.806	0.000*
Invasive ventilation		0	20(mean0.40 ±2.828[-0.403-1.20]	-1.000	0.320
Total		13.8 ± 8.54 (11.37 –16.22)	32.52 ± 12.367 (29.00-36.03)	-8.806	0.000*

- The baseline heart rate was 151.09 ± 7.170 and 151.08 ± 8.154 beats per minute respectively in the study and control groups.
- The baseline respiratory rate was found to be 70.60 ± 5.318 cycles per minute among the study group and 70.76 ± 5.173 cycles per minute in the control group.
- The mean oxygen saturation at admission was 91.90 ± 1.854%among the study group and 91.52 ± 1.446% among the controls.

- The mean Downe's score in the study group and the control group was (3.74 ± 1.026) and (3.76 ± 1.001) respectively at admission.

- At 4 hours after Budesonide nebulisation,
- the mean oxygen saturation was noted to be 94.24 ± 1.533% compared to that 92.10 ± 1.418% in the placebo group with p-value (0.000).
- Mean Downe's score in the budesonide group (2.56 ± 1.128) was significantly less compared to placebo group(3.40 ± 0.948). (p value-0.000)
- Mean respiratory rate also had a significant decrease at 4 hours in budesonide group (62.28 ± 9.536) compared to placebo group(67.16 ± 10.413) with p- value (0.016).
- Mean heart rate almost equally decreased in the both groups at 4 hours.
- Decrease in mean respiratory rate at 4 hours was more in study group (62.28 ± 9.536) compared to the control group(67.16 ± 10.413) (p = 0.016).

- At 12 hours after nebulisation:
- The mean respiratory rate, oxygen saturation and Downe's score were 54.60± 8.9, 95.90± 1.29 ,0.90± 1.05 in Budesonide group compared to 63.08± 9.75, 93.32± 1.332 and 2.59± 0.832 in placebo group respectively.

- At 24 hours after nebulisation:
- The mean respiratory rate, oxygen saturation and Downe's score were 51.96± 3.6, 96.86± 1.01 ,0.20± 0.57 in Budesonide group compared to 59.64± 8.6, 94.52± 1.31 and 1.46± 0.994 in placebo group respectively.

- At 48 hours after nebulisation:
- Even at 48 hours after nebulisation, there was significant difference in improvement of respiratory rate, mean oxygen saturation and Downe's score in Budesonide group.
- The total mean duration of respiratory support was found to be around 32.52 ± 12.367hours among the placebo group and 13.8 ± 8.54 hours among the budesonide group (p=0.000).
- The mean duration of NICU stay was found to be around 2.5 days in case of budesonide group, while it was almost 4 days in case of placebo group (p = 0.000).

- Placebo group had more frequency of nosocomial infections (14 subjects) compared to the budesonide group (5 subjects) ($p = 0.022$).
- There was no significant difference in occurrence of hypoglycaemia and hypertension in both groups.

Conclusion:-

The early inhaled corticosteroid (budesonide) in TTN improved the clinical course of TTN with early reduction of respiratory rate, Downe's score, improvement in oxygen saturation with reduced duration of respiratory support and hospital stay, without any significant side effects.

In conclusion inhaled budesonide can be used as a option in management of TTN in late preterm and term neonates.

References:-

1. Lowe NK, Reiss R. Parturition and fetal adaptation. J ObstetGynecol Neonatal Nurs. 1996 May;25(4):339–49.
2. Liggins GC. Growth of the fetal lung. J Dev Physiol. 1984 Jun;6(3):237–48.
3. Strang LB. Fetal lung liquid: secretion and reabsorption. Physiol Rev. 1991 Oct;71(4):991–1016.
4. Heinonen S, Süvari L, Gissler M, Pitkänen O, Andersson S, Helve O. Transient tachypnea of the newborn is associated with an increased risk of hospitalization due to respiratory syncytial virus bronchiolitis. Pediatric Infectious Disease Journal. 2019 Apr1;38(4):419–21.
5. Raimondi F, Yousef N, Rodriguez Fanjul J, de Luca D, Corsini I, Shankar-Aguilera S, et al. A multicenter lung ultrasound study on transient tachypnea of the neonate. Neonatology. 2019;115(3):263–8.
6. Miller LK, Calenoff L, Boehm JJ, Riedy MJ. Respiratory distress in the newborn. JAMA. 1980 Mar 21;243(11):1176–9.
7. Tudehope DI, Smyth MH. Is "transient tachypnoea of the newborn" always a benign disease? Report of 6 babies requiring mechanical ventilation. AustPaediatr J. 1979 Sep;15(3):160–5.
8. Clark RH. The epidemiology of respiratory failure in neonates born at an estimated gestational age of 34 weeks or more. J Perinatol. 2005 Apr;25(4):251–7.
9. Elfarargy MS, Abu-Risha SE, Younis RL. Therapeutic effect of inhaled budesonide in transient tachypnea of newborn: A placebo-controlled study. Journal of Population Therapeutics & Clinical Pharmacology. 2020 Jun 5;27(2):e89–97.
10. Jain L, Eaton DC. Physiology of fetal lung fluid clearance and the effect of labor. Semin Perinatol. 2006 Feb;30(1):34–43.
11. Venkatesh VC, Katzberg HD. Glucocorticoid regulation of epithelial sodium channel genes in human fetal lung. Am J Physiol. 1997 Jul;273(1 Pt 1):L227-33.
12. Delara M, Chauhan BF, Le ML, Abou-Setta AM, Zarychanski R, W'tJong GW. Efficacy and safety of pulmonary application of corticosteroids in preterm infants with respiratory distress syndrome: a systematic review and meta-analysis. Arch Dis Child Fetal Neonatal Ed. 2019 Mar;104(2):F137–44.
13. Bruschettini M, Moresco L, Calevo MG, Romantsik O. Postnatal corticosteroids for transient tachypnea of the newborn. Cochrane Database of Systematic Reviews. 2018 Dec 8;
14. Bassler D, Shinwell ES, Hallman M, Jarreau PH, Plavka R, Carnielli V, et al. Long-term effects of inhaled budesonide for bronchopulmonary dysplasia. New England Journal of Medicine. 2018 Jan 11;378(2):148–57.
15. Bassler D. Inhaled budesonide for the prevention of bronchopulmonary dysplasia. J Matern Fetal Neonatal Med. 2017 Oct;30(19):2372–4.