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# Utility of Neonatal Pain, Agitation and Sedation Scale and Amplitude Integrated Electroencephalogram to Differentiate the Different Levels of Sedation in Neonatal Intensive Care Units

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## ABSTRACT

**Background:** Neonates admitted in any Neonatal Intensive Care Unit (NICU) are constantly subjected to several stressful and painful conditions and require pain and sedation management. Ineffective sedation has severe consequences. Excessive sedation can prolong the duration of mechanical ventilation. On the other hand, inadequate sedation may lead to asynchronization with the ventilator and inability of adequate ventilation. The objective of the current study is to evaluate the use of Neonatal Pain, Agitation and Sedation Scale (N-PASS) parameters and double channel amplitude integrated electroencephalography (aEEG) to differentiate between light and deep sedation in neonatal patients.

**Patients and methods:** A total of 30 full term neonates mechanically ventilated with congenital pneumonia were recruited for the current study. Neonates of the study were divided into 2 groups according to the dose of sedative received into *Lightly sedated* group and *Deeply sedated*. All studied neonates were subjected to N-PASS and aEEG monitoring before starting sedation and after 2 hours of sedation. **Results:** Parameters of Burdjalov score (Continuity, Cycling, bandwidth span) and its total score showed a statistically significant decrease after sedation with median in the in non-sedated patients than deeply sedated patients (12 (11 - 12) vs. 8 (8 - 9), respectively ($p<0.001$).There was also a difference which was statistically significant between deeply sedated patients than lightly sedated patients [8 (7 - 8) vs. 9 (9 - 9), respectively ($p<0.00$)]. When applying ROC analysis, aEEG total (Burdjalov) score at a cut-off value of ≤8 was predictive of deep sedation with 100% sensitivity and specificity. **Conclusion:** aEEG can be used to differentiate between states of awake and sedation, and can also be used to differentiate the different sedation levels.

**Keywords:** Neonate, Sedation levels, Amplitude integrated electroencephalogram, NICU, aEEG, Pain, Burdjalov score, Ain Shams University.

## INTRODUCTION

Neonates in many Neonatal Intensive Care Units (NICU)s often experience many painful interventions and situations that require analgesics and sedative drugs such as mechanical ventilation, diagnostic, as well as therapeutic procedures and therefore are in need of pain and sedation management [1,2]. The utilization of analgesics and sedative drugs is often difficult and complicated by the inability of neonates to express their sensation of pain, and therefore is completely dependent on the subjective judgment of their care givers [3].

Inappropriate sedation has serious consequences. Excessive sedation can prolong the duration of mechanical ventilation as a result of prolonged recovery from sedation and this can lead to ventilator associated pneumonia and lung injury. On the other hand, inadequate sedation may lead to asynchronization with the ventilator and prolonged duration of ventilation. It can also lead to severe agitation and stress leading to cardiac ischemia [4] . Therefore, the proper titration of sedation is very useful. Trying to avoid over and under sedation, would ensure the neonates′ comfort and would decrease the response to stress related to trauma or inflammation. This is a challenge for the whole NICU teams worldwide. Therefore, sedation targets and levels should be regularly defined and maintained within optimal ranges. This can be established by using standard protocols that should be based on objective methods.

Sedation scores and sedation-measuring devices have been used to reduce the risks of over-sedation, especially excess drug given and drug withdrawal reactions [5]. The use of different itemized scales has improved the sedative and analgesic management in neonates and children [6]. However, scales based on clinical parameters are not often objective, and they often have a subjective element which may lead to bias that could affect a patient′s proper assessment. Among the variety of scales that have been published in the literature, the Neonatal Pain, Agitation and Sedation Scale (N-PASS), has been proven to be an effective scale, and is proposed to be able to differentiate different sedation levels. It includes five items (crying, behavior state, irritability, facial expression, vital signs and extremities tone) [7].

Amplitude integrated electroencephalography (aEEG) is used for continuous long-term brain monitoring that has been proven effective and useful in neonates of all gestational ages and is gaining a more wider role in NICUs recently. This is due to the handiness of application of the electrodes and even a simpler way of interpretation which facilitates its application by the neonatal staff, and the interpreter reliability is mostly



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excellent. The aEEG on its own, being interpreted by the Burdjalov score[8], revealed the ability to differentiate wakefulness vs. light sedation and also vs. deep sedation, but was not able to distinguish the states of light sedation vs. deep sedation. However, a reduction in all of the parameters was seen with more levels of analgesia and sedation [9].

While none of the two methods mentioned were able to distinguish precisely between light and deep sedation, the current study aimed to evaluate the use of N-PASS parameters and double channel aEEG to differentiate between light and deep sedation in neonatal patients. This will facilitate proper titration of the sedative drugs used.

## PATIENTS AND METHODS

This cross-sectional study was done on 30 full term neonates with congenital pneumonia admitted to the NICU of Pediatrics Hospital, Ain Shams University during the period of March 2021 to August 2022. They were all mechanically ventilated and receiving sedation and analgesia (Midazolam and Fentanyl). Patients with History suggestive of hypoxic ischemic encephalopathy, abnormal neurological signs or symptoms, any cerebral malformations, intraventricular hemorrhage, or cystic periventricular leukomalacia and patients receiving muscle relaxants were excluded.

Neonates of the study (n=30) were identified into 2 groups according to the dose of sedative and analgesic received, and which was determined by the expert's opinion according to each patient's needs and his clinical condition. The Lightly sedated group (n=11) received a dose of 0.03 mg/kg/hour of Midazolam infusion and a dose of 0.5 µg/kg Fentanyl shot. The Deeply sedated group (n=19): received a dose of 0.06 mg/kg/hour of Midazolam infusion and 1 µg /kg Fentanyl shot. [10]

All studied neonates were subjected to N-PASS and aEEG monitoring before starting sedation and after 2 hours of sedation.

**N-PASS** consists of five parameters (crying, behavior state, irritability, facial expression, vital signs and extremities tone) graded from 0 to 2 for pain or agitation and 0 to -2 for sedation. The total score is obtained by adding up the score for each item. An elevated score (+10) indicates a more painful behavior, and a decreased score (−10) indicates a sedated level [11].

Brain activity monitoring using **aEEG** was measured continuously using double channeled EEG. The aEEG derived from the EEG signal is rectified, smoothed, filtered (2-15 Hz) and compressed in time to (6 cm/h). Its amplitude, minimal and maximal amplitude, background activity and sleep wake cycling, were assessed using Burdjalov score[8]. Five electrodes were put C3, C4, P3, P4, and FpZ. Epochs with artifacts were not analyzed Visual analysis of the aEEG was done, blinded to the patient, clinical assessment and level of sedation of the participants

## ETHICAL CONSIDERATIONS:

**Approvals from the Pediatric Department and Ethics Committee, Faculty of Medicine, Ain Shams University were obtained. The patients' legal guardians were subjected to an informed consent before enrollment in the study. This work was performed in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.**

### Data Management and Analysis:

Revision, coding and tabulation of the collected data were done and analyzed using the Statistical Package for Social Sciences **(SPSS version 25).** Data was presented and analyzed according to its type. Descriptive statistics included mean, standard deviation (SD) and range for numeric parametric data, while median and interquartile range (IQR) for numeric non-parametric data. Frequency and percentage were used to summarize non-numerical data. Analytical statistics included: Student's t test to assess the difference between the means of two study group. Chi-Square test is used to test the association between two qualitative variables. Fisher's exact test to test the relationship between two qualitative variables when the expected number is less than 5 in more than 20% of cells. The ROC Curve (Receiver Operating Characteristic) to assess the sensitivity and specificity for quantitative diagnostic measures that categorizes cases into one of two groups. P- Value for significance level; $P>0.05$ is Nonsignificant (NS). $P \leq 0.05$ is significant (S).

## RESULTS

A total of 30 full term neonates with congenital pneumonia were included in our study, demographic data of the studied neonates are presented in ***table 1***. The mean gestational age in our patients was 38.34 (SD 0.87) ranging from 37.14-40 weeks' gestation. They were 16 (53.3%) females and 14 (46.7%) males, with a mean birth weight of 3.06 (SD 0.5) kg (Range 2.1-4.3 kg).

All our studied patients presented with respiratory distress or failure that necessitated them to be mechanically ventilated. Regarding medications used in the treatment of the studied neonates, all of them were receiving antibiotics. Only 8 (26.6%) of the neonates were on cardiovascular inotropic support, while the reminder of neonates 22 (73.3 %) were off inotropic support. A total of 9 (30%) of the neonates of the study were complicated with sepsis and 7 (23.3%) developed pneumothorax. Regarding outcome, 12 (40%) of them had a fatal outcome.

**Table 1: Demographic data and medications used in the treatment of studied patients (n=30)**

| Variable | | Mean ±SD | N(%) | Median (IQR) | Range |
|---|---|---|---|---|---|
| GA(in weeks) | | | | 38.5 (37.43 - 39.14)** | (37.14 - 40) |
| Gender | Male | | 14(46.7%) | --- | |
| | Female | | 16(53.3%) | | |
| Weight (in kg) | | 3.06 ± 0.50* | --- | | (2.1 - 4.3) |
| Sedative groups | Light sedation | | 11(36.7) | --- | |
| | Deep sedation | | 19(63.3) | | |
| Inotropes | No | | 22(73.3%) | | |
| | Yes | | 8(26.7%) | | |
| **Sepsis** | No | 21 | 70.0% | | |
| | **Yes** | **9** | 30.0% | | |
| **Pneumothorax** | No | 23 | 76.7% | | |
| | **Yes** | **7** | 23.3% | | |
| **Outcome** | Discharged | 18 | 60.0% | | |
| | **Died** | **12** | 40.0% | | |

*Mean ± SD for parametric measures **Median (IQR) for non-parametric measures.

Both lightly sedated and deep sedated groups were matched for their gestational ages, birth weights and gender distribution. There was a significant increase in the mean number of patients who needed inotropes in deeply sedated patients than lightly sedated patients (P-value 0.014). There was a statistically significant increase in the mean (SD) of TLC in deeply sedated patients more than in lightly sedated patients (p-value 0.001). Differences in other lab findings were found insignificant (Table 2). There was a significant decrease in the mean of $PCO_2$ after sedation in deeply sedated patient more than in lightly sedated patient (p-value 0.034).

**Table 2: Comparison of demographic data, medication and lab parameters between lightly and deeply sedated patients (n=30)**

| Variable | | Sedation group | | | | Test of significance | | |
|---|---|---|---|---|---|---|---|---|
| | | Light sedation (n=11) | | Deep sedation (n=19) | | | | |
| | | Mean ± SD N (%) | Row N (%) | Mean ± SD N (%) | Row N (%) | Value | P-value | Sig. |
| GA(in weeks) | | 38.38±0.8 | --- | 38.32 ± 0.93 | --- | ***t*= 0.181*** | 0.858 | NS |
| Gender | Male | 4(36.36%) | 28.6% | 10 (52.63%) | 71.4% | $X^2$= 0.741** | 0.389 | NS |
| | Female | 7(63.64%) | 43.8% | 9 (47.37%) | 56.3% | | | |
| weight (kg) | | 2.91±0.43 | --- | 3.14 ± 0.53 | --- | ***t*= -1.242*** | 0.225 | NS |
| Inotropes | No | 11 (100%) | 50.0% | 11 (57.89%) | 50.0% | Fisher's Exact test | 0.014 | S |
| | Yes | 0 (0%) | 0.0% | 8 (42.11%) | 100.0% | | | |
| **CBC parameters** | | | | | | | | |
| Total leucocytic count | | 9.26 ± 1.56 | | 13.46 ± 4.59 | --- | -3.640* | 0.001 | S |
| Hemoglobin (gm/dl) | | 15.04 ± 1.76 | | 14.92 ± 2.62 | | 0.130* | 0.898 | NS |
| Patelet count | | 299.18 ± 79.1 | | 233.68 ± 114.78 | | 1.671* | 0.106 | NS |
| Creactive protein | | 17.37 ± 11.39 | | 21.84 ± 35.34 | | -0.507* | 0.617 | NS |
| **VBG parameters** | | | | | | | | |
| pH_Before sedation | | 7.25 ± 0.05 | | 7.27 ± 0.1 | --- | -0.670* | 0.508 | NS |
| HCO3:Before sedation | | 19.05 ± 1.44 | | 21.01 ± 5.96 | | -1.369* | 0.185 | NS |
| PCO2: Before sedation | | 45.76 ± 13.57 | | 45.54 ± 9.86 | | 0.052* | 0.959 | NS |
| pH: After sedation | | 7.3 ± 0.05 | | 7.32 ± 0.1 | | -0.499* | 0.621 | NS |
| $HCO_3$: After sedation | | 23.06 ± 1.43 | | 21.36 ± 3.86 | | 1.728* | 0.096 | NS |
| $PCO_2$: After sedation | | 51.52 ± 10.47 | | 43.36 ± 9.2 | | 2.227* | 0.034 | S |
| Sepsis | No | 9(81.82%) | 42.9% | 12 (63.16%) | 57.1% | Fisher's Exact test | 0.419 | NS |
| | Yes | 2(18.18%) | 22.2% | 7 (36.84%) | 77.8% | | | |
| Pneumothorax | No | 6(54.55%) | 26.1% | 17 (89.47%) | 73.9% | Fisher's Exact test | 0.068 | NS |
| | Yes | 5(45.45%) | 71.4% | 2 (10.53%) | 28.6% | | | |
| Outcome | Discharge | 6(54.55%) | 33.3% | 12 (63.16%) | 66.7% | Fisher's Exact test | 0.712 | NS |

*Student t-test (t). **Chi-Square test ($X^2$). $PCO_2$: carbon dioxide $hco_3$: bicarbonate PH: the negative logarithmic of the hydrogen ion concentration

In comparing the studied patients before or after sedation, the median of N-PASS parameters (crying, vitals, behavior, facial, tone) and its total score, all were significantly decreased after sedation. Also the median Burdjalov score parameters (Continuity, Cycling, Amp lower border, Bandwidth span) and total score Median (IQR), all were significantly lowered after sedation (**Table 3**)

**Table 1: comparison between N-PASS parameters and aEEG Burdjalov parameters before and after sedation among all studied neonates (n=30)**

| Variable | | Before | After | Wilcoxon sign rank test | | |
|---|---|---|---|---|---|---|
| | | Median (IQR) | Median (IQR) | Z | p value | sig. |
| NPASS | Crying | 1 (1 - 1) | -1 (-2 - -1) | -4.92 | <0.001 | S |
| | Vitals | 0 (0 - 0) | -1 (-1 - 0) | -4.29 | <0.001 | S |
| | Behaviour | 1 (0 - 1) | -1 (-1 - -1) | -4.74 | <0.001 | S |
| | Facial | 1 (1 - 1) | -1 (-1 - -1) | -4.81 | <0.001 | S |
| | Tone | 1 (1 - 1) | -1 (-2 - -1) | -4.89 | <0.001 | S |
| | Total N-PASS score | 3.5 (3 - 4) | -6 (-7 - -3) | -4.80 | <0.001 | S |
| aEEG | Continuity | 2 (2 - 2) | 1 (1 - 1) | -5.20 | <0.001 | S |
| | Cycling | 4 (3 - 4) | 2 (2 - 2) | -4.60 | <0.001 | S |
| | Amplitude of lower border | 2 (2 - 2) | 2 (2 - 2) | -2.07 | 0.038 | S |
| | Bandwidth span | 4 (4 - 4) | 3 (3 - 3) | -4.58 | <0.001 | S |
| | Total Burdjalov score | 12 (11 - 12) | 8 (8 - 9) | -4.85 | <0.001 | S |

**Wilcoxon sign rank test*

There was a statistically significant decrease of the median value in all parts of N-PASS (crying, vitals, behavior, facial and tone) and its total score in deeply sedated patients in comparison to lightly sedated patients (-7 vs. -3 in total score respectively $p<0.001$). There was also a statistically significant lowering in the median (IQR) of the parameters of Burdjalov score (Continuity, Cycling, bandwidth span) and its total score in deeply sedated patients than lightly sedated patients (8 vs. 9 in total score, respectively; $p<0.001$). Meanwhile, the amplitude of lower border was not significantly affected ($p>0.05$). When applying ROC analysis, aEEG total (Burdjalov) score at a cut-off value of ≤8 is predictive of deep sedation with 100% sensitivity and specificity.

**Table 2: Comparison of N-PASS parameters and aEEG Burdjalov parameters between the light and deep sedated groups**

| Variable | | Light sedation (n=11) | Deep sedation (n=19) | Mann Whitney test | | |
|---|---|---|---|---|---|---|
| | | Median (IQR) | Median (IQR) | Z | P value | Sig. |
| **NPASS after sedation** | Crying | -1 (-1 - -1) | -2 (-2 - -1) | -3.58 | <0.001 | S |
| | Vitals | 0 (0 - 0) | -1 (-1 - -1) | -5.39 | <0.001 | S |
| | behavior | 0 (-1 - 0) | -1 (-1 - -1) | -3.78 | <0.001 | S |
| | Facial | -1 (-1 - 0) | -1 (-2 - -1) | -3.05 | 0.002 | S |
| | Tone | -1 (-1 - -1) | -2 (-2 - -1) | -3.36 | 0.001 | S |
| | total score | -3 (-3 - -2) | -7 (-7 - -6) | -4.61 | <0.001 | S |
| **Burdjalov score after sedation** | Continuity | 1 (1 - 2) | 1 (1 - 1) | -2.36 | 0.018 | S |
| | Cycling | 3 (2 - 3) | 2 (2 - 2) | -3.06 | 0.002 | S |
| | amp lower border | 2 (2 - 2) | 2 (2 - 2) | -1.10 | 0.273 | NS |
| | bandwidth span | 3 (3 - 3) | 3 (2 - 3) | -2.41 | 0.016 | S |
| | total score | 9 (9 - 9) | 8 (7 - 8) | -4.74 | <0.001 | S |

**Mann Whitney test*

**Table 3: ROC Curve for diagnostic performance of total Burdjalov score in sedated neonates to predict deep sedation**

| AUC | 95% CI | Sig. | Cut-off value | Sensitivity | Specificity | +PV | -PV |
|---|---|---|---|---|---|---|---|
| 1.00 | 0.884 to 1.000 | <0.001 | ≤8 | 100 | 100 | 100 | 100 |

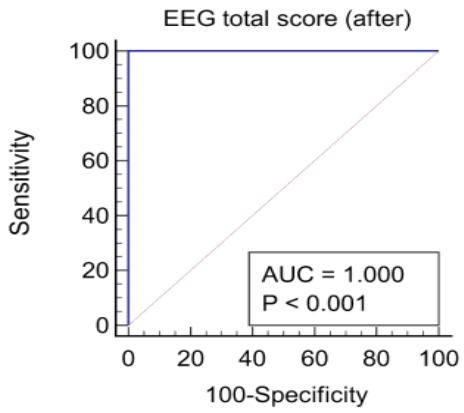


**Figure 1: ROC Curve for aEEG total (Burdjalov) score in sedated neonates to predict deep sedation.**

## DISCUSSION

Proper sedation of neonates in NICUs is quite a challenge for neonatologists worldwide. Differentiating if the patient is lightly or deeply sedated was previously acknowledged by expert opinion. The emergence of several scoring systems has tried to solve this subjectivity of this by using predefined set parameters. But still, to choose which of which is still based on the subjectiveness and the experience of the interpreter. The development of the NPASS scoring system has proven very beneficial with good reproducibility. But the search for a more objective method is still under research. Application of single channel amplitude integrated EEG has shown previous ability to differentiate sedation from non-sedation states, but lacked the differentiative-ability between light and deep sedation. [7,9]

We found that using a double channel aEEG can effectively differentiate between sedation and non - sedation states with a significant reduction in Mean±SD of total aEEG Burdjalov score in neonates after sedation in comparison to before sedation (the non-sedation) (7.53 ± 0.77 vs. 11.47 ± 0.51, respectively with (p-value <0.001). This is in accordance with those findings previously reported by **Giordano *et al***. They studied 27 neonates in 3 categories (no sedation, light sedation and deep sedation) aiming to assess the ability of the different methods (N-PASS, aEEG, and Bispectral Index), and their use together, in picking up different sedation levels. They reported a significant decrease in total Burdjalov score after sedation less than before sedation (p-value <0.001). [7]

Differentiating between light and deep levels of sedation was the key investigative question in our study. Using a double channel aEEG showed a significant reduction in mean ±SD of total Burdjalov score after sedation between lightly and deeply sedated patient (9±0 Vs 8±1 respectively with (p-value <0.001). Similar findings, however, could not be proven by **Giordano *et al.*** who reported that no significant differences were found between light and deep sedation regarding the single channel aEEG score used **.**[7]

There was a decrease (which was statistically significant) in the mean number (frequency) of sleep wake cycling (SWC) after sedation vs. before (non-sedation): {2(1-4) vs. 4(3-4) before & after sedation, respectively}. On the contrary, **Olischar *et al*.** suggested that morphine and midazolam did not influence the emergence of SWC, and it was most likely indicative of cerebral pathology rather than being related to sedative drugs used post-operatively.[9]

In the current study a decrease which was statistically significant in the mean of aEEG continuity after sedation was detected (2 vs. 1 before and after sedation, respectively (p<0.001). This observation is similar to the finding reported by **Eaton *et al.*** who tested the effect of pethidine on neonates. They had found that there were changes in the normal pattern of discontinuity of the EEG in association with its administration. However, these changes were not related to the gestational age or postnatal age at the time the dose was given. [12]

Similarly, in their study, **Bernet *et al.*** reported that most newborn cardiac patients showed a discontinuous normal voltage activity after receiving sedation postoperatively, and returned to a continuous normal voltage pattern after stopping the sedative drug. Also, the onset of SWC in patients who received midazolam was significantly developed later; also impressively continuous low voltage or flat trace in aEEG was seen when fentanyl was administered. [13]

***Bell et al.*** studied the effect of morphine before and after on the amount of burst in preterm neonates. In preterm neonates, morphine did not affect burst rate expression. They also studied the effect of Administration of a single dose of diazepam during endotracheal tube placement and showed an increased depression effect on the EEG depression which was prolonged for 11-12 hours after sedation was received.[14]

The study of ***Young et al.*** showed that Morphine produced a marked reversible change in the EEGs at various gestations. The main effects were the prolonged parts with electrical quiescence (PPEQs) and increased interictal epileptiform activity. The PPEQs resolved after the morphine was discontinued and the EEG background rhythms resolved to normal [15]**.** In the study of ***Bell et al.*** and ***Young et al.*** they used conventional EEG instead of aEEG. We proved that aEEG on its own could differentiate between light and deep sedation.

Regarding mean and SD of pCO2, we compared its value after sedation in both light and deep sedation and there was a marked decrease in pCO2 in deeply sedated

than lightly sedated patients (43.36 ± 9.2 Vs 51.52 ± 10.47, respectively; p <0.034). This can be attributed to more synchrony of patient with deep sedation with mechanical ventilation. This was in contrast to ***Giordano et al.*** results who reported that no significant difference regarding mean and SD pCO2 between light sedation 46.0 (SD 10) mm Hg and deep sedation 50.4 (SD 10.9) mmHg (P= 0.65).[7]

In the present study the results demonstrated that a cut-off value of ≤8 in total Burdjalov score was indicative that the patient has been deeply sedated with 100% sensitivity and specificity. Since all the parameters of N-PASS are dependent on clinical decisions and liable to be different according to interpersonal judgment. The use of double channel aEEG would be more conclusive.

Not all patients in NICU respond equally to the dose of midazolam given, some are completely sedated at lower dose than others. Finding which dose is effective is quite intriguing. We claim that the use of double channel aEEG is very useful to differentiate whether patients are sedated or not, moreover the use of two channel aEEG had the ability to differentiate deep from light sedation. Patients in NICU can be evaluated by double channel aEEG to detect at which dose of midazolam infusion and additional fentanyl shots is needed to reach a deep sedated state.

In conclusion, double channel aEEG can be used bedside in NICUs effectively to differentiate between patients who are sedated or not. Moreover, we recommend its use as it can differentiate between light or deep sedation states.

## Conflicts of interest and funding

The authors declare that there were no conflicts of interest.

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