Pravara Med Rev; March 2024, 16 (01), 37 - 45
DOI: 10.36848/PMR/2024/10000.51115

Original article

Evaluation of neonatal trigger score (NTS) as an early warning system (EWS) in postnatal ward- a prospective observational study

Dr Naveen Kumar B[1], Dr Sudha Reddy V R[2*]

Department of Pediatrics, Sri Devaraj Urs Medical College, Tamaka, Kolar 563103, Karnataka, India.
Correspondence: Dr Sudha Reddy V R, Professor and Head, Department of Pediatrics, Sri Devaraj Urs Medical College,Tamaka, Kolar, Karnataka 563101, India.

ABSTRACT

Objectives: To determine the utility of NTS as a clinical tool for identification of new-borns in the Postnatal ward requiring medical intervention in the ward and admission to Neonatal Intensive Care Unit (NICU) and to study the outcome of neonates triggered by NTS.

Study Design: Prospective observational study

Participants: All neonates delivered and admitted in postnatal wards of rural tertiary care Hospital, Kolar during January 2018 to December 2018.

Intervention: NTS observation and scoring chart was applied on neonates. Scores were obtained every 2 hours after birth till 12 hours and then every 4hours until 48 hours old.

Results: NTS was applied on a total of 1495 neonates who fulfilled the inclusion criteria. 152 neonates triggered the NTS chart of which 21 neonates did not require any medical intervention while 131 required intervention (53 in Postnatal ward& 78 in NICU). The area under the ROC curve for the NTS was 0.997 with NTS score of 2 or more predicting admission to NICU (78.57% sensitivity, 99.80% specificity). A score of 0 was strongly predictive of being well enough to remain in the postnatal ward without intervention (P<0.001) and a score of 1 or more predicted need for intravenous antibiotics (76.92% sensitivity, 100% specificity).

Conclusions: Results from this study shows that NTS observation chart acts well as an adjunct to clinical assessment in the postnatal ward, with its simplicity allowing for the successful and safe use by non-specialists.

Keywords: Neonatal Trigger Score (NTS), Early Warning System (EWS), Neonatal Intensive Care Unit (NICU), Postnatal Ward.

INTRODUCTION

The early postnatal period is a critical phase in the lives of new-born babies. Major changes occur during the neonatal period because of adjustments to extra-uterine life, physiological immaturity, or exposure to intrapartum risks such as infections. Following birth, majority of apparently "healthy" neonates are cared for in the postnatal or maternity wards. In majority of hospitals, post-natal wards are not designed to take care of unwell neonates. Beforeacute deterioration and subsequent transfer to the neonatal intensive care unit (NICU), neonates often show signs of illness which are often subtle that are not recognized. Moreover, they can deteriorate quite rapidly thereby increasing morbidity and mortality. Sudden, unexpected neonatal deaths in the postnatal ward are also an increasingly recognized problem.Early identification and management of these potentially "at risk" neonates are of paramount importance. Based on physiological observations such as heart rate, respiratory rate etc., early warning score (EWS) systems have been validated in adult and paediatric populations to detect deterioration with prompt interventions to reduce morbidity and mortality [1,2].

Paediatric early warning score (PEWS) systems are designed for use in "unwell" children at risk for deterioration, which allow for early intervention either in the paediatric ward or emergency room thereby minimizing intensive care unit (ICU) admissions. PEWS is unsuitable for use in neonates in postnatal wards because they are seemingly "healthy" but "at risk" for clinical deterioration hence the need for a standardized clinical scoring system for neonates.In recent years there has been a growing interest in the development of early scoring systems for neonates, but the available literature is sparse [3-6].There is an urgent need to establish a neonatal early warning

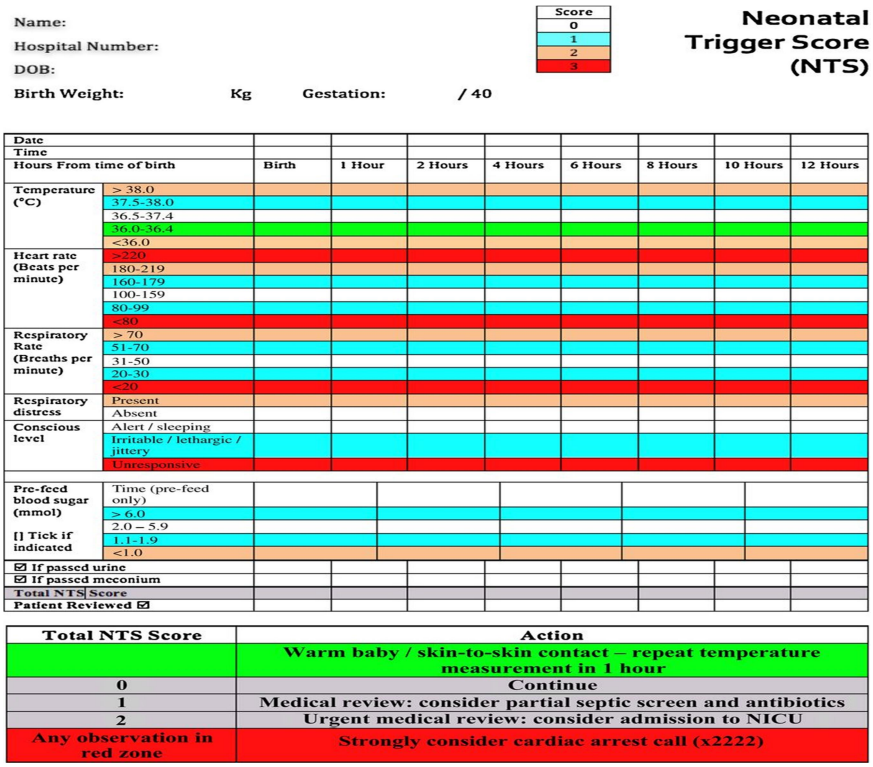
PMR P ISSN: 0975-0533, E ISSN: 0976-0164

(NEW) system, which can be used by both doctors and nurses to observe neonates in postnatal wards for early detection and prompt intervention of illness. The Whitt Neonatal Trigger Score (W-NTS) is one such observation chart designed for neonates at risk of deterioration in postnatal and labour wards which can be performed and interpreted by nurses and non-specialist doctors [7].By including NTS charts in neonatal case sheets and documenting the observations by nurses or doctors, this study is aimed at the early identification and management of neonates thereby reducing the potential negative impact of any medical problems.

MATERIALS AND METHODS

This prospective observational study was conducted at a rural tertiary care hospital in Kolar, Karnataka from January 2018 to December 2018. Study was started after obtaining ethical clearance from our institutional ethical committee. All neonates delivered and admitted in postnatal wards during the study period were included in the study. Neonates weighing <2.2kg at birth and with a gestational age of <35weeks (Institutional Protocol – direct admission to NICU) and neonates admitted directly to NICU from labour ward were excluded from the study.

All the postgraduates and interns of the Department of Paediatrics and nurses posted in Labour and Post-natal wards were sensitized regarding the use of NTS observation chart. Sensitization was done at repeated intervals for interns and nurses who were posted in labour and postnatal wards according to their rotation postings.After obtaining written informed consent from the parents of the neonates, detailed history was taken and NTS observation and scoring chart (designed and developed by Holme et al.) [4](Figure 1) was applied. Scores were obtained at 1, 2, 4, 6, 8, 10 and 12 hours after birth and then every 4th hourly until 48 hours old. Those neonates requiring medical intervention were followed up till discharge to observe for the following outcomes: medical intervention, length of NICU/hospital stay, mortality.



Name:
Hospital Number:
DOB:
Birth Weight: Kg Gestation: / 40

Score
0
1
2
3

Neonatal Trigger Score (NTS)

		Birth	1 Hour	2 Hours	4 Hours	6 Hours	8 Hours	10 Hours	12 Hours
Date									
Time									
Hours From time of birth									
Temperature (°C)	> 38.0								
	37.5-38.0								
	36.5-37.4								
	36.0-36.4								
	<36.0								
Heart rate (Beats per minute)	>220								
	180-219								
	160-179								
	100-159								
	80-99								
	<80								
Respiratory Rate (Breaths per minute)	> 70								
	51-70								
	31-50								
	20-30								
	<20								
Respiratory distress	Present								
	Absent								
Conscious level	Alert / sleeping								
	Irritable / lethargic / jittery								
	Unresponsive								
Pre-feed blood sugar (mmol) [] Tick if indicated	Time (pre-feed only)								
	> 6.0								
	2.0 – 5.9								
	1.1-1.9								
	<1.0								
☑ If passed urine									
☑ If passed meconium									
Total NTS Score									
Patient Reviewed ☑									

Total NTS Score	Action
	Warm baby / skin-to-skin contact – repeat temperature measurement in 1 hour
0	Continue
1	Medical review: consider partial septic screen and antibiotics
2	Urgent medical review: consider admission to NICU
Any observation in red zone	Strongly consider cardiac arrest call (x2222)

Figure 1: Neonatal Trigger Score (NTS) observation chart designed and developed by Holme et al.

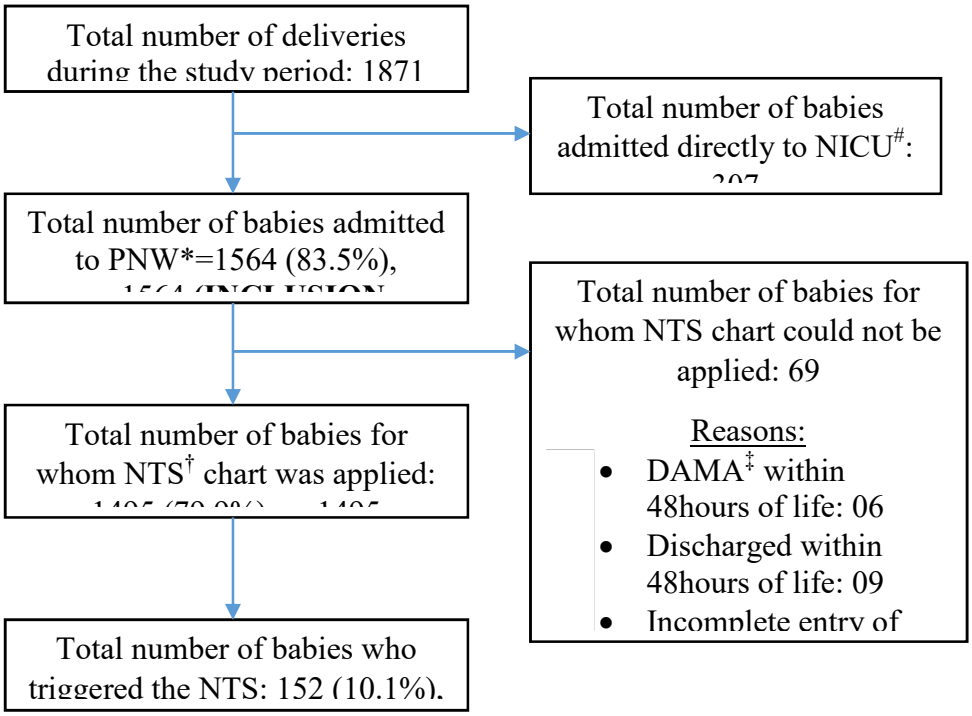
PMR P ISSN: 0975-0533, E ISSN: 0976-0164

STATISTICAL METHODS

Data collected were entered in a Microsoft Excelspreadsheet and analysed using SPSS version 22.0 and R environment version 3.2.2. In the present study, descriptive and inferential statistical analysis was carried out. Results on categorical measurements werepresented as numbers (%) and results on continuous measurements were presented as Mean± SD (Min-Max). A 5% level of significance was set for analysis.To find the significance of study parameters on a continuous scale between two groups (Intergroup analysis),Student t-test (two-tailed, independent) was used on metric parameters. Homogeneity of variance was assessed by the performance of Leven`s test for homogeneity of variance. Evaluation of score sensitivity and specificityweredone using receiver operating characteristics (ROC) curves. Chi-square/ Fisher exact test was used to find the significance of study parameters on a categorical scale between two or more groups and a non-parametric setting for qualitative data analysis. Fisher exact test was used when cell samples were very small.

RESULTS

NTS chart was applied on a total of 1495 neonates of which majority were male babies (53.9%).3.8% neonates had tachypnea, 3% had respiratory distress, 4.3% had abnormal levels of consciousness, 1.4% had hyperthermia, 0.4% had hypothermia and 3.7% had tachycardia. 152 (10.2%) neonates triggered the NTS chart of which 21(13.81%) neonates did not require any medical intervention while 131 (86.18%) required intervention (53 in PNW and 78 in NICU)(Figure 2).



Abbreviations: *PNW- Post natal ward; #NICU- Neonatal Intensive Care Unit; †NTS- Neonatal Trigger Score; ‡DAMA- Discharge against Medical Advice

Figure 2: Flow Diagram of recruitment and selection of study participants.

PMR P ISSN: 0975-0533, E ISSN: 0976-0164

Majority (48.8%) of neonates requiring medical intervention triggered NTS at 1-8hours of life. 64.12% of neonates who triggered NTS had a score of 2, while all the neonates who triggered NTS but did not require medical intervention scored 1(Table 1 and Table 2).Neonates requiring medical intervention in PNW had asymptomatic hypoglycemia (n=42, 79.2%), probable sepsis (n=9, 16.9%) and fever following immunization (n=2, 3.77%). No mortality was noted in these babies (Table 2). Common conditions among neonates who triggered NTS and required medical intervention in NICU were Transient Tachypnea of New-born(TTNB) (n=30), probable sepsis (n=15), Meconium aspiration syndrome (MAS) (n=12) and hyponatremic dehydration (n=8). One neonate required lumbar puncture and CSF analysis to rule out neuro-infection and 2 neonates required mechanical ventilation. Both neonates on mechanical ventilation died (one due to aspiration pneumonia and the other due to TGA) (Table 3).

Table 1: Time of Triggering NTS among study participants requiring medical intervention (n=131).

Time (Hours of life)	**Requiring intervention in PNW (n=53)**		**Requiring intervention in NICU (n=78)**		**Total (n=131)**	
Time	**Frequency**	**Percentage**	**Frequency**	**Percentage**	**Frequency**	**Percentage**
1-8	23	43.39	41	52.56	64	48.8
9-12	12	22.64	10	12.82	22	16.79
13-24	10	18.86	09	11.53	19	14.50
25-48	08	15.09	18	23.07	26	19.84

Table 2: Characteristics of study participants who triggered NTS requiring intervention in PNW (n=53)

Intervention required	**Place of intervention**	**Diagnosis**	**Nature of intervention**	**Outcome**
Yes	PNW	Asymptomatic Hypoglycaemia (n=42)	Spoon feeding with EBM* / Formula in addition to direct breastfeeding, Nutritional Education, and GRBS# monitoring.	Discharged
		Probable Sepsis (n=09)	Intravenous antibiotics, Septic workup.	Discharged
		Fever following immunization (n=02)	Antipyretics, Reassurance.	Discharged
Abbreviations: *EBM: Expressed breast milk, # GRBS: Glucometer random blood sugar				

Table 3: Characteristics of Neonates who triggered NTS requiring intervention in NICU (n=78)

Intervention required	**Place of intervention**	**Diagnosis**	**Nature of intervention**	**Outcome**
Yes	NICU	TTNB* (n=30)	Oxygen support, Intravenous fluids	Discharged
		MAS# (n=12)	Oxygen support, Intravenous fluids& Intravenous antibiotics	Discharged
		Hypernatremia Dehydration (n=08)	Dehydration correction by Intravenous fluids, blood investigations	Discharged
		Hypoglycaemia (n=4) Asymptomatic: 1 Symptomatic: 3	Intravenous glucose infusion, blood investigations	Discharged
		Probable sepsis (n=15)	Intravenous antibiotics, septic work up	Discharged
		Aspiration Pneumonia (n=2)	Oxygen support, Intravenous fluids, Intravenous antibiotics, blood	Discharged= 1 Death=1

PMR P ISSN: 0975-0533, E ISSN: 0976-0164

			investigations. Mechanical ventilation: 01	
		Asymptomatic Polycythaemia (n=1)	Intravenous fluids, blood investigations	Discharged
		Neonatal seizures (n=1)	Intravenous fluids, Oxygen support, Intravenous antiepileptics.	Discharged
		Congenital Heart disease (n=3) ACHD[†]: 2, CHD[‡]: 1	Intravenous fluids, Oxygen support, blood investigations, Chest radiograph, 2D ECHO Mechanical ventilation: 01	Discharged=1 Death= 1
		Fever following immunization (n=1)	Intravenous fluids, blood investigations	Discharged
		Significant weight loss with hyperbilirubinemia. (n=1)	Intravenous fluids, phototherapy and blood investigations	Discharged

Abbreviations: [*]TTNB- Transient tachypnoea of new-born; [#]MAS- Meconium aspiration syndrome; [†]ACHD- A cyanotic congenital heart disease; [‡]CHD- Cyanotic congenital heart disease

NTS score of 2 had high sensitivity (78.57%) for admission to NICU while specificity (99.80%) was high in NTS score of ≥3. For requirement of septic workup and starting IV antibiotics, NTS score of 2 had high sensitivity (76.92%) and specificity (100%). NTS score of ≥3 had high specificity (100%) but a low sensitivity (20%) (Table 4).

Table 4: Sensitivity & Specificity of NTS score requiring admission to NICU and septic screen.

	Neonates Admitted to NICU		**Neonates requiring septic screen and antibiotics**	
NTS Score	**Sensitivity**	**Specificity**	**Sensitivity**	**Specificity**
1	60%	97.88%	45.40%	98.57%
2	78.57%	97.22%	76.92%	100
≥3	57.14%	99.80%	20%	100

It was also noted that all single variables except heart rate were significantly different between NTS triggered and non triggeredneonates (P<0.001) (Table 5 and Table 6).The Receiver operating characteristics curve (ROC)was following the left-hand border and the top border of ROC space indicating NTS score was more accurate in identifying neonates who are deteriorating and requiring medical intervention in PNW/NICU. The Area under the ROC curve was 0.997 with 95% confidence interval of 0.992-0.999 and standard error of 0.00327 (Figure 2). The value was statistically significant (P<0.0001) indicating the NTS chart as excellent test for identifying sick neonates in PNW (Figure 3).

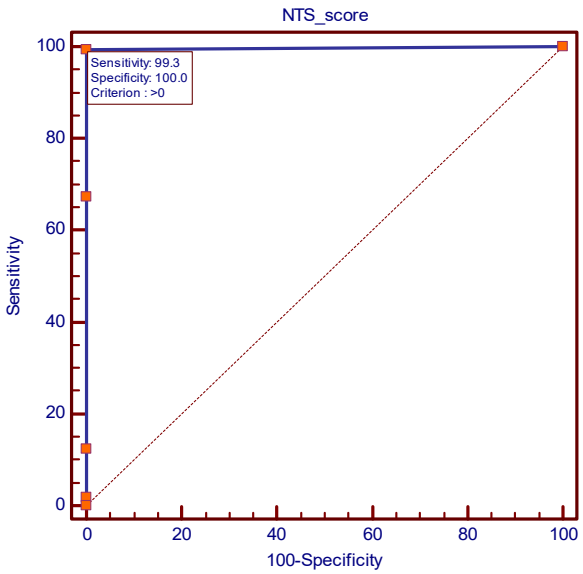
Table 5: Correlation of temperature, heart rate and respiratory rate in relation to NTS triggered and non-triggered neonates.

Variables	**NTS Triggered**		**Total (n=1495)**	**P value**
	No (n=1343)	**Yes (n=152)**		
Temperature				
<36	0(0%)	2 (1.3%)	2 (0.1%)	**<0.001****
36-36.4	23(1.7%)	4 (2.6%)	27 (1.8%)	
36.5-37.4	1320(98.2%)	109 (71.7%)	1429 (95.5%)	
37.5-38.0	0(0%)	37 (24.34%)	37 (2.4%)	
>38	0(0%)	0(0%)	0(0%)	
Heart Rate (bpm)				

<80	0(0%)	0(0%)	0(0%)	0.503
80-99	0(0%)	0(0%)	0(0%)	
100-159	1343(100%)	143(94%)	1486 (99.3%)	
160-179	0(0%)	9(5.9%)	9(5.9%)	
180-219	0(0%)	0(0%)	0(0%)	
>220	0(0%)	0(0%)	0(0%)	
Respiratory Rate				
<20	0(0%)	0(0%)	0(0%)	**<0.001****
20-30	0(0%)	0(0%)	0(0%)	
31-50	1343 (100%)	95(62.5%)	1438(96.1%)	
51-70	0(0%)	39(25.6%)	39(2.6%)	
>70	0(0%)	18(11.8%)	18(1.2%)	
Chi-Square/Fisher Exact Test was applied. (** Strongly significant P≤0.01)				

Table 6: Association of categorical variables- respiratory distress and level of consciousness in relation to NTS triggered and non-triggered neonates.

Variables	**NTS Triggered**		**Total (n=1495)**	**P value**
	No (n=1343)	**Yes (n=152)**		
Respiratory distress				
• Absent	1343(100%)	106(70.6%)	1449(97%)	**<0.001****
• Present	0(0%)	46(29.4%)	46(3%)	
Level of consciousness				
• Alert/sleeping	1343(100%)	87(58.2%)	1430(95.7%)	**<0.001****
• Irritable/lethargy	0(0%)	65(41.8%)	65(4.3%)	
Chi-Square/Fisher Exact Test was applied. (**Strongly significant P ≤ 0.01)				



Area under the ROC curve (AUC)	0.997
Standard Error	0.00327
95% Confidence interval	0.992 to 0.999
z statistic	152.000
Significance level P (Area=0.5)	<0.0001

Figure 3: Receiver operating characteristic (ROC) curves for the NTS.

DISCUSSION

The patient, family members and caregivers have the right to expect and receive the best possible medical care. An important component of this expectation is early recognition of any clinical deterioration occurring in hospitalized patients. In the adult and paediatric population, numerous early warning scoring systems are in widespread use [1,2]. There has been a growing interest in the development of a similar structured scoring system for new-born babies in recent years. The W-NTS is one such scoring system that has been successfully used in the United Kingdom as an adjunct to clinical assessment by non-specialists, in the early identification of neonates requiring extra care. As explained earlier, a literature review regarding the use of such a scoring system in the neonatal population is sparse [3-6],hence this prospective observational study was carried out.

In our study, it was observed that an NTS score of 1 was a cut-off score at which a neonatal doctor should be informed for a medical review (Sensitivity 70%, Specificity 98.56%). The observations were found similar when compared to the recommendations postulated from a retrospective study conducted by Holme et al. (Sensitivity 92.7%, Specificity 71.6%) [4] and a prospective study conducted by Robinson et al.(Sensitivity 100%, Specificity 86.1%)[7].

The cut-offs for sensitivity and specificity of the NTS for NICU admissions are shown.The area under the ROC curve was 0.997. There was a strong association with an increased need for intensive care admission ($p < 0.001$) with a score of 2(Sensitivity 78.57%, Specificity 97.22%), whereas there was a prophecy of being well enough to remain in PNW ($p<0.001$) with a score of 0. These observations are similar when compared to the recommendations postulated by a retrospective study conducted by Holme et al. (Sensitivity 79.3%, Specificity 93.5%) [4] and a prospective study conducted by Robinsonet al. (Sensitivity 82.5%, Specificity 95%) [7].

The sensitivity and specificity cut-offs of the NTS for septic screen and starting antibiotics are shown and was observed that neonates scoring 2 were more likely to need an intervention in the form of IV antibiotics and septic screen (Sensitivity 76.92%, Specificity 100%). Robinson et al. [7] in their prospective study postulated that a score of ≥1 was more likely for considering septic screen and IV antibiotics (Sensitivity 100%, Specificity 86.1%). When compared to Robinson et al. [7] the cut-off scores in the present study were not similar as sensitivity for score 1 was 45.40%& specificity was 98.57%. The poor sensitivity is explained by the misinterpretation of level of consciousness (irritability- NTS score 1) and respiratory rate >50 cycles per minute (NTS score-1) as tachypnoea in new-born by NTS in good neonates.

A score of 2 was observed to be strongly associated with an increased need for NICU admission in our study. However, in the present study, 23.07% of neonates requiring NICU admission scored <2 (n=18). This is because 4 neonates had hypoglycaemia which did not improve with supplementary feeds, and 8 neonates were misinterpreted as having tachypnea (respiratory rate of >50 to <60 cycles per minute is interpreted by NTS as score 1, which is a normal respiratory rate for a new-born). Two neonates each had persistent vomiting and excessive cry, one neonate had convulsions, and one neonate had icterus till soles which were not incorporated in the scoring system.It was also found that 21 “well” neonates triggered the NTS chart but did not require any medical intervention. This is because there was a misinterpretation of the level of consciousness (irritability- NTS score 1) and respiratory rate >50 cycles per minute (NTS score-1) as tachypnea in “well” neonates.

The NTS was produced as an established track and trigger scoring system in a neonatal population where early warning systems were unexplored topics [7]. The postulated score cut-offs from retrospective research by Holme et al. [4] and Robinson et al. [7]was supported by the present prospective evaluation that medical review was more likely required in neonates scoring ≥1 and NICU admission was required in neonates with a score of ≥2. Sensitivity isimportant over specificity, while using a score to determine which babies potentially need septic screens/antibiotics, and thereby showing that an optimum score of 2 is required for intervention. To avoid unnecessary admissions and neonate-mother separations, a higher specificity is desirable when choosing a “consider admission” trigger score.

Not all neonates requiring NICU admission reached the presumptive NTS score cut-

off of 2(n=18, 23.07%) as discussed above. To reduce such unnecessary admissions and to increase the sensitivity of the NTS score, the following modifications to the NTS chart were suggested:

We suggest that neonates who are on blood sugar monitoring in PNW should be viewed as high risk with an NTS score of 1 due to poor sensitivity in cases of hypoglycaemia (n=4). To trigger a review/intervention it is suggestedto include neonates with the following risk factors (infants of diabetic mothers, neonates with >2.2kg – 2.5kg, neonates with >36weeks gestation to 36+5 days of gestation, neonates born to mothers with PROM >18hours etc.,) as an immediate score 1 which will effectively reduce the score threshold.

Regarding those neonates who scored havingtachypnea as per the NTS chart but hadthe normal respiratory rate in actual (n=8) and required unnecessary NICU admission, the cut-off range to trigger the NTS score 1 in the Respiratory rate parameter (colour code- Blue) needs to be changed from (Respiratory rate 50-70 cycles/min) to (Respiratory rate 60-70 cycles/min).

A significant pathology is indicated by some non-specific clinical signs and symptoms (Bilious vomiting, excessive crying, icterus till palms & soles, refusal of feeds, decreased urine output etc.,) but does not fit into an observation style chart like the NTS chart. It is suggested to include them to increase the sensitivity and specificity of the chart, inserting a “tick if present” box with an immediate score of 2 requiring prompt medical review.

If NTS is to be used as an aid in decision-making, it is important to know the indications for admission to NICU in different institutions (which could depend on the nursing skill, presence of high dependency unit etc.). This highlights the importance of multi-centre NTS score validation.

Without dictating specific-score dependent interventions and the scorers (non-specialists, nursing staff, junior residents etc., were not directly involved in any clinical-decision making and a specialist doctor (Paediatrician/Neonatologist) deciding on the necessary treatment, the NTS chart was solely used as an observational chart. This shows that there was no dependence on the score to guide subsequent primary treatment measures for non-specialists during an emergency (if the specialist doctor is not available).

CONCLUSION

NTS is used as a valuable tool for the assessment of neonates in PNW in this prospective observational study. It supports the recommendations postulated by previous retrospective and prospective researches done in UK that: The neonatal doctor should be requested to review and strongly consider performing a septic screen and starting IV antibiotics if the neonates score 1. The neonatesshould be reviewed immediately as there is a high chance that they might need NICU care if they score 2 or more. A very urgent medical attention is needed and a cardiac emergency call should be considered if the neonates score 3 (red column on the chart).To identify babies that may require an escalation in their care, and by enabling earlier detection of the sick neonate, NTS can be successfully used as an adjunct to clinical assessment by non-specialists.It has proven to be of clinical value.By offering clear guidance on when to seek senior assistance it provides a comprehensive assessment checklist and empowers novice trainees, health care assistants and midwives. When the babies are being regularly monitoredsystematically the parental anxiety is reduced. Further research on the early warning systems in the neonatal population is required in India as this is a new concept which needs to be explored.

Acknowledgement:

The authors gratefully acknowledge Indian Council for Medical Research for funding this study. They also acknowledge patient families, faculty, staff, residents and biostatistician for their support in conduct of this study.

Funding: Indian Council for Medical Research; ICMR, No. 3/2/June-2017/PG-Thesis-HRD(41)

REFERENCES

1. Stubbe CP, Kruger M, Rutherford P, et al. Validation of a modified early warning Score in medical admissions. Q J Med 2001;94(10):521-526. https://doi.org/10.1093/qjmed/94.10.521
2. Duncan H, Hutchison J, Parshuram C. The pediatric early warning system score: A severity of illness score to predict urgent medical need in hospitalised children. J Crit Care 2006;21(3):271-278. https://doi.org/10.1016/j.jcrc.2006.06.007
3. Roland D, Madar J, Connolly G. The Newborn Early Warning (NEW) system: development of an at-risk infant intervention system. Infant 2010;6(4):116-20.
4. Holme H, Bhatt R, Koumettou M, et al. Retrospective evaluation of a new neonatal trigger score. Pediatrics 2013;131(3):837-42. https://doi.org/10.1542/peds.2012-0640
5. British Association of Perinatal Medicine. Newborn Early Warning Trigger and Track (NEWTT). A framework for practice 2015 [online]. 2015. https://www.bapm.org/resources/38-newborn-early-warning-trigger-track-newtt-a-framework-for-practice-2015
6. Ahmed M, Phillips I, Karupaih A, et al. Newborn Observation Track and Trigger (NOTT) Chart. J CollPhysiciansSurg Pak 2016;26(3):234-7.
7. Robinson A, Winckworth LC, Eleftheriou G, et al. Prospective evaluation of the Whitt Neonatal Trigger Score in an 'at-risk' neonatal population. J Paediatr Child Health 2017;53(10):950-6. https://doi.org/10.1111/jpc.13618