Acute consciousness disorders in intensive care medicine – value of its grading for prognostic conclusion

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Abstract

OBJECTIVES: To understand consciousness we have to understand the mechanism of its function, which is to effectively organize sensory inputs from our environment. Consciousness is the basic, essential outcome of the process of organizing these sensory inputs, resulting in cognitive, mental, emotional, executive, instinctual or other marginally aware states. This reciprocal process of the CNS implies that organization is an act, which precedes consciousness, i.e. preconscious function. Most scientific explanations portray consciousness as an "emergent property" of classical computer-like activities in the brains neural networks. Doctors at ICU work daily with patients with altered human consciousness. Therefore, they must recognize and manage it skilfully and use adequate approaches for definite solutions. **MATERIAL AND METHODS:** We observed a series of patients with traumatic and non traumatic brain injuries admitted to the ICU. The quality of life of these patients during the course of intensive care was very elementary and the final outcome GCS (oGCS) for future life was defined as a comatose state or apallic state, very rarely was it restored to premorbid condition as far as lucidity, attention, cognition, and executive functions. **RESULTS:** We found that a significant oGCS increase in relation to condition at admission or intake GCS (iGCS) in the group with 184 patients total ($p<0.00001$), in cardio-pulmonary resuscitation (CPR), traumatic brain injury (TBI) subgroups ($p<0.00001$) and in spontaneous haemorrhage (SH) ($p<0.05$) represents the only basic prerequisite for further improvement. It is not easy to find good therapeutic approaches after traumatic and non traumatic brain injury. A statistically significant oGCS increase in relation to iGCS due to quite intense medical care and keeping disclosed the state of unconsciousness with further probable evolution through the following possible ways: death in fluent comatose state, delirium and awakening, delirium ending in death, direct awakening from comatose state. Therefore significantly increased oGCS is the only basic prerequisite for pragmatically optimal "quality of life" in the course of later life. **CONCLUSION:** We raise general questions for both scientists and clinicians that will assist in their efforts to understand the basic endogenous conscious biological processes, their pathological changes and the links between them.

ORIGINAL ARTICLE

INTRODUCTION

Human consciousness is one of the principal properties of the human brain, a highly evolved system; it must therefore have a useful function to perform (Crick & Koch 1992; 1995). It is a state that defies definition, but which may involve: thoughts, sensations, perceptions, moods, emotions, feelings, dreams, and an awareness of self, although not necessarily all of these. Consciousness is a puzzling state dependent property of certain types of complex, adaptive systems. The best example of one type of such system is a healthy and attentive interacting human brain. Crick and Koch (1998) assumed that the function of the neuronal correlate of consciousness (NCC) is to produce the best current interpretation of the environment in the light of past experience and to make it available. The NCC are the minimal (minimal, since it is known that the entire brain is sufficient to give rise to consciousness) set of neurons and structures, most likely distributed throughout certain cortical and subcortical areas, whose firing directly correlates with the perception of the subject at the time. These structures are synchronized action potentials in neocortical pyramidal neurons – sufficient for a specific conscious perception or conscious (explicit) memory. Most scientific explanations portray consciousness as an "emergent property" of classical computer-like activities in the brain's neural networks. Consciousness must be the product of neural activity. An understanding anatomic structures necessary to maintain consciousness is required. Clinical observations suggest that the lesions of specific structures of the brain may lead to specific malfunction of consciousness, therefore, consciousness must be the product of neural activity.

Consciousness is normally controlled by different parts of the brain. These systems keep a person alert and aware of himself and his environment.

According to Hameroff (2010), consciousness is generally considered to emerge from microtubules and synaptic computations among the brain neurons and are "orchestrated" by neuronal/synaptic input (objective reduction-OR) mechanisms. Quantum effects mediated by endogenous London forces in hydrophobic pockets of select neural proteins may be necessary for consciousness. Gamma synchrony involves gap junctions, or electrical synapses – direct open windows between adjacent cells formed by paired collars consisting of classes of proteins called connexions. Gap junctions occur between: brain neuronal dendrites, between axons and axons, between neurons and glia, between glia, and between axons and dendrite – bypassing chemical synapses and electrically coupling neuronal depolarization.

Consciousness is defined by two fundamental elements: awareness and arousal.

The use of Bispectral analysis (BIS) in the ICU allows for monitoring and analysis of direct brain wave signals (sleeping or conscious). It measures the brain activity 2000 times a second. The BIS monitor works by monitoring a single channel EEG signal from the patient's frontal lobe. This signal is converted to a number, with 100 being completely awake and with lower numbers representing the change of consciousness. The number 40–60 is most suitable for surgical operation. Signs and symptoms will depend on how bad the patient's consciousness is affected (Fatovich *et al.* 2006).

Disorders of consciousness are conditions where the state of lucidity-clearance, i.e. confusion of consciousness, dispersed attention, awareness is disturbed. This may range from mild confusion (cannot think clearly) to being totally unconscious (passed out).

1. The first, and by far the most serious, stage in the disorders of consciousness is that of coma; a state of profound (deep) unconsciousness in which the person is unable to move, open his/her eyes, or respond appropriately in any way to external stimulation. Coma is a state of profound unresponsiveness, usually the result of a severe brain injury (traumatic or non traumatic cause). Comatose patients typically lie with eyes closed and cannot be roused to respond appropriately to vigorous stimulation (Brown *et al.* 2010). Coma is a sleep-like state of unconsciousness. The patient does not respond or cannot be awakened by any stimuli, such as voice, light touch, or pain.
2. Delirium is a neuropsychiatric syndrome of disordered consciousness whose hallmark impaired attention – that is, it represents acute failure of the brain. Delirium is not a disease but a syndrome with multiple causes that result in a similar constellation of symptoms. It is defined as a transient, usually reversible cause of cerebral dysfunction and is manifested clinically by a wide range of neurologic-psychiatric abnormalities. Core features of delirium include disordered attention, altered consciousness, global disturbances of cognition, fluctuating course with a rapid onset, perceptual abnormalities with evidence of a physical cause, psychomotor disturbances (hypo- or hyperactivity), disturbances of the sleep/wake cycle (insomnia, daytime drowsiness, disturbing dreams or nightmares), emotional disturbances (depression, anxiety or fear, irritability, euphoria, apathy), or wandering in perplexity. Delirium is often unrecognized or misdiagnosed, commonly mistaken for dementia, depression, or a reflection of old age (older patients are expected to get confused in the hospital). Delirium, or a state of acute confusion, is a transient global disorder of attention and consciousness. Delirium results from a wide variety of structural or physiologic insults (Cole 2004). There are provocative and causative factors of delirium: delirium due to a general medical condition or general or regional anaesthesia (surgical delirium), substance-intoxication delirium, substance-withdrawal delirium, delirium due to multiple aetiologies, and delirium not otherwise specified. Other factors associated with a delirium state include use

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of a bladder catheter, use of physical restraints, any iatrogenic event, malnutrition, or use of 3 or more medications. Dementia is one of the strongest, most consistent risk factors underlying delirium, occurring in 25% to 50% of cases of delirium. The presence of dementia increases the risk of delirium by 2 to 3 fold (Sániová & Drobný 2009).

Delirium has been reported in approximately 40% of patients admitted to intensive care units (Pandharipande *et al.* 2006). The incidence of delirium after general surgery is 5% to 10%. In patients experiencing near death, up to 80% develop delirium. Delirium usually occurs as an acute, fluctuating condition during the first postoperative days. The patient loses orientation and has impaired attention and cognition. The incidence of delirium is approximately 10% in elderly patients but is much higher in elderly patients after cardiac procedures or surgery for hip fractures (Marcantonio *et al.* 1998; 2001).

The causes of delirium can be divided into predisposing and precipitating factors. Predisposing factors include: advanced age; any brain impairment (e.g. stroke; dementia; traumatic brain injury, infection,) a history of delirium; chronic medical problems; and impaired vision or hearing. The other factors include: recent surgery and exposure to anaesthesia; acute medical problems; and medications.

Alertness is mediated by the reticular activating system (RAS), which ascends from the brainstem through the thalamus to both hemispheres; attention is subserved by inputs to this system from the neocortex and the limbic system. Theoretically, therefore, any structural deformation of these fibres could result in the disordered alertness and attention observed in delirious patients. Because the RAS is a cholinergic system, a decrement in acetylcholine could compromise the normal functioning of this arousal network. These anatomical and chemical hypotheses are consistent with the clinical recognition of anticholinergic deliria, which occur after deliberate overdoses or therapeutic use of any agent with substantial anticholinergic properties (e.g. tricyclic antidepressants diphenhydramine, and some neuroleptic medications).

Another theory posits that delirium represents a hyperdopaminergic state. In animals, stress enhances dopamine output in the mesocortical and mesolimbic tracts. It is postulated that the stress associated with surgery and with critical medical illness in humans may do the same. This hypothesis coincides squarely with the efficacy of dopamine-blocking drugs in the treatment of delirium. These anticholinergic and hyperdopaminergic theories of delirium can be considered complementary, rather than competing, hypotheses.

Acute brain dysfunction or delirium occurs in the majority of mechanically ventilated medical intensive care unit (ICU) patients and is associated with increased mortality. Unfortunately, delirium often goes undiagnosed as health care providers fail to recognize in particular the hypoactive form that is characterized by depressed consciousness without the positive symptoms such as agitation. Recently, clinical tools have been developed that help to diagnose delirium and determine the subtypes. Their use, however, has not been reported in surgical and trauma patients. The objective of this study was to identify the prevalence of the motoric subtypes of delirium in surgical and trauma ICU patients.

Treatment of the disorders of consciousness depends on the cause of the disorder of consciousness. The primary clinical objective after severe brain trauma is to prevent secondary injury, a common sequel to the primary, mechanical impact. The concept is to prevent cerebral hypoxia by maintaining sufficient oxygen delivery to meet the oxidative metabolic needs of the intracranial neural tissues. This implies that cerebral blood flow, arterial oxygen saturation, and hemoglobin concentration in a specific patient need to be adequate. The consequences after brain damage depend on the severity of ischemia and reperfusion, and include: cellular energy failure (abolished ATP production), oxidative stress resulting from reactive oxygen species (ROS), exacerbation of excitotoxicity through impaired calcium buffering, activation of arachidonic acid cascades due to phospholipid peroxidation resulting in an MDA level increase, cytoplasmic swelling, protein oxidation, and finally, DNA damage, and in both cases either necrosis or apoptosis.

MATERIALS AND METHODS

The total group of 184 patients, average age 57.88 yrs (male 136, female 48), were included in an open clinical trial (see Table 1).

The Glasgow Coma Scale (GCS) as a clinical state criterion for grading unconsciousness was assessed before admission to the ICU (iGCS). In the trial, we aimed for outcome GCS (oGCS) as a basic presumption for this group's subsequent quality of life.

All patients with traumatic and non traumatic brain injury admitted between January 1, 2010 and July 31, 2011 to the Department of Anaesthesiology and Intensive Care Medical University Hospital in Martin were included in the series.

Tab. 1. Absolute and relative frequencies of patients and average age with respect to sex.

	GENDER		Grand Total
	Male	Female	
Number of Patients	136	48	184
Percentage	73.91%	26.09%	100.00%
Average Age	55.49	64.63	57.88

Inclusion criteria

Inclusion criteria were the following: age over 18 years, comatose state and ventilation support. There were three cohorts according to diagnostic conclusion (Tables 2–4).

a. traumatic brain injury (TBI) – closed head injury reports the number of patients and average age.
b. spontaneous haemorrhage (SH)
c. cohort after cardio-pulmonary resuscitation (CPR)

The ancillary neurologic investigation at admission was moreover characterized by a semi-quantitative grading state of consciousness as intake-Glasgow Coma Scale (iGCS). Primary hospital data included history parameters, data about somatic state, results of other ancillary investigations and all medical treatment procedures. At all times, vital parameters, blood pressure, SaO_2, heart rate, and $ETCO_2$, were measured using accessible equipment. Patients with a GCS 3 (deeply comatose) and non-reactive dilated pupils at admittance were also included. We determined the number of patients with oGCS >9 with respect to appearance of delirium (n=43) in relation to particular oGCS in the range between 9–15 (see results). A low oGCS grade (below grade 9) was not a required condition for delirium.

Tab. 2. Traumatic brain injury subgroup.

TBI subgroup	GENDER		Grand Total
	Male	Female	
Number of Patients	63	12	75
Percentage	84.00%	16.00%	100.00%
Average Age	51.46	53.83	51.84

Tab. 3. Spontaneous haemorrhage subgroup.

SH subgroup	GENDER		Grand Total
	Male	Female	
Number of Patients	29	12	41
Percentage	70.73%	29.27%	100.00%
Average Age	57.21	63.42	59.02

Tab. 4. After cardio-pulmonary resuscitation subgroup.

CPR subgroup	GENDER		Grand Total
	Male	Female	
Number of Patients	44	24	68
Percentages	64.71%	35.29%	100.00%
Age Average	60.14	70.63	63.84

RESULTS

This study is presented within the following embedded tables, charts, contingency tables, and histograms. The structure of the observed sample is expressed in absolute frequencies according to iGCS level (number of patients in rows) and oGCS level (number of patients in columns) and given in the following contingency Table 5.

Figure 1 is XY chart used to graph paired data. The variable X is oGCS and the Y variable is iGCS of a given patient. As the parametric t-test of difference between oGCS and iGCS population means requires a pair of random samples whose differences are approximately normally distributed, which was not approved by nei-

Tab. 5. Absolute patient frequencies according to iGCS (rows) and according to oGCS (columns).

Absolute patient frequencies															
Number of Patients	GCS Outcome														
GCS Intake	3	4	5	6	7	8	9	10	11	12	13	14	15	Grand Total
3	85	12	11	6	5	2	2	4	3	3	4	10	12	159
4	4	1		1		1							1	8
5		1							1					2
6	2													2
7	2		1						1					4
8	1		1											2
9	1		1											2
10					1								1	2
12										1				1
13												1		1
15												1		1
Grand Total	95	14	14	7	6	3	2	4	5	4	4	12	14	184

t-Test: Paired Two Sample for Means		
	GCS Admission	GCS Outcome
Mean	3.548913043	6.032608696
Variance	3.210709195	18.53444999
Observations	184	184
Pearson Correlation	0.162716614	
Hypothesized Mean Difference	0	
Df	183	
t-Stat	–7.681826944	
p(T<=t) one-tail	4.59191E–13	
t Critical one-tail	1.653222803	
p(T<=t) two-tail	9.18382E–13	
t Critical two-tail	1.973011915	

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ther Kolmogorov-Smirnov nor Pearson's chi square goodness-of-fit test, we applied also Wilcoxon test as a nonparametric alternative to the t-test. In the total group of patients (n=184) both, the paired t-test of the difference between population means and Wilcoxon signed rank nonparametric test of significance of the difference between population distribution of the two samples consisting of matched pairs, i.e. iGCS and oGCS of the same patient gave the following results:

Wilcoxon Signed Rank Test Statistic = 491.5000
Correction for Ties = 298.5000
Asymptotic without Continuity Correction:
Z-Statistic = 6.7958
Two-Tail Probability <0.00001
Asymptotic with Continuity Correction:
Z-Statistic = 6.7940
Two-Tail Probability <0.00001

Therefore, we can conclude the statistical significance of higher oGCS than iGCS (probability distribution for oGCS is shifted to the right, i.e. to the higher values).

The structure of the sample specified for each diagnosis CPR, SH, TBI is given separately in three successive contingency Tables 6–8. A similar result was obtained in the sub-groups CPR (p<0.00001), TBI (p<0.0001) and SH with the lowest level of significance in the SH sub-group (p<0.05).

The parametric paired t-test of the difference between population means and Wilcoxon signed rank nonparametric test of significance of the difference between population distribution of the two samples consisting of matched pairs, i.e. iGCS and oGCS of the same patient with CPR diagnosis, had the following results (Table 6):

Wilcoxon Signed Rank Test Statistic = 3.0000
Correction for Ties = 15.2500
Asymptotic without Continuity Correction:
Z-Statistic = 4.8935
Two-Tail Probability <0.00001
Asymptotic with Continuity Correction:
Z-Statistic = 4.8841
Two-Tail Probability <0.00001

Therefore, we can conclude the statistical significance of higher oGCS than iGCS for patients with CPR diagnosis (probability distribution for oGCS is shifted to the right, i.e. to the higher values).

The parametric paired t-test of the difference between population means and Wilcoxon signed rank nonparametric test of significance of the difference between population distribution of the two samples consisting of matched pairs, i.e. iGCS and oGCS of the same patient with SH diagnosis, gave the following results (Table 7):

Wilcoxon Signed Rank Test Statistic = 47.0000
Correction for Ties = 4.2500
Asymptotic without Continuity Correction:
Z-Statistic = 2.387
Two-Tail Probability = 0.0170 <0.05
Asymptotic with Continuity Correction:
Z-Statistic = 2.3696
Two-Tail Probability = 0.0151 <0.05

Therefore, we can conclude the statistical significance of higher oGCS than iGCS for patients with SH diagnosis (probability distribution for oGCS is shifted to the right, i.e. to the higher values).

Tab. 6. Absolute patient frequencies in CPR subgroup according to iGCS (rows) and according to oGCS (columns).

CPR subgroup												
Number of Patients	oGCS											
iGCS	3	4	5	6	8	9	10	11	13	14	15	Grand Total
3	36	4	3	3	1	1	2		2	6	7	65
4	1				1							2
5								1				1
Grand Total	37	4	3	3	2	1	2	1	2	6	7	68

t-Test: Paired Two Sample for Means		
	iGCS	oGCS
Mean	3.058823529	6.338235294
Variance	0.086040386	21.89881475
Observations	68	68
Pearson Correlation	0.083149214	
Hypothesized Mean Difference	0	
Df	67	
t-Stat	–5.79769074	
p(T<=t) one-tail	9.93384E–08	
t Critical one-tail	1.667916114	
p(T<=t) two-tail	1.98677E–07	
t Critical two-tail	1.996008354	

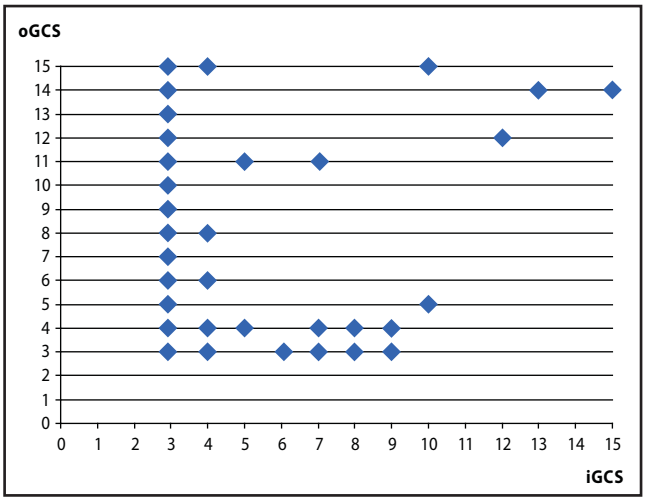

Fig. 1. Dependence of oGCS and iGCS in the total group.

Tab. 7. Absolute patient frequencies in SH subgroup according to iGCS (rows) and to oGCS (columns)

SH sungroup											
Number of Patients	GCS Outcome										
GCS Admission	3	4	5	6	7	12	13	14	15	Grand Total
3	19	2	2	1	2	1	1	3	2	33
4		1								1
5		1								1
6	1									1
7			1							1
8	1									1
10					1					1
13								1		1
15								1		1
Grand Total	21	4	3	1	3	1	1	5	2	41

Tab. 8. Absolute patient frequencies in TBI subgroup according to iGCS (rows) and to oGCS (columns).

TBI subgroup															
Number of Patients	oGCS														
iGCS	3	4	5	6	7	8	9	10	11	12	13	14	15	Grand Total
3	30	6	6	2	3	1	1	2	3	2	1	1	3	61
4	3			1									1	5
6	1													1
7	2								1					3
8			1											1
9	1		1											2
10													1	1
12										1				1
Grand Total	37	6	8	3	3	1	1	2	4	3	1	1	5	75

t-Test: Paired Two Sample for Means		
	GCS Admission	GCS Outcome
Mean	4.073170732	6
Variance	7.519512195	19.45
Observations	41	41
Pearson Correlation	0.308014839	
Hypothesized Mean Difference	0	
Df	40	
t-Stat	–2.79254823	
p(T<=t) one-tail	0.00399152	
t Critical one-tail	1.83851013	
p(T<=t) two-tail	0.007983041	
t Critical two-tail	2.02107539	

t-Test: Paired Two Sample for Means		
	GCS Admission	GCS Outcome
Mean	3.706666667	5.773333333
Variance	3.399279279	15.33981982
Observations	75	75
Pearson Correlation	0.162836041	
Hypothesized Mean Difference	0	
df	74	
t-Stat	–4.42126154	
p(T<=t) one-tail	1.65457E –05	
t Critical one-tail	1.665706893	
p(T<=t) two-tail	3.30914E–05	
t Critical two-tail	1.992543495	

The parametric paired t-test of the difference between population means and Wilcoxon signed rank nonparametric test of significance of the difference between population distribution of the two samples consisting of matched pairs, i.e. GCS admission and GCS outcome of the same patient with TBI diagnosis, gave the following results (Table 8):

Wilcoxon Signed Rank Test Statistic = 154.5000
Correction for Ties = 31.8750
Asymptotic without Continuity Correction:
Z-Statistic = 3.9824
Two-Tail Probability <0.0001
Asymptotic with Continuity Correction:
Z-Statistic = 3.9765
Two-Tail Probability <0.0001

Therefore, we can conclude the statistical significance of higher oGCS than iGCS for patients with TBI diagnosis (probability distribution for oGCS is shifted to the right, i.e. to the higher values).

If we consider only the patients with a GCS outcome greater than or equal to 10, the analysis of this sub sample can be expressed by contingency Table 9 and by contingency graph in Figure 2 as follows respectively.

Absolute frequencies for patients with oGCS greater than 9 with respect to appearance of delirium are summarized in the contingency table (Table 12*)* and in contingency Figure 3 as well.

Implementation of the Pearson Chi-square test did not detect a significant statistical dependence of GCS outcome and delirium (χ^2=6.98, df=5, p=0.2297).

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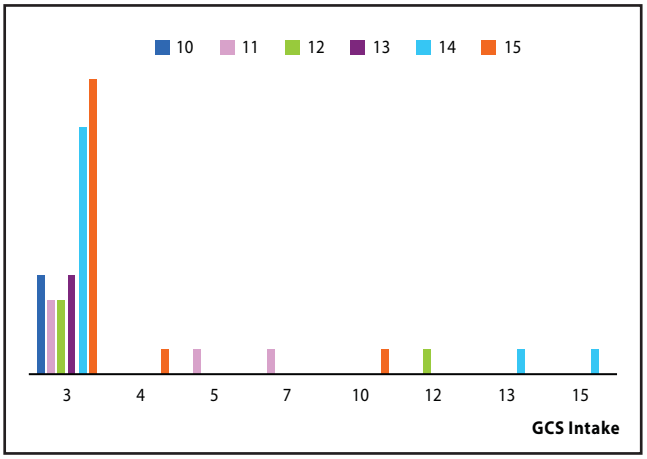

Fig. 2. Patients with distribution of oGCS equal or greater than 10.

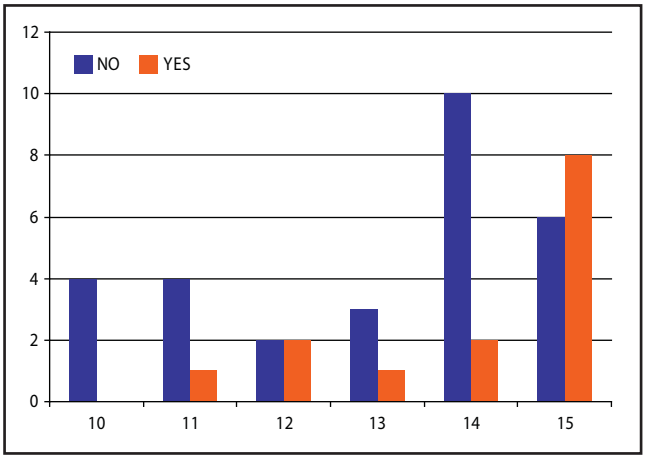

Fig. 3. Frequencies for patients with oGCS greater than 9 with respect to delirium appearance.

Tab. 9. Patients with distribution of oGCS equal or greater than 10.

Number of Patients	GCS Outcome						
GCS Intake	**10**	**11**	**12**	**13**	**14**	**15**	**Grand Total**
3	4	3	3	4	10	12	36
4						1	1
5		1					1
7		1					1
10						1	1
12			1				1
13					1		1
15					1		1
Grand Total	**4**	**5**	**4**	**4**	**12**	**14**	**43**

Tab. 10. Delirium appearance in oGCS intervals 10–12 and 13–15.

	DELIRIUM		
GCS Outcome	**NO**	**YES**	**Grand Total**
10–12			
Number of Patients	10	3	13
Percentage	23.26%	6.98%	30.23%
13–15			
Number of Patients	19	11	30
Percentage	44.19%	25.58%	69.77%
Total Number of Patients	**29**	**14**	**43**
Total Percentage	**67.44%**	**32.56%**	**100.00%**

Tab. 11. Delirium appearance in particular oGCS grades in the level 10 or more.

	DELIRIUM		
GCS Outcome	**NO**	**YES**	**Grand Total**
10			
Number of Patients	4		4
Percentage	9.30%	0.00%	9.30%
11			
Number of Patients	4	1	5
Percentage	9.30%	2.33%	11.63%
12			
Number of Patients	2	2	4
Percentage	4.65%	4.65%	9.30%
13			
Number of Patients	3	1	4
Percentage	6.98%	2.33%	9.30%
14			
Number of Patients	10	2	12
Percentage	23.26%	4.65%	27.91%
15			
Number of Patients	6	8	14
Percentage	13.95%	18.60%	32.56%
Total Number of Patients	**29**	**14**	**43**
Total Percentage	**67.44%**	**32.56%**	**100.00%**

Also, other tests of significance (Phi, Cramer's and contingency coefficient) and measures of association (Somers' Delta, Goodman-Kruskal's Gamma, Kendall's Tau-b and Tau) support a statistical null hypothesis that GCS outcome level is statistically independent of delirium appearance:

Somers' Delta (col) = –0.3768
Somers' Delta (row) = –0.2131
Goodman-Kruskal's Gamma = –0.4679
Kendall's tau b = –0.2834
Kendall's tau c = –0.331

Tab. 12. Frequencies for patients with oGCS greater than 9 with respect to delirium appearance.

Number of patients	DELIRIUM		
GCS Outcome	**NO**	**YES**	**Grand Total**
10	4		4
11	4	1	5
12	2	2	4
13	3	1	4
14	10	2	12
15	6	8	14
Grand Total	**29**	**14**	**43**

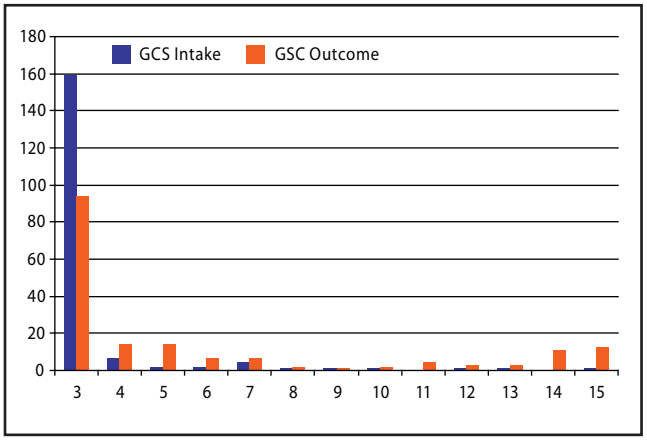

Fig. 4. iGCS and oGCS values distribution in 184 patients.

Distribution of GCS intake values (iGCS) and GCS outcome (oGCS) values of 184 patients is charted in Figure 4.

Distribution of iGCS values and oGCS values of selected 43 patients with oGCS greater than 9 is charted in the Figure 5

Comparison of pairs of values, iGCS and oGCS of each from the selected 43 patients with oGCS greater than 9, is in the Figure 6.

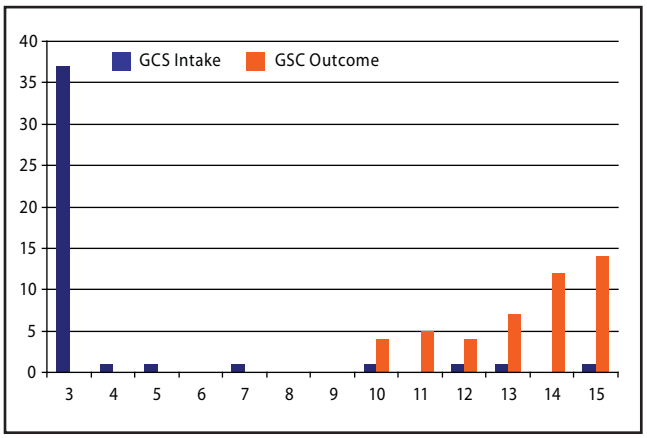

Fig. 5. Distribution of iGCS values and oGCS values of selected 43 patients with GCS outcome greater than 9.

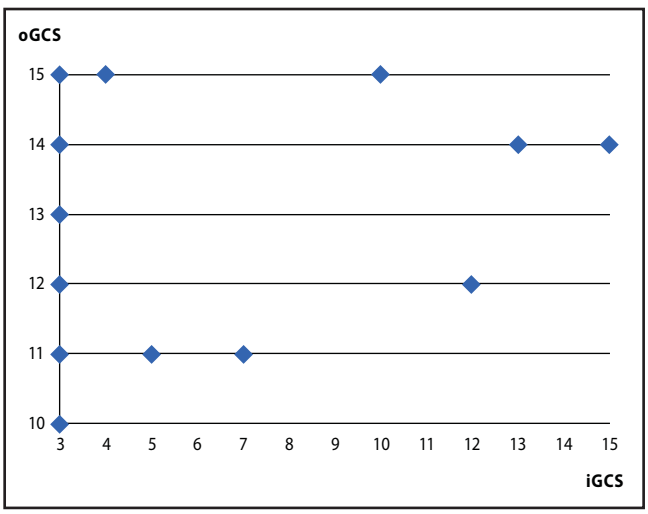

Fig. 6. Dependence of oGCS on iGCS for oGCS >9.

DISCUSSION

The Glasgow Coma Scale, which measures a patient's ability to respond to verbal, sensory, and motor stimulation, can be used to evaluate and monitor trends in the patient's level of consciousness (LOC) (Teasdale & Jennett 1974).

The Glasgow Coma Scale (GCS) was developed to describe consciousness level in traumatically head injured (TBI) patients. It measures the best eye, motor and verbal responses, and is a widely used and accepted prognostic score for both traumatic and non traumatic altered consciousness levels (Crick & Koch 1992). The group of traumatic brain injury represents 27% of the total amount of admitted patients to the ICU (Sániová & Drobný 2011).

Our open clinical study's main aim was to compare iGCS and oGCS mutually and oGCS values to evaluate them in relation to delirium appearance. We found that there is no statistically significant relation between grade of oGCS and delirium appearance. These two variables are in our series mutually independent. Elevation of oGCS in relation to iGCS is statistically significant but it does not currently indicate a significant risk for delirium. However, delirium is partly a risk, but partly a marker of a patient's revival. Elevation of oGCS is simply a marker of arousal in unconscious patients and it does not imply optimal final outcome from the ICU but only a basic prerequisite for further possible improvement of brain stem vital function. A further degree of CNS function restoration depends upon the following genetically transmitted human brain properties or treatment quality:

- Neuroplasticity
- Neurotrophicity
- Neuroprotection

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These are the most important biological processes that act together under genetic control to generate endogenous defensive activity (EDA) which attempts to counteract pathophysiologic processes (Sániová & Drobný 2011). We obtained the following statistical results testing total group iGCS versus oGCS ($p<0.00001$) in sub-groups of CPR iGCS versus oGCS ($p<0.00001$), TBI iGCS versus oGCS ($p<0.0001$) and SH with the lowest level of significance in the sub-group iGCS versus oGCS ($p<0.05$)

If we take into account the favourable preliminary results according to oGCS increase relating to the iGCS the total group of patients together with CPR have the best prognostic forecast, in comparison to TBI and SH respectively. The worst early prognosis was characterized by the SH sub-group in many epidemiologic stroke studies. In the SH-sub-group the lowest oGCS increase in early stage after onset of SH-stroke signifies a definite fatal prognosis. During the first hours after TBI, catecholamine levels in cerebral spinal fluid are increased, but production consistently decreases thereafter. Decreased dopaminergic stimulation leads to impaired neurologic function. pharmacologic enhancement of the dopaminergic system may stimulate nerve system restoration. Our experience in the TBI group with such dopaminergic stimulation by means of amantadine sulfate group = statistical significance ($p<0.05$) i.e. significantly higher vigilance was recorded in the active medication group compared to the placebo group. In the group of patients with severe brain injuries treated with standard therapy plus amantadine sulphate the outcome GCS was higher and the case fatality rate lower than in the group treated with standard therapy alone (Sániová & Drobný 2011). As an example, the circumstances of cardiopulmonary resuscitation (CPR) can affect prognosis after a cardiac arrest in terms of GCS, survival and quality of life. In spite of a higher average age of the CPR sub-group (CPR mean age = 63.84 years, SH mean age = 59.02 years, TBI mean age = 51.84 years) the early oGCS extreme increase undoubtedly influences our effort in such cases in the ICU. In one study of out of hospital cardiac arrest, 44 percent of patients receiving CPR survived initially, 30% were alive at 24 hours, 13% at one month, and only 6% were alive after 6 months (Berek *et al.* 1997; de Vos *et al.* 1999; Drake *et al.* 2006). In other studies, variables such as age >70, stroke or renal failure prior to admission, and recent congestive heart failure were associated with a worse prognosis, and factors such as a witnessed arrest and an initial rhythm of ventricular fibrillation or tachycardia have correlated with a better prognosis (Saklayen *et al.* 1995). We believe the increased GCS improved comatose states after traumatic and non-traumatic brain injury during the interval of intensive care (oGCS), which denotes a favourable forecast for survival. The favourable fate of such patients in the subgroup of 43 patients can be divided into the less favourable forecast with delirium (26 patients) and more favourable forecast (17 patients) without delirium. An increase of oGCS to a particular level within the interval 10–15 grade of GCS does not correlate with delirium appearance in the 43 patients of the subgroup.

A significantly higher oGCS relating to iGCS indicates the efficacy of intensive care management relating to lucidity of consciousness (arousal). Arousal means improvement of vital function control and better homeostasis maintenance.

CONCLUSION

Traumatic brain injury (TBI) in the new millennium represents a severe – "epidemic problem" for an industrial country. This epidemic problem brings not only loss of life, but also modification of the quality of life for this group of victims and an economic problem for their families. *Non traumatic brain injury* (SH, CPR) causes irreversible and fatal damage to part of the affected neurons, the reperfusion and readmission of oxygen that follows may also be detrimental.

We found that patients with severe brain injury treated with standard therapy plus amantadine sulphate had a higher outcome GCS and a lower mortality rate then patients treated with standard therapy alone (Sániová & Drobný 2004; 2006).

Among many neuroprotectants, amantadine sulphate PK-Merz represents a voltage-dependent NMDA antagonist whose efficacy was observed not only in the comatose state but also in agitated head injury patients (Chandler *et al.* 1988). Cytoprotective amantadine sulphate's action is focused on blocking the NMDA receptors rendering them passive and thus reducing disequilibrium between dopaminergic inhibition and glutamatergic stimulation not only in the basal ganglia, but also in reticular formation (RF) and allocortical neurocytes. Therefore, amantadine sulphate infusion has also proved effective in vigilance and drive disturbances (Sawyer *et al.* 2008).

Our preliminary results of ongoing trials have been encouraging and should become, in the near future, one important part of complex neuroprotective strategies, which provide an improved outlook for head injury victims. In our open clinical study we investigated patients treated with amantadine sulfate in coma and compared them to the control group. The results obtained demonstrate a higher quality of life of patients treated with amantadine sulfate. The results of our analysis underline the importance and contribution of the use of this drug in indicated cases in comatose states. Significantly, greater vigilance was recorded in the active medication group compared to the placebo group. Neurological outcome is a very important traumatic brain injury criterion for evaluating treatment efficacy. Early and focused treatment procedure administered for focal or global brain ischemia is also frequently directed to neurocyte protection by means of direct-acting dopamine

agonist – amantadine sulphate. This pathogenic mechanism will be of use namely in cerebrovascular high-risk traumaticaly injured persons acting towards secondary CNS disorder performance matters.

After closed head injury, there is a potent secondary damaging mechanism – mediated by excitotoxic amino acid overproduction.

Our results with significantly increased oGCS relating to iGCS indicate a good level of treatment and remaining in the ICU as a basic prerequisite for an unmitigated positive outcome for comatose patients.

We found, that patients with severe brain injury treated with standard therapy plus amantadine sulphate had higher outcome GCS and lower mortality then patients treated with standard therapy alone.

Neurological outcome is a very important traumatic brain injury criterion evaluating treatment efficacy. Early and focused treatment procedure administered for focal or global brain ischemia is also frequently directed to neurocyte protection by means of direct-acting dopamine-agonist amantadine sulphate.

In the near future, the use of novel drugs will be combined with up-to-date approaches to management for improved outcome.

Early prognostic criterion of comatose state consisting of increased iGCS to higher oGCS is the first forecasting platform in intensive care for traumatic or non-traumatic brain lesions underlying coma and delirium as one of the two basic scenarios due to brain failure.

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