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EFFECT OF NEUROMUSCULAR BLOCKING AGENTS AND PEEP ON VENTILATOR INDUCED DIAPHRAGMATIC DYSFUNCTION IN MECHANICALLY VENTILATED CHILDREN : A PROSPECTIVE OBSERVATIONAL STUDY

Paediatrics

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ABSTRACT

Objective: To assess the effect of maximal PEEP provided and exposure to neuromuscular blocking agent on diaphragmatic atrophy.To evaluate the predictors of baseline diaphragmatic thickness at end expiration such as age, height, weight and sex. **Study Design:** In this hospital based descriptive type of observational study, conducted at the Pediatric intensive care unit of Department of Pediatrics, National Institute of Medical Science & Research 46 children aged 1month to 18 years; who required invasive MV for more than 24 hours and did not meet exclusion criteria were enrolled. The patients underwent their first USG assessment of diaphragmatic thickness within twelve hours of intubation to obtain baseline measurements. Thereafter USG measurements were taken daily to look the effect of PEEP on diaphragmatic atrophy rate. **Results:** Total of forty six pediatric patients were evaluated, with a median age of 7.2 years and were ventilated for a median of 4 days. The baseline TDe was 1.71mm, TDi was 2.09mm and DTF was 22.47%. There was significantly increased atrophy in children who were exposed to NMB agents (3.7%) as compared to those not exposed (2.2%). Baseline TDe was found to be strongly correlated with Age (0.717), Height (0.774) and Weight (0.676) however no difference in baseline muscle mass was found between males and females. **Conclusions:** Use of diaphragmatic ultrasound to evaluate diaphragmatic function is both feasible and simple. There is a consistent increased rate of ventilator induced diaphragmatic dysfunction (VIDD) occurring in the mechanically ventilated pediatric population who were exposed to neuromuscular blocking agents.

KEYWORDS

Ventilator, Diaphragmatic Dysfunction, Children, PEEP, Neuromuscular Blocking Agent

OBJECTIVE

Mechanical ventilation is an essential and frequently used tool in today's paediatric intensive care units. It is estimated that approximately one third of patients admitted in PICU require mechanical ventilation (MV) for a median of 4–6 days.[1,2] However, mechanical ventilation can be a double edged sword as recent evidence, especially within adult critical care literature supports the existence of ventilator induced diaphragmatic dysfunction (VIDD). VIDD has been defined as MV induced loss diaphragmatic force-generating capacity specifically related to the use of mechanical ventilation. The weakness cannot be readily explained by other factors such as sepsis, drugs, metabolic derangements, and so forth.[3,4,5] VIDD is pathologically characterized by muscle fiber atrophy, myofibril necrosis, and disorganization.[6,7] Multiple studies have validated USG guided assessment of diaphragm thickness as a reliable assessment of diaphragmatic function.[8–10] USG is a non-invasive bedside alternative for assessment of diaphragmatic morphology and function.[11] Nueromuscular blocking agents are regularly used for mechanically ventilated children in pediatric intensive care unit. These agents can increase diaphragmatic atrophy by eliminating spontaneous respiration and potentiating disuse atrophy. Data generated by this study can help assess the effect of neuromuscular blocking agents and PEEP on VIDD in the pediatric population and may also be used to develop USG guided weaning predictors in children.

Methods

This study was conducted in the Pediatric Intensive Care Unit of Department of Pediatric Medicine, National Institute of Medical Science & Research, Jaipur from July 2022 to December 2023. A convenience sample of forty six subjects aged 1month to 18 years who required invasive MV for more than 24 hours and did not meet exclusion criteria were enrolled. Included subjects were endotracheally intubated and mechanically ventilated with clinician intent to continue MV for more than 24 hours.

Children mechanically ventilated for more than 24 hours before PICU admission or died within 24 hours of admission were excluded. Children with pre-existing diagnoses of diaphragm paresis or neuromuscular weakness and children with chronic respiratory failure were also excluded. This study was prospective type of observational study.

After duly informed consent, demographic information including age, sex, height, weight, endotracheal tube size and primary PICU admission diagnosis were recorded. The patients underwent their first assessment of diaphragmatic thickness at end expiration (TDe), diaphragmatic thickness at end inspiration (TDi) within twelve hours of intubation to obtain baseline measurements. For prediction of diaphragmatic atrophy and dysfunction, information regarding daily ventilation details including mode of ventilation, tidal volume, PEEP, FiO2 and respiratory rate were recorded during each reading. All children were ventilated as per unit's existing disease specific ventilation and sedation protocols. The initial mode of ventilation was pressure regulated volume control with pressure support, and sedative and ventilatory setting were titrated to encourage spontaneous breathing.Thereafter measurements of TDi and TDe were taken daily until the child was extubated, underwent tracheostomy or died. The measurements were continued until 14 days in cases of prolonged ventilation. In case of extubation one measurement was taken between 12 to 24 hours after extubation. Need for re-intubation within 48 hours of extubation was classified as extubation failure. Clinical outcomes like hospital mortality, need for tracheostomy and duration of mechanical ventilation were documented.

The diaphragm thickness was measured using a Philips Sonosite machine with 8 - 10 MHz linear ultrasound probe. Measurements were made of the right hemidiaphragm since the feasibility and repeatability of right hemidiaphragm measurements have been found superior in literature due to the liver being used as an echogenic window. Subjects were imaged in a semi-recumbent position with the head of bed at a 30-degree angle. The transducer was positioned perpendicular to the chest in the midaxillary line at the zone of apposition between the ninth and tenth intercostal space.In this area, the diaphragm is imaged as three-layer structure, including two parallel echoic lines (the diaphragmatic pleura and the peritoneal membrane) and a hypo-echoic structure between them (the muscle itself). On the frozen images, the distance from the middle of the pleural line to the middle of the peritoneal line was taken as the diaphragm thickness.

The diaphragm thickness measurement was taken three times on the same scan and the average value was calculated. At this position, B-mode US was utilized to measure resting TDe and TDi. TDi was measured during a spontaneous breath for subjects who were capable

of spontaneous triggering and during a controlled breath for those who were not spontaneously breathing. In this same position, motion mode ultrasonography as used to measure TDi and TDe in order to ascertain diaphragm thickening fraction. The mean value of three separate measurements was used for analysis. All measurements in the study were performed by a single paediatric intensivist.

TDe represents the diaphragm at rest and is not influenced by level of sedation, and respiratory efforts. Hence, TDe was used as representative of diaphragmatic muscle bulk, and was used for diaphragmatic atrophy estimation. Diaphragmatic atrophy (%) was defined as percentage change in TDe over first 14 days, or completed days of ventilation if extubated/ died from baseline TDe as follows: [(baseline TDe – last TDe) X 100 / baseline TDe]. Diaphragmatic atrophy rate (% per day) was defined as average daily diaphragmatic atrophy as follows: [(baseline TDe – last TDe) X 100/ (days of ventilation X baseline TDe)]. Diaphragm thickening fraction (DTF) was calculated as follows DTF = [(TDi – TDe) X 100 / TDe]. The DTF for each patient was the mean of the values measured in three breaths.

Continuous data was described as mean (SD) for parametric data or median (IQR) for non-parametric data and categorical data was represented as absolute numbers and percentages. For continuous data, the Saphiro-Wilk test was performed to assess the normality and where appropriate the data was analyzed with required statistical tests and descriptive statistics. Degree of association of predictors of baseline DT and diaphragmatic atrophy rate were analyzed by Mann Whitney-U test and Spearman correlation co-efficient for categorical and continuous variables, respectively. As the Data was determined to be non-parametric it was analyzed by Mann-Whitney U test and Spearman correlation co-efficient. Likewise, Spearman co-efficient correlation test was used to find the association of diaphragmatic thickness fraction with demographic variables. Microsoft Word 2016 and Microsoft Excel 2016 were used for data recording and analysis. Data was analyzed using statistical software SPSS version 25.0. For all statistical tests, the p-value was taken less than 0.05 to indicate the valid evidence for statistical significance of the data.

Clearance from Departmental Ethics Committee was taken prior to the start of the study. All participants had the option to withdraw from the study anytime during their hospital stay.

RESULTS

In this prospective observational study, a total of 50 pediatric patients who were intubated and mechanically ventilated were assessed, of these 46 patients were finally enrolled. Out of 46 children maximum of the study participants were in the age group of 11-17 years (34.8%). The mean age of the study participants was observed to be 7.2±5.5 years. Majority of the study participants were males (63%), while 37% of them were females. Male to Female ratio was 2:1 in this study. We looked for indications of intubation among the study participants, which showed the most common being respiratory (39.1%), followed by cardiac (30.4%) and neurological (26.1%).

A notable portion of study participants (28.3%) experienced death. In contrast, a substantial number (30.4%) were successfully extubated and transitioned to non-invasive ventilation (NIV), demonstrating a positive response to treatment. Additionally, 34.8% were extubated to oxygen or room air (RA), suggesting that a significant proportion of participants could be weaned off from mechanical ventilation. Only one participant (2.2%) required. Finally, 4.3% of participants underwent tracheostomy, which is indicative of chronicity of illness in severe cases.

The mean baseline TDi value was 2.09 mm with a standard deviation of 0.25 mm while mean baseline TDe value was 1.71 mm with a standard deviation of 0.22 mm. Out of forty six enrolled children; five children received neuromuscular blocker (NMB) as intermittent bolus doses rather than as continuous infusion. This is in line with our unit's standard ventilatory practice to allow for spontaneous breathing unless it is clinically judged to be counterproductive and is mainly used during the ventilatory initiation phase. We used Atracurium at a dose of 0.3mg/kg/ to 0.5mg/kg/dose. The data revealed that patients who received NMB had a higher median average daily atrophy percentage of 3.7% with an IQR of 2.4-3.9%. In contrast, patients who did not receive NMB had a lower median average daily atrophy of 2.2% with an IQR of 1.8-2.6% (Table 1). The p-value associated with the Mann Whitney U test was 0.042, indicating a statistically significant difference in the average daily atrophy percentage between patients who received NMB and those who did not. This suggested that NMB status may have an impact on diaphragmatic atrophy within the study population, with higher atrophy percentages observed in the NMB group.

In this study we tried to determine whether the level of maximum PEEP that the child was exposed to, would change the rate of diaphragmatic atrophy. In cases without any lung pathology, we set the PEEP at five however in cases of ARDS in line with current low tidal volume and open lung strategy we set the ideal PEEP by assessing the driving pressures and compliance of the lung. In our study, the Pearson correlation coefficient was -0.281, further indicating a negative correlation between the two variables. A value of -0.281 indicated a relatively weak negative correlation. The p-value was 0.058, suggesting that the correlation observed may be statistically significant at a significance level of 0.05. However, it's important to note that the p-value was close to the significance threshold, so the relationship may not be strongly significant (Figure 1).

We wanted to compare the baseline TDe reading against the Age, Weight, Height and Sex to see whether these factors have a bearing on the initial diaphragmatic thickness. Of the above-mentioned variables age, height and weight had a strong positive correlation with the diaphragmatic thickness which was statistically significant. This suggests that there is growth in the diaphragmatic muscle mass as there is increase in the age, height and weight. However, the difference in baseline TDe between the two sexes, were found not to be statistically significant.

Table 1 :Distribution of Study Patients Based on Average Daily Atrophy and NMB status (n=46)

Average daily atrophy %	NMB – Given		NMB- Not given		p value*
	Median	IQR	Median	IQR	
	3.7	2.4-3.9	2.2	1.8-2.6	0.042

* Independent Sample Mann Whitney U test was applied

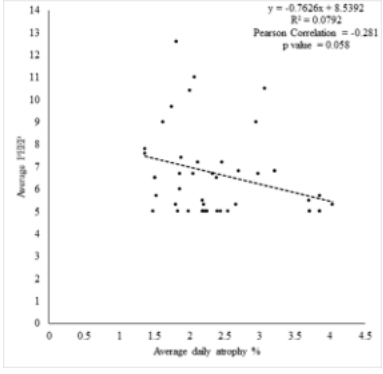

Figure 1 : Correlation Between Average Daily Atrophy% and Average PEEP (n=46)

Table 2 : Distribution of study patients based on gender and baseline TDe (n=46)

Baseline TDe	Male		Female		p value*
	Median	IQR	Median	IQR	
	1.72	1.56-1.82	1.71	1.56-1.77	0.665

*Independent Sample Mann Whitney U test was applied

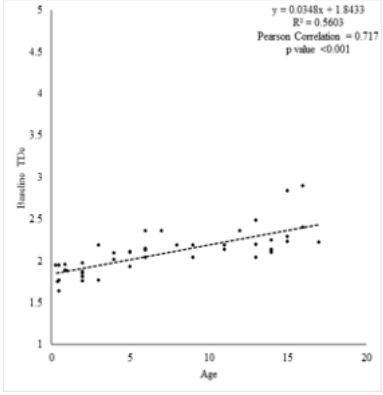

Figure 2 : Correlation Between Average Age and Baseline TDe (n=46)

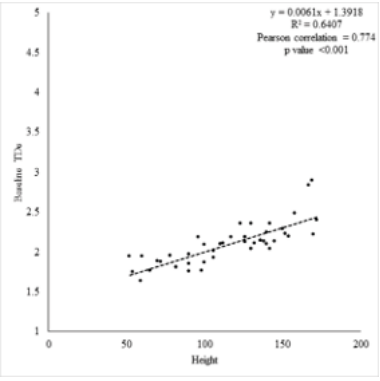

Figure 3 : Correlation Between Average Height and Baseline TDe (n=46)

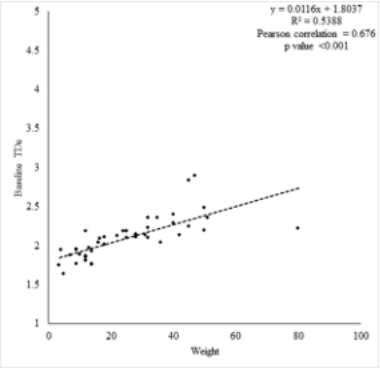

Figure 4 : Correlation Between Average Weight and Baseline TDe (n=46)

DISCUSSION

This prospective observational study was carried out in a tertiary PICU in northern India. With a sample size of forty six subjects, it was done primarily to assess the effect of mechanical ventilation on the diaphragm of pediatric patients. This study tried to evaluate if ventilator induced diaphragmatic dysfunction was affected was use of neuromuscular blocking agents and PEEP used during ventilation. Evaluation of VIDD was done primarily by assessing the diaphragmatic atrophy rate and thickening fraction.

The baseline values of diaphragmatic thickness found in our study (TDe 1.71mm) were higher than the values found by Mistri et al[12], similar to the values obtained by Lee et al[13] and lower than the baseline values found by Montoro et al[14] and Glau et al[3]. It is important to note that while conducting the same measurement the four studies have used slightly different techniques. The studies by Lee et al and Montoro et al, similar to our study, used the mid-point of the pleural and peritoneal layers to calculate baseline TDe and TDi. However, the study by Mistri et al used only the hypoechoic layer and excluded the pleura and peritoneal midpoint which may explain why the baseline TDe values were lower in this cohort. The higher values seen in the study by Glau et al are likely due to the fact that they have included the entire pleural and peritoneal layer in their measurement of values. However, the nutritional component as a cause of increased baseline values in western studies cannot be negated.

We examined the effect of NMB on diaphragmatic atrophy, and were able to demonstrate a statistically significant increased atrophy 3.70% vs 2.20% in the five patients who were exposed to NMB. This is consistent with finding of Glau et al[3] and Montoro et al[15] who found that NMB infusion was associated with a reduction in both TDi (22% vs. 6% p = 0.009) and an increase in the daily atrophy rate (2.2% vs 1.4%). Similarly, Glau et al[3] concluded "subjects exposed to NMB had a longer median length of MV than those not exposed to NMB (158 hr [IQR, 121–245) vs 117 hr [IQR, 80–182]; p = 0.019). There was a trend toward increased daily rates of atrophy among subjects exposed to NMB (– 5.2%, [IQR, –14.8 to –1.9]) when compared with unexposed patients (–3.0%, [IQR, –5.1 to 0]; p = 0.065)".[3] Furthermore, they were able to demonstrate even within the cohort of children that had a spontaneous breathing fraction of less than 0.5, that there was a larger degree of atrophy in children receiving NMB than those without exposure. This suggests that there may be a possible link of NMB with atrophy beyond the lack of spontaneous breathing. However, while increased atrophy was also found by Mistri et al[12] in the exposed vs non exposed it did not reach statistical significance. They concluded "given the small size of our study, it is difficult to conclude if these predictors really had no association or association could not be detected". Our study is significant because as compared to the other studies we did not use NMB infusions. The five patients exposed to NMB agents we only given intermittent bolus dosing to limit exposure to these agents. Despite this fact we found increased atrophy in the exposed group, suggesting that NMB drugs may have a much larger effect on VIDD than previously thought. It could be an avenue of future research to evaluate the NMB dose and atrophy relationship.

Adult studies have various reported the baseline diaphragmatic thickness to range from 1.9mm to 2.4mm[15]. We tried to evaluate if the baseline muscle mass increases with increasing age by extension increasing height and weight. This is vital because as diaphragmatic atrophy rate is a proportion of baseline TDe, difference in the initial muscle mass could affect the atrophy rates. Furthermore, the development of normative data in different age group could help standardize the atrophy data and help serve as an age-independent parameter. We found that there is strong correlation between baseline muscle mass and Age (0.717), Height (0.774) and Weight (0.676). We did not find any differences in the baseline TDe between the sexes. Mistri et al[12] who had also conducted a similar comparison found that "predictors with baseline TDe demonstrated moderate correlation with weight (r = 0.52, p <0.001), weak correlation with length (r = 0.46, p <0.001) and age (r = 0.45, p <0.001)". Similar to our study they also did not find any difference between males and females. Our finding as also correlate with a study conducted by Laviola et al[16] who were comparing the diaphragm of healthy children and children with Duchene Muscular dystrophy. They also found a progressive increase in the baseline diaphragmatic thickness in healthy children.

It is important to acknowledge the limitations of this study. Firstly, due to the small sample size the study was not powered to further analyze the various predictors of diaphragmatic atrophy, even though the sample size was comparable to other similar studies. Secondly, we did not analyze various other parameters that may have affected the diaphragmatic function such as steroid or inotropic use and severity scores that may have had a bearing on the final outcome. Finally, since the difference in measurement were only a few millimeters, despite using a standardized USG protocol we can not guarantee the reproducibility of our data values.

CONCLUSION

Ultrasonography is an excellent non invasive tool to evaluate baseline and dynamic diaphragmatic functions. Larger, well powered future studies are required to identify various predictors of diaphragmatic atrophy in ventilated children . There is a need to follow up the children for a longer period post extubation to determine the time duration in which diaphragmatic indices return to baseline values.

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