Background. The Bispectral Index (BIS) monitor has been suggested as a potential tool to measure depth of sedation in paediatric intensive care unit (PICU) patients. The primary aim of our observational study was to assess the difference in BIS values between the left and right sides of the brain. Secondary aims were to compare BIS and COMFORT score and to assess change in BIS with tracheal suctioning.

Methods. Nineteen ventilated and sedated PICU patients had paediatric BIS sensors applied to either side of their forehead. Each patient underwent physiotherapy involving tracheal suctioning. Their BIS data and corresponding COMFORT score, assessment as by their respective nurses, were recorded before, during, and after physiotherapy.

Results. Seven patients underwent more than one physiotherapy session; therefore, 28 sets of data were collected. The mean BIS difference values (and 95% CI) between left BIS and right BIS for pre-, during, and post-physiotherapy periods were 9.2 (5.9–12.5), 15.8 (11.9–19.7), and 7.5 (5.2–9.7), respectively. Correlation between mean BIS, left brain BIS, and right brain BIS to COMFORT score was highly significant ($P<0.001$ for all three) during the pre- and post-physiotherapy period, but less so during the stimulated physiotherapy period ($P=0.044$, $P=0.014$, and $P=0.253$, respectively).

Conclusions. A discrepancy between left and right brain BIS exists, especially when the patient is stimulated. COMFORT score and BIS correlate well between light and moderate sedation.

Pharmacological intervention is required to control sedation and analgesia in paediatric intensive care unit (PICU) patients. Sedation is necessary to prevent emotional and physical discomfort. Adequate sedation is defined by intensivists as the level of sedation when patients are asleep but easily arousable. These drugs need to be titrated to effect, so as not to over or under sedate the patient. Determining the appropriate level of sedation is important as over-sedation can be detrimental to the patient and underestimation fails to achieve the intended goal.

Arguably, the most practical sedation scoring system in the PICU setting is the COMFORT score. The COMFORT score, which is a non-intrusive measure of psychological distress, includes eight dimensions (five behavioural; three physiological). The COMFORT score can be divided into three categories: 8–16 points corresponds to deep sedation, 17–26 points to light sedation, and 27–40 points to inadequate sedation.4

The Bispectral Index (BIS) (Aspect Medical Systems) is a statistical interpretation of EEG parameters including a time domain, a frequency domain, and spectral array data (bispectral analysis) that can be reported as a single number. Generally, BIS values near 100 reflect an awake state, 40–60 reflects a hypnotic level adequate to prevent awareness under general anaesthesia in adults, and $<40$ is considered a deep hypnotic state or coma.

Previous studies have compared COMFORT score with BIS. All demonstrate varying degrees of correlation.
between the two variables, but less so when comparing at very deep sedation. None of these studies though has investigated the phenomenon of BIS asymmetry. BIS asymmetry has, however, been demonstrated in children recovering from anaesthesia and adults sedated in the intensive care. BIS asymmetry is the difference between the left- and the right-sided BIS recordings. This difference may be calculated for BIS readings occurring at the same time or at different times, but during the same period of stimulation or non-stimulation. Recently, one of the authors (C.A.M.) who presented initial data from our study at an international forum reported the occurrence of BIS asymmetry in children sedated in PICU.

The primary aim of this observational study was to investigate this phenomenon of brain BIS asymmetry. We also wanted to extend the information about BIS in PICU patients and to compare COMFORT score and BIS and to analyse the change in BIS with stimulation.

Methods

After South East Wales local research ethics committee approval and written informed consent from the patient’s parents or guardian, 19 PICU patients were included in this prospective single-blinded observational study. The inclusion criteria were all children aged 0–16 yr requiring sedation and ventilation admitted to a tertiary level university hospital PICU. The exclusion criteria were patients ventilated using neuromuscular blocking agents, received ketamine, brain injury (as this may cause potential confounding effects on BIS measurement), or imminent expected demise.

A maximum of four sets of data per patient, collected over a 2 day period, was permitted. BIS paediatric sensors (Aspect Medical Systems, Newton, MA, USA) were applied to the left and right side of the head in accordance with the manufacturer’s specifications after correct preparation of the skin. As ‘electrode one’ of the BIS paediatric sensor is placed on the centre of the forehead, left and right ‘electrode one’ were randomly assigned to be placed above and below each other for each set of data collection. The two BIS paediatric sensors were attached to two Aspect XP BIS monitors (Aspect Medical Systems, software version 3.12, Model A-2000™, Natick, MA, USA). The BIS monitors were switched (left for right) midway through the study to avoid any machine bias. If the signal quality index (SQI) was <50% for a sensor, then it was reapplied. If the SQI was still <50%, the BIS data were not deemed reliable and were excluded. The data were recorded onto a laptop computer, using LabView Version 7 software (National Instruments, Austin, TX, USA). The smoothing time used was 15 s.

The data collection was planned to coincide with patient physiotherapy. BIS data were collected separately for left and right cerebral hemispheres throughout. Ten minutes before physiotherapy, the PICU nurse caring for the patient was asked to calculate a COMFORT score (pre-physiotherapy). This coincided with the routine assessment of COMFORT score used as measure of sedation in this PICU. Adequate sedation is usually titrated to a COMFORT score of 17–26. The titration of sedation agents before physiotherapy was independent of the researchers. Physiotherapy, which always included tracheal suctioning, commenced for a duration of between 4 and 16 min (median of 9 min) and again the nurse was asked to calculate the maximum COMFORT score (during physiotherapy) for this stimulated period. Other forms of stimulation that may have a varying intensity for arousal included: physiotherapy fibrillation, percussion, and patient turning. Ten minutes post-physiotherapy, the nurse was again asked to calculate the COMFORT score (post-physiotherapy). The nurse was blinded to the BIS value throughout the data collection. Pre- and post-physiotherapy periods were grouped as unstimulated COMFORT scores. The unstimulated periods were times when no stimulation of the patient could have led to an arousal. Each COMFORT score was performed over a 2 min interval as recommended. For unstimulated COMFORT scores, the corresponding BIS values were determined as a 2 min average before the COMFORT score calculation was complete. For the stimulated COMFORT score, the corresponding BIS value was determined as the highest mean average over 2 min for the time physiotherapy took place. This was done to mirror the time it took to perform a COMFORT score. This is unlike previous studies that averaged the BIS data over 1 min.

Paediatric Index of Mortality score, sedative agents used, demographic data, and medical diagnosis were recorded.

Statistical analysis

Mean and standard deviations were used to describe weight, and median and range were used to describe the age and Paediatric Index of Mortality scores. Statistical analysis was performed using SPSS statistical software (version 13, SPSS Inc., Chicago, IL, USA) and Microsoft Excel where appropriate. The presence of correlation between COMFORT score and BIS values was done using Spearman’s rank correlation testing. These BIS values were an average of the left and right BIS measurements for the same time. These BIS values were also divided into four depths of sedation categories: 81–100 was defined as light sedation, 61–80 as moderate sedation, 41–60 as deep sedation, and ≤40 as very deep sedation. The mean COMFORT scores were determined for each BIS category of depth of sedation and Kruskal–Wallis multi-group analysis used to determine any difference between the groups. To test arousal by tracheal suctioning, the change in mean BIS during the pre-physiotherapy period to mean peak BIS (an average of left and right BIS measurements) during the physiotherapy period was
compared with the four BIS depths of sedation categories mentioned above. This and all the subsequent statistical analyses were done using analysis of variance (ANOVA). We then assessed the BIS difference values between left and right BIS for each of the pre-, during, and post-physiotherapy periods. We also compared this BIS difference value to each of the four depths of sedation categories. Finally, we compared mean left-sided BIS with mean right-sided BIS for each occasion of pre-, during, and post-physiotherapy, and the change in left or right BIS highest value for each unstimulated and stimulated occasion. A $P$-value of $<0.05$ was considered statistically significant in all tests.

**Results**

Of the 19 patients recruited, 28 sets of data were collected. Each set of data included a pre-physiotherapy, during physiotherapy, and post-physiotherapy periods. Six patients had two sets of data and one patient had four sets of data recorded. The remaining 12 patients each had only one set of data collected (Table 1). There were no adverse reactions to the application of the BIS sensors.

Eighty-three COMFORT scores were recorded ranging from 9 to 34. Each set of data had three COMFORT score readings, except for one, which only had two COMFORT score readings. This patient was extubated and sedation turned off before the third and final COMFORT score could be calculated. The COMFORT score range (median) was 9–27 (13.5) during the pre-physiotherapy period, 10–34 (25) during the stimulated period, and 11–24 (14) during the post-physiotherapy period.

The mean BIS value (SD) was 58.4 (19.0) during the unstimulated periods, and 69.0 (18.8) during the stimulated period. The paired $t$-test showed a significant difference of $P=0.002$ between the mean BIS values of the unstimulated and stimulated periods.

The data in Table 2 demonstrate a good correlation between COMFORT scores and BIS values during the unstimulated periods, but this correlation is much weaker during the stimulated period. This significant correlation during the unstimulated period is shown in Figures 1–3.

**Table 1** Demographic data of the patients

<table>
<thead>
<tr>
<th>Age (yr) [median (range)]</th>
<th>1.5 (0.55–9.7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (kg) [mean (sd)]</td>
<td>12.7 (6.7)</td>
</tr>
<tr>
<td>Male:female</td>
<td>10:9</td>
</tr>
<tr>
<td>Paediatric Index of Mortality score [median (range)]</td>
<td>0.057 (0.007–0.244)</td>
</tr>
<tr>
<td>Medical reason for PICU admission</td>
<td>n=19</td>
</tr>
<tr>
<td>Respiratory</td>
<td>7</td>
</tr>
<tr>
<td>Airway</td>
<td>5</td>
</tr>
<tr>
<td>Sepsis</td>
<td>3</td>
</tr>
<tr>
<td>Cardiac</td>
<td>2</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>1</td>
</tr>
<tr>
<td>Hepatic</td>
<td>1</td>
</tr>
</tbody>
</table>

Sedative agents used for the 28 sets of data

<table>
<thead>
<tr>
<th>Medication</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Midazolam</td>
<td>27 of 28</td>
</tr>
<tr>
<td>Morphine</td>
<td>26 of 28</td>
</tr>
<tr>
<td>Chloral hydrate</td>
<td>22 of 28</td>
</tr>
<tr>
<td>Trimeprazine tartrate</td>
<td>7 of 28</td>
</tr>
<tr>
<td>Clonidine</td>
<td>3 of 28</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>2 of 28</td>
</tr>
</tbody>
</table>

**Table 2** Comparisons of BIS values to COMFORT scores

<table>
<thead>
<tr>
<th>Condition</th>
<th>Spearman’s correlation coefficient</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unstimulated periods</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean BIS to COMFORT score</td>
<td>0.603</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Left BIS to COMFORT score</td>
<td>0.569</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Right BIS to COMFORT score</td>
<td>0.584</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Stimulated period</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peak mean BIS to COMFORT score</td>
<td>0.383</td>
<td>0.044</td>
</tr>
<tr>
<td>Peak left BIS to COMFORT score</td>
<td>0.459</td>
<td>0.014</td>
</tr>
<tr>
<td>Peak right BIS to COMFORT score</td>
<td>0.223</td>
<td>0.253</td>
</tr>
</tbody>
</table>

**Fig 1** (a) Scatter-gram of COMFORT score and left BIS values during the pre-physiotherapy period ($\rho=0.557$, $P=0.002$). (b) Scatter-gram of COMFORT score and right BIS values during the pre-physiotherapy period ($\rho=0.486$, $P=0.009$).
81–100 were defined as light sedation, 61–80 as moderate sedation, 41–60 as deep sedation, and ≤40 as very deep sedation. Mean COMFORT scores were calculated for each category of sedation. Kruskal–Wallis multi-group analysis between the groups showed a significant (P<0.001) overall difference. The most statistically significant difference for COMFORT scores were between the light and the moderate sedation groups (Fig. 4).

To test possible arousal by tracheal suctioning, the change in mean BIS of the pre-physiotherapy period to the peak mean BIS of the physiotherapy period was compared with the four BIS depths of sedation categories. There were no statistically significant differences between the four depths of sedation categories, except between the light sedation category and all the other sedation categories (light to very deep, P=0.007; light to deep, P=0.003; and light to moderate, P=0.012). However, this should be treated with caution as there were only two sets

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**Fig 2** (a) Scatter-gram of COMFORT score and left BIS values during the physiotherapy period (r=0.459, P=0.014). (b) Scatter-gram of COMFORT score and right BIS values during the physiotherapy period (r=0.223, P=0.253).

**Fig 3** (a) Scatter-gram of COMFORT score and left BIS values during the post-physiotherapy period (r=0.356, P=0.003). (b) Scatter-gram of COMFORT score and right BIS values during the post-physiotherapy period (r=0.667, P<0.001).

**Fig 4** Box and whisker plots of COMFORT score vs the four categories of levels of sedation as defined by BIS (≤40 very deep sedation; 41–60 deep sedation; 61–80 moderate sedation; and >81 light sedation). Box denotes inter-quartile range and median, whiskers denote range ignoring outliers and extremes.
of data in this light sedation group and unexpectedly the mean BIS value decreased rather than increased. Next, we determined the BIS difference values between the left BIS and the right BIS readings. The values for each period of stimulation or unstimulation can be seen in Table 3 with an overall significance of $P < 0.001$ for occasion. We then compared these left/right BIS differences to each occasion of pre-, during, and post-physiotherapy (Table 4).

When comparing the BIS difference values for left and right BIS with the four BIS depths of sedation categories mentioned above, we found no statistical significance between groups for the unstimulated period ($P = 0.591$) or the stimulated period ($P = 0.825$).

We finally wanted to examine if one side of the brain consistently portrayed a higher BIS value. When comparing the mean BIS values for the left or the right side of the brain for each occasion of pre-, during, and post-physiotherapy, there was no statistically significant hemispheric BIS dominance found for any of the three occasions ($P = 0.68$). When assessing the change in the higher brain hemispheric BIS value from left to right or right to left for a change in occasion, the following was found. Of the 28 sets of data, the higher brain hemispheric BIS value changed in 11 for pre-physiotherapy to physiotherapy, nine for physiotherapy to post-physiotherapy, and six for pre-physiotherapy to post-physiotherapy. Of the 11 sets of data that had changed their side of BIS dominance from the pre-physiotherapy to physiotherapy period, seven reverted back to their initial pre-physiotherapy side of BIS dominance when entering the post-physiotherapy period. Of the seven patients who had multiple sets of data recorded, six had the same left or right side BIS dominance for the pre-physiotherapy period, seven for the physiotherapy period, and only three for the post-physiotherapy period.

### Discussion

The primary aim of our study was to investigate the phenomenon of brain BIS asymmetry. We also wanted to compare the COMFORT score with BIS. The COMFORT score is well known to be a common and practically useful measure of sedation in PICU. The COMFORT score has been validated for all paediatric ages, showing high internal consistency and interrater agreement. It can be used in patients with varying neurodevelopment and does not require an arousal stimulus. It, however, cannot be used in patients receiving neuromuscular block.

Another criticism is that heart rate and arterial pressure (two of the dimensions of the COMFORT score) may not be a reliable measure of comfort in children, and can be iatrogenically influenced by ino- and chronotropic drugs. This is one criticism of Triltsch and colleagues who admitted that the majority of the patients included in their study were postoperative cardiac surgical patients who had received catecholamines. Also, deeper levels of sedation are less reliably assessed using clinical sedation scores.

BIS values reflect the hypnotic or sedative state of the brain not the concentration of a particular drug. The BIS monitor, although a monitor of level of anaesthesia, may have a place in titrating sedative drugs required for patients sedated in PICU. Although BIS was designed for an adult population, a strong linear correlation has been demonstrated between BIS and mean alveolar concentration of volatile agents in children. However, doubt has been cast on the suitability of the adult-derived algorithm to be used to assess children’s BIS values. Also, children aged <1 yr demonstrate lower pre-awakening BIS values compared with those older than 1 yr. Another study has shown no correlation between BIS and sevoflurane concentration in children <1 yr old.

Various factors, such as body temperature, critical illness, hypotension, equipment electrical interference, and EMG interference from forehead muscle activity, may confound BIS scores. The newest software version for the BIS monitor (version 4.0) has reduced the EMG interference problem significantly. Bryan and colleagues found, importantly for our study, that changes in EMG power or EEG components of BIS did not reflect BIS asymmetry. Catecholamine infusions are another source of interference for BIS and although propofol and benzodiazepines show a dose-dependent change in BIS, opioids show a poor correlation in adults and children.

In the critically ill child, Berkenbosch and colleagues suggested that opioids do provide sedation and may alter the BIS. Our patients’ main form of sedation was with midazolam and morphine.
Sedation scoring systems other than COMFORT score have been correlated with BIS. Two papers, comparing Ramsay Sedation Score and BIS in critically ill children showed a good to moderate correlation with BIS. However, Mason and colleagues concluded that BIS had a limited ability to distinguish between moderate and deep Ramsay sedation levels in children receiving pentobarbital for diagnostic imaging. In the papers that compared COMFORT score with BIS, two found that the COMFORT score was unable to distinguish between deep (BIS 41–60) and very deep (BIS ≤ 40) sedation. Our study is in agreement with these two papers showing a statistically significant correlation between light and moderate sedation. Triltsch and colleagues showed a good correlation between light and moderate sedation and BIS. However, this is an observational study. We used peak mean BIS values (the maximum of a 2 min rolling average throughout the physiotherapy period) during the physiotherapy period rather than an average value as there were many fluctuations in BIS during this stimulating period. This could be that individual patients respond differently to a varying type and intensity of stimuli. Also we wanted this BIS value to correspond with the maximum COMFORT score value of this period and therefore the most intense stimulus for that patient. All mean BIS values were averaged over 2 min rather than other studies which have used 1 min, as we wanted the BIS reading to reflect the COMFORT score reading which takes 2 min to measure. We noticed a varying time for the BIS response to start to alter after an arousal method and that the BIS value, though changing, fluctuated considerably for each 15 s interval.

A final criticism of our paper is that morphine used routinely in sedating patients in PICU may not only affect the accuracy of the BIS, but also alter the validity of the COMFORT score. Although analgesia is pivotal to sedation, our patients sedated with a combination of drugs, including morphine, may have demonstrated higher COMFORT scores during the stimulated period if morphine had been omitted.

Both BIS and COMFORT score have limitations, but it is important to note that they each reflect different states. COMFORT score measures the global comfort of the PICU patient, which includes pain, emotional distress, and sedation. BIS merely deduces a level of consciousness. Therefore, one may have a patient with high BIS values, but be comfortable with a low COMFORT score. Conversely, a heavily sedated patient may have low BIS values, but still be able to feel pain and be agitated when stimulated.

In conclusion, our data have shown a discrepancy between the BIS values of the left brain and right brain in the same sedated PICU patient and these alter significantly when stimulated. Finally, our data showed a strong correlation between BIS of either cerebral hemisphere to COMFORT score in an unstimulated paediatric patient. In a stimulated paediatric patient, however, this correlation is significant only for the left cerebral hemisphere and is not statistically significant for the right cerebral hemisphere. COMFORT score and BIS correlated well between light and moderate sedation as defined by the four BIS depths of sedation categories.
Funding
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