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**Continuous non-invasive monitoring of barbiturate coma in critically ill children
using the Bispectral™ (BIS™) Index Monitor**

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Abstract

Background

Traumatic brain injury (TBI) and generalized convulsive status epilepticus (GCSE) are conditions which need aggressive management. Barbiturates are used to lower intracranial pressure (ICP) or to stop epileptiform activity with the aim to improve neurological outcome. Dosing of barbiturates is usually guided by the extent of an induced burst-suppression pattern on the electroencephalogram (EEG). Dosing beyond the point of burst suppression may increase the risk of complications without offering further therapeutic benefits. For that reason, careful monitoring of EEG parameters is mandatory. A prospective study was conducted to evaluate the usefulness of the bispectral index suppression ratio for monitoring barbiturate coma.

Methods

A prospective observational pilot study was performed at a Pediatric (surgical) intensive care unit including all children with barbiturate-induced coma after traumatic brain injury or generalized convulsive status epilepticus (GCSE). The BIS™ monitor expresses a suppression ratio, which represents the percentage of epochs per minute in which the electroencephalogram (EEG) was suppressed. Suppression ratios of the BIS monitor were compared with suppression ratios of full-channel EEG as assessed by quantitative visual analysis.

Results

Five patients with GCSE and three patients after traumatic brain injury, with a median age of 11.6 years (range, 4 months to 15 years), were included. In four patients, the correlation between the suppression ratios of the BIS and EEG could be determined; average correlation was 0.68. In two patients, suppression ratios were either high or low, with no intermediate values. This precluded determination of correlation values, as did

the iso-electric EEG in yet two other patients. In the latter, the BIS suppression ratio showed a mean of 95 ± 1.6 .

Conclusions

Correlations between the suppression ratios of the BIS and EEG were found to be only moderate. In particular, asymmetrical EEGs and EEGs with short bursts (less than 1 second) may result in aberrant BIS suppression ratios. The BIS monitor potentially aids monitoring of barbiturate-induced coma, as it provides continuous data on EEG suppression between full EEG registrations, but should be used with caution.

Introduction

Traumatic brain injury (TBI) and generalized convulsive status epilepticus (GCSE) are conditions which need aggressive management. Barbiturates are used to stop epileptiform activity with the aim to improve neurological outcome. Side effects of high barbiturate levels are a decrease in cerebral metabolism and blood flow, which also are favourable in the treatment of severe epilepsy.[1] However, barbiturate therapy has serious side effects, in particular cardiovascular depression and hypotension.[2, 3] Dosing of barbiturates is guided by the extent of an induced burst-suppression pattern on the electroencephalogram (EEG).[4] Dosing beyond the point of burst suppression may increase the risk of complications without offering further therapeutic benefits.[3] For that reason, careful monitoring of EEG parameters is mandatory.

Several methods of monitoring a barbiturate coma are available, interval or continuous EEG monitoring, and regular testing of barbiturate blood levels. Winer et al.[5] demonstrated in 10 adult patients that continuous EEG monitoring was the best modality, as it showed the presence of burst suppression on a moment-to-moment base. They also found poor correlations between serum and cerebrospinal fluid barbiturate levels at any given time, suggesting that barbiturate levels are difficult to interpret given a specific patient's distribution and metabolism[5]. Another possibility is that barbiturate levels are difficult to interpret because of changes in receptor sensitivity[6].

When EEG is used to determine the optimal depth of a barbiturate coma, the goal is to induce a burst suppression pattern[5] A practical drawback of the standard EEG recording method is that recording and interpretation requires qualified EEG technicians and a clinical neurophysiologist. In addition, most centers do not have the facilities to monitor EEGs and have the EEG interpreted by qualified clinical neurophysiologists continuously for hours to days or even weeks.[7-9]

In summary, clinical evaluation of a pentobarbital coma is difficult; barbiturate blood levels may not be reliable and continuous full-channel EEG monitoring is not feasible in many centers as in ours. This leaves monitoring of a barbiturate coma with the BIS™ monitor as a possibility. This monitor provides a suppression ratio (SR-BIS) and raw EEG traces, which are continuously displayed, thus enabling monitoring of cerebral function. The BIS monitor is relatively easy to use, and nurses and physicians can be taught how to interpret recordings.

We hypothesized that if the optimal SR-BIS values and EEG trace displayed on the BIS monitor are comparable with the full channel EEG and remain stable, the BIS monitor might be used as continuous monitor of the suppression ratio. If supplemented by a full-channel EEG once a day, it could replace the need for continuous full-channel recordings. Against the background of the scarcity of data on barbiturate-induced coma in children,[10] we therefore conducted a study to explore the usefulness of the BIS monitor during a barbiturate induced coma in critically ill children needing intensive neuro-monitoring. For this purpose, BIS recordings were compared with standard full-channel EEG recordings.

Materials and methods

Patients

We conducted a prospective observational pilot study at the pediatric surgical intensive care unit (PSICU) and the pediatric intensive care unit (PICU) of our level-three children's hospital. Because of the strictly observational and non-invasive nature of the study, the institutional review board waived the need for approval. Annually, our PSICU admits some 10 patients with a Glasgow Coma Score ≤ 8 after TBI, which is considered an indication for intracranial pressure monitoring. In about half of these patients, it is necessary to induce a barbiturate coma, after failure of all other methods to decrease ICP.[11] In addition, our PICU yearly admits 3 - 4 patients with refractory GCSE for treatment of their condition with a barbiturate coma. All children with TBI or GCSE in whom a barbiturate coma was induced from November 2002 until July 2004 were eligible for this study. Patients with TBI facing imminent brain death were not included.

Procedure

After admission to the ICU, the child's neurological status was evaluated by a standard 24-channel EEG. Barbiturate comas were induced on clinical grounds, independent of the present study. Subsequently, EEGs as well as barbiturate blood levels were requested and repeated on the basis of clinical signs and/or changes in medication. There is no validated therapeutic range for barbiturate plasma levels; these were mainly monitored to avoid toxic concentrations. After informed parental consent, BISTM electrodes were applied as described below during the course of the barbiturate coma. All other interventions were recorded.

BIS monitor

We used an A-2000 Bispectral™ (BIS™) index monitor version 3.12 (Aspect Medical Systems, Newton, MA, USA) with commercially available BIS™ pediatric sensor strips with three electrodes. One electrode is placed on the center of the forehead, one directly above and parallel to the eyebrow and one in the temple area. The BIS monitor is regularly used in anesthesiology to quantify the hypnotic effects of anesthetic drugs by means of a processed cortical two-channel EEG. The monitor uses Fourier transformation and bispectral analysis to compute a number (BIS value) ranging from 0 (iso-electric) to 100 (fully awake). In addition, the EEG recorded by the BIS is continuously displayed (BIS-EEG), together with the device's estimate of the suppression ratio (SR). The SR calculated by the BIS (SR-BIS) represents the percentage of epochs in the past 63 seconds in which the EEG signal is considered suppressed.

The algorithm within the BIS monitor sets limits for electrode impedance and signal quality, and no BIS and SR-BIS values are displayed if the signal has too many artifacts. The standard settings of the device were used for artifact rejection. For offline analysis, all BIS data were downloaded to a laptop computer using the WINHIST and WINLOG program provided by the manufacturer of the BIS monitor.

EEG

The EEG was recorded with silver-silver chloride electrodes attached to the skin with Elefix at electrode positions defined by the International 10 - 20 system (16 channels; Fp1/2, F7/8, T3/4, T5/6, O1/2, F3/4, C3/4, and P3/4). The EEG was digitally recorded (sample frequency 512 Hz, -3dB bandpass filter settings 0.13 - 70 Hz) using a Brainlab device (OSG, Rumst, Belgium). The EEG was visually assessed and for each 10 second EEG epoch, total duration of suppression of cerebral activity (amplitudes below 20 μ V) was measured. Subsequently, the SR was calculated as percentage of EEG suppression during 1 minute (SR-EEG), as closely matched to the corresponding BIS epoch as possible (see below). Of EEG registrations lasting > 1 hour, the first 11 minutes of every full hour were captured, of which SR-EEG was calculated.

Data management

Relevant clinical data during the treatment period were collected. Drugs administered during the pentobarbital coma were abstracted from an electronically guided patient data management system.

Synchronization between the SR-BIS and SR-EEG data proved to be a challenge.

There seemed to be differences in the algorithms that are used to determine SR-BIS and SR-EEG. The algorithm of the BIS monitor seems less accurate in detecting burst offset than a visual assessor, which led to an underestimation of the SR-BIS.

Synchronization was established in several ways. First, we synchronized the computer clocks of the BIS monitor and EEG equipment so that recordings could be linked.

Second, in the first four included patients, the software available at that time did not allow recording and exportation of the raw EEG data. Therefore, in these patients we matched patterns in SR-BIS and SR-EEG so that their correlation in time was optimal (see Fig. 3). For this purpose, we compared SR-BIS to the six SR-EEG data sets that

could be determined from the abovementioned 10-s epochs. That is, the first set was calculated over full minutes running from 0:00-1:00, 1:00-2:00, ..., 9:00-10:00, yielding ten (or more, if only a single EEG file of less than an hour's duration was available) SR-EEG values. The second set consisted of SR-EEG values obtained from epochs running from 0:10-1:10, 1:10 - 2:10, ... 9:10 -10:10, while the last set was based on epochs of 0:50:1:50, 1:50-2:50, ... , 9:50-10:50. With this approach, realized synchronization may have been off by 5 s at most. In the last four patients, the BIS monitor's raw EEG was captured using a laptop with WINLOG software provided by Aspect Medical Systems.

Statistical analysis

The data were analyzed using SPSS for Windows (version 10,0; SPSS, Chicago, IL). The correlation between the SR-BIS and SR-EEG during burst suppression was tested using the Spearman rho correlation coefficient. In case of bimodal data, the correlation was calculated over subsets of data.^[12] These subsets of data were found in two patients whose EEGs showed either continuous epileptic activity (i.e., SR-EEG < 40) or (some) suppression (SR-EEG ≥ 40), while no registrations with intermediate SR-EEG values were available. Statistical differences were considered significant if $P < 0.05$. Correlations from 0.80 to 1.00 were considered large.^[13]

Results

Eight patients were included during a period of eighteen months. Three patients received barbiturates after TBI and five received barbiturates to treat GCSE. Patient characteristics are listed in Table 1. Raw BIS EEG data were collected from patients 1, 3, 5 and 6, the last four included patients.

Correlation between SR-BIS and SR-EEG

The paired observations of all patients are displayed in Figure 1. Correlations between SR-BIS and SR-EEG could be calculated for four patients only (3, 4, 6 and 7). The individual correlations between SR-BIS and SR-EEG for these patients were 0.67, 0.64, 0.70 and 0.70, respectively. In patients 1 and 2, the SR distribution was bimodal, as shown by the two “data clouds” (Figure 2). This precluded determination of reliable correlation values, as did the iso-electric EEG (SR-EEG=100 and constant) in patients 5 and 8. In the latter patients, SR-BIS ranged from 43 to 100 (mean of 95, standard deviation 1.6)

For patients 1 and 2, correlations between SR-BIS and SR-EEG were calculated for the relevant subsets of data (individual clouds in Figure 2). The highest correlations in these patients were 0.5 and 0.4, respectively.

In a patient with a burst-suppression pattern with bursts of less than 1 second duration (patient 3), SR-BIS tended to underestimate the suppression ratio (see Fig. 4).

SR-EEG and barbiturate blood levels

A total of eleven barbiturate blood levels in 8 patients with corresponding SR-EEG values were available, ranging from 18 to 33 mg/l with a mean of 24 corresponded to SR-EEG values ranging from 55 to 100. In the two patients with an iso-electric EEG, blood levels ranged from 15 to 33 mg/l.

Discussion

The aim of this study was to evaluate the usefulness of the BIS monitor during a barbiturate coma in PICU patients, as proposed by Arbour and Jaggi et al.[9, 14] We found its application as continuous monitor of the burst suppression pattern promising. The BIS monitor is relatively easy to use, and nurses and physicians can easily be taught how to interpret recordings. SR-BIS and recorded EEG traces are continuously displayed, thus enabling continuous monitoring of cerebral function.

The continuously displayed real time raw EEG traces correlated well with the full-channel EEG, both at bedside and at comparison between the EEG of the BIS and the full-channel EEG afterwards. However, correlations between SR-BIS and SR-EEG were found to be only moderate. To some extent this may be caused by suboptimal synchronization, but it is likely that some of the discrepancy is caused by differences in the algorithms that are used to determine SR-BIS and SR-EEG. For example, the algorithm of the BIS monitor seems to overestimate the length of the burst and, therefore, underestimate the SR-BIS (Patient 3, Fig. 4). This underestimation might be caused by the EEG signal's slow return to baseline after a high-amplitude burst. That is, the computerized BIS algorithm may be less accurate in detecting burst offset than a visual assessor. The effects of this bias are more pronounced in situations with many short-duration bursts (less than 1 second) than in a situation with equal SR-EEG but only a few long-duration bursts. However, visually the BIS traces corresponded well with the real time EEG in all patients.

Additional caution should be in taken in cases where the EEG is (or might be expected to become) asymmetric. Because the BIS monitor is applied to only one side of the head, significant changes may be overlooked and/or correlation between SR-BIS and

SR-EEG may be poorer than expected. This was illustrated by a patient who had suffered a TBI resulting in intra-cranial hemorrhage at the left side of the head (patient 4). His EEG was asymmetrical and as SR-BIS was recorded over the right side, the correlation between SR-BIS and SR-EEG was low (0.64). In these and similar cases, the best option seems simultaneous application of two BIS monitors or making a “baseline” EEG to direct us to the right place to apply the BIS electrodes.

Barbiturate blood levels within the normal range corresponded with SR-EEG values ranging from 55 to 100, that is, with a brain that is electrically silent at least half of the time. Children with an iso-electric EEG (SR-EEG=100) had barbiturate blood levels ranging from 15 to 33. Apart from showing these children’s individual susceptibility to barbiturates, these findings confirm the results of Winer et al.[5] that blood levels are inappropriate to titrate barbiturates.

Our study has several limitations. First, although we managed to include most eligible patients presenting to our unit, group size is small due to the rare occurrence of barbiturate- induced coma. In this respect, it should be noted that our hospital serves as a level three PICU and regional trauma center (1100 admissions a year, reference area 4.10^6 inhabitants), implying that not many units will admit more patients requiring a barbiturate coma. In turn, this suggests that larger studies should be designed as multicenter projects.. Second, we did not monitor EEGs continuously, due to organizational limitations. This has significantly reduced the amount of available data.

Conclusion

Based on the experience gained from this pilot study, we suggest the following protocol to be used in future applications. First, a patient’s brain function needs to be evaluated using a full-channel EEG, combined with BIS monitoring, on an individual basis. This

combination should be employed to dose barbiturates and to familiarize all those involved in the relation between EEG patterns and visual display of BIS EEG trace in this particular patient. If the optimal dosage has been established, and if the corresponding EEG trace and concomitant BIS trace remain stable, a full-channel EEG once a day probably suffices to check and evaluate dosage and settings. A new EEG must be made upon significant changes in the EEG pattern of the BIS or the SR-BIS values, or upon changes in clinical situation or medication. Under these conditions, the additional advantages of continuous full-channel EEG do probably not outweigh the practical barriers for this modality. Of course, for objective evaluation of the safety and efficacy of barbiturate-induced comas in children larger prospective studies are required, combining pharmacokinetic and pharmacodynamic studies with continuous EEG and BIS monitoring.

Key messages:

1. BIS monitor provides continuous data on EEG suppression and potentially aids monitoring of barbiturate-induced coma in children.
2. An EEG must be made upon significant changes in EEG pattern, BIS or SR-BIS values, upon changes in clinical situation or medication.
3. Larger prospective studies are required, combining pharmacokinetics and pharmacodynamics with continuous EEG and BIS monitoring to determine the safety and efficacy of barbiturate induced comas in children.

List of abbreviations

BIS monitor = Bispectral Index Monitor.

GCSE = generalized convulsive status epilepticus.

EEG = electroencephalogram.

TBI = traumatic brain injury.

ICP = intracranial pressure.

P(S)ICU = pediatric (surgical) intensive care unit.

SR = suppression ratio.

Competing interests

The author(s) declare that they have no competing interests.

Authors contributions

Sandra A. Prins carried out the study, analysed and interpreted the data and drafted the manuscript .

Matthijs de Hoog participated in the design of the study and the interpretation of the data.

Joleen H. Blok participated in the interpretation of the data and helped to draft the manuscript.

Dick Tibboel conceived the study and participated in the design of the study.

Gerhard H. Visser participated in the design of the study and the management of the data.

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Figure legends

Figure 1. Scatter plot of SR-BIS versus SR-EEG for all 8 patients.

Figure 2. Scatter plots SR-BIS versus SR-EEG for individual patients during burst suppression.

Figure 3. Effect of synchronization. For patient 6, correlation between SR-BIS and SR-EEG in one EEG was poor (-0.003). After they were synchronized, moving the SR-BIS values 5 minutes back in time, the correlation improved to 0.92.

Figure 4. Burst suppression pattern with short-duration bursts in patient 3. The SR-BIS algorithm yields a value that represents an underestimate of the true EEG suppression.

Table 1 Patient characteristics

Patient	Age	Sex	Diagnosis	Outcome*	Medication other than pentobarbital	Duration barbiturate coma	Max. barbiturate blood level
1	4 months	Boy	GCSE after asphyxia	P	Midazolam Valproic acid	9 days	20 mg/l; day 2
2	3 years	Boy	GCSE due to Lennox-Gastaut syndrome	M	Lamotrigine Topiramate Valproic acid	3 days	37 mg/l; day 3
3	3.5 years	Girl	GCSE due to viral encephalitis	D	Midazolam Carbamazepine Phenytoin Topiramate	14 days	70 mg/l; day 12
4	11 years	Boy	TBI; hit by baseball bat	D	Propofol	5 days	
5	12 years	Girl	GCSE next to mental retardation	D	Midazolam	2 days	193 mg/l; day 7
6	12 years	Boy	GCSE due to viral encephalitis	D	Valproic acid Midazolam	> 3 weeks	83 mg/l; day 6
7	15 years	Boy	TBI, hit by car	F	Midazolam Morphine Propofol Fentanyl	16 hours	54 mg/l; day 2
8	15 years	Boy	TBI, hit by car	M	Morphine	23 hours	47 mg/l; day 2

* *Outcome:*

D *death*

P *major neurological impairment*

M *minor neurological impairment*

F *full recovery*

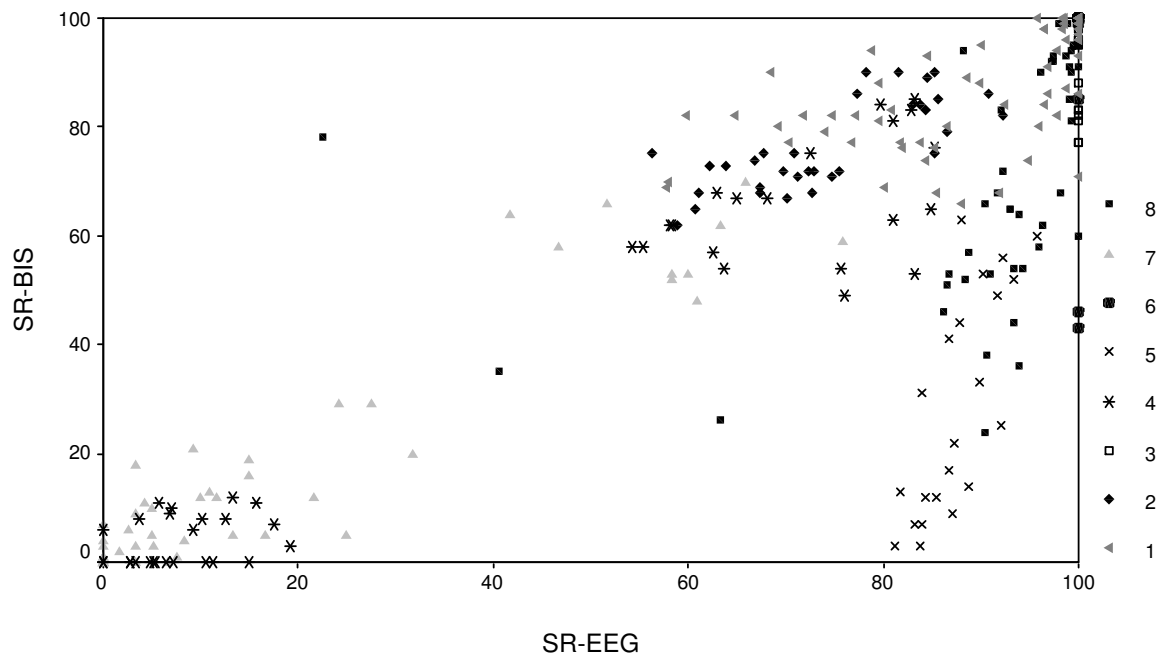


Figure 1

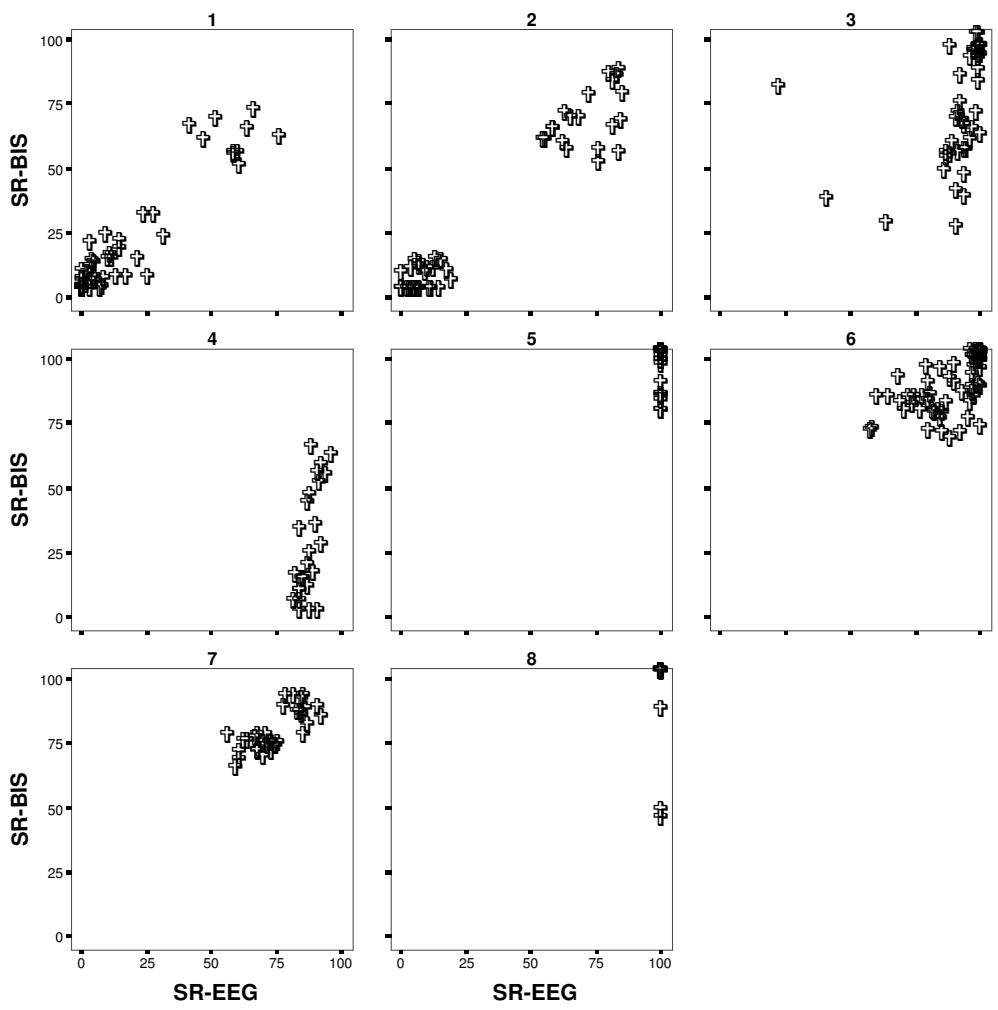
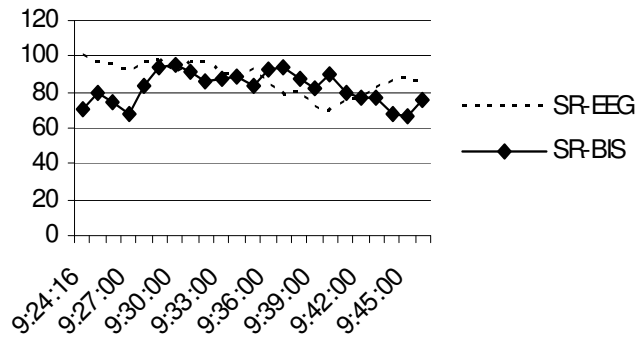
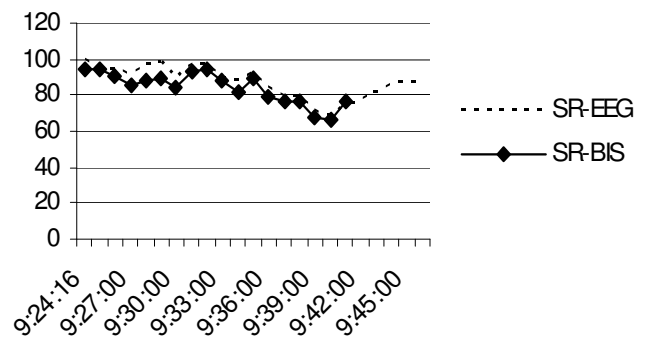


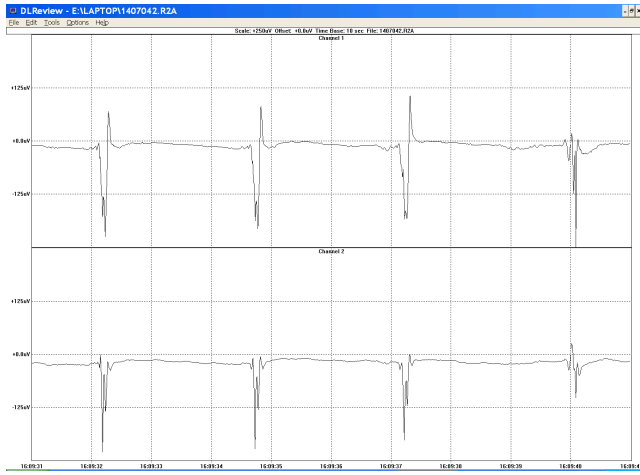
Figure 2



Before



After



SR-BIS = 70%



SR-EEG = 88%