The Effect of Methylphenidate on Attention in Acquired Brain Injury as Recorded by Useful Field of View

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KEY WORDS: acquired brain injury, traumatic brain injury, subarachanoid hemorrhage, methylphenidate, Useful Field of View.

Objectives: To assess the ability of the Useful Field of View (UFOV) test to measure change in attention of patients with acquired brain injury (ABI) when given methylphenidate in an inpatient rehabilitation unit.

Design: This study reviewed data from consecutive patients who were given methylphenidate while being monitored for visual processing speed, divided attention, and selective attention with the UFOV test. Changes in UFOV scores were also compared with changes in Functional Impairment Measures (FIM).

Patients: A series of 16 patients diagnosed with traumatic brain injury (n = 12) and subarachnoid hemorrhage (n = 4) were followed before and after taking methylphenidate, as a part of treatment for clinically identified attentional deficit.

Results: The introduction of methylphenidate correlated with an improvement in processing speed loss, divided attention loss, and selective attention loss on the UFOV test. Methylphenidate use was further correlated with improvement on FIM Cognition and FIM Activity of Daily Living subscales.

Conclusions: Methylphenidate use, in an inpatient population of patients with ABI, resulted in a significant improve-

ment in attention and divided attention, which can be measured by the UFOV. This change in attentional ability seems to correlate with improvement in the cognitive and the Activity of Daily Living subscales of the FIM.

INTRODUCTION

In the United States approximately 70,000 to 90,000 individuals incur acquired brain injury (ABI) every year, resulting in long-term substantial loss of functioning.[1] One of the intransigent and pervasive sequels of ABI is hypoattention. This is often seen as a serious barrier to the management, rehabilitation, and vocational adjustment of patients with ABI.[2] Impaired attentional functioning is likely to simulate or amplify other cognitive and emotional impairments, as well as intensify difficulties with activities of daily living.[3] The long-term outcome of patients with ABI is thought to be limited as much by hypoattention as by physical or other cognitive impairments.[4]

At present, the neuropsychological literature does not offer a clear account of which aspects of attention are most vulnerable to ABI[5] despite the fact that such information might shed some light on paths for appropriate strategies for rehabilitation. One reason for this lack of clarity is that clinicians and researchers do not have a sufficiently broad and efficient set of assessment tools with which to measure different forms of attention impairment.[2] With the rapid growth of outcome evaluation in this era of predictive medicine,[6] there is a need for comprehensive measurements and outcome tools that are clinically meaningful, easy to use, and valid in a wide variety of settings.

Ball et al[7] have operationalized the concept of attention in terms of the speed of processing, the ability to divide attention between central and peripheral targets, and the ability to detect stimuli embedded within a cluttered background. Such conceptualization has culminated into a visual field or useful field of view (UFOV) measurement tool. Although the UFOV is essentially designed to diagnose and measure the severity of attentional impairment among elderly motor vehicle drivers, its application has generally been found to be useful in a wide range of geriatric populations.[8,9] Numerous studies have established that UFOV is one of the best, and most consistent, indices of assessing motor vehicle accident risk among elderly drivers[10], suggesting ecological validity of the UFOV. More recently, it has also been employed for driving readiness in ABI populations.[11-15] These reports support the use of UFOV in ABI patients. However, it is more salient to clinicians to ask whether the UFOV test might be of benefit in the assessment of clinically relevant attention impairment in patients with ABI.

Both experimental and clinical reports have suggested that drugs with affinity to catecholaminergic neurotransmissions have a strong influence in modulating attention of both ABI patients[16] and children with attention deficit disorder.[17] It is plausible that injury to the brain, due to tearing and shearing, may compromise the integrity of the neuronal projections involved in attention.[18] In parallel with these observations, other studies have shown that various neurotransmission systems can be dramatically affected by brain injury.[19,20] It may be hypothesised from these findings that ABI disruption of catecholaminergic functioning may have consequences for goal-directed behaviour, with patients showing poor attention in a wide range of situations. Catecholamines, which include dopamine, noradrenaline, and adrenaline, are important neurotransmitters and hormones that regulate visceral functions, motor coordination, and arousal in adults.[21,22] Disruption of the

relevant circuitry involved in catecholaminergic transmission would have observable effects at the three levels of attention as detected with the UFOV; namely, processing speed, divided, and selective attention.

Several studies have reported a reversal of diminished attention with medications that release catecholamine (eg, amantadine, amphetamine, bupropion, methylphenidate, and selegiline) for attentional deficits following ABI.[23,24] As previous studies of the UFOV have suggested that the UFOV can provide a quick quantitative measure of attention and divided attention,[25] it would be useful to know whether the UFOV could be used to measure the influence of the catecholaminergic medications on this important index of cognition. In doing so, albeit indirectly, the usefulness of the UFOV in delineating attention deficits in the ABI population can be ascertained while using drugs with an affinity to catecholaminergic transmission as pharmacological challenge.[26] To our knowledge, there are no studies that have examined the effect of these compounds on the performance of the UFOV in an ABI population.

The present study was designed to test, using quantitative measures in a consecutive series of patients with attention impairment following ABI, whether treatment with methylphenidate, would increase a patient's UFOV score. If so, this would not only substantiate the reports available so far on the effect of methylphenidate on attention,[16] but it would the first study to examine the ability of the UFOV to quantify the effect of methylphenidate on specific measures of attention. As this study is also one of the first to apply the UFOV to an ABI patient population, in exploring these predictions, an essential part of this research is to gauge the clinical utility of this tool. The variations between field of view score before and after treatment with methylphenidate was used as measures of the treatment impact and, by implication, treatment validation.[26] As there are a paucity of studies examining how UFOV may affect day-to-day functioning,[27] this study also examined whether the fluctuations in the attentional abilities measured by the UFOV test would in tandem impact indexes of functional independence as measured with Functional Independent Measures (FIM).[28]

The specific aim of this pilot study is (1) to examine whether the UFOV can serve as a useful repeatable measure of an important cognitive variable during inpatient rehabilitation, (2) to examine whether improvement in attention occurs in tandem with improvement with Functional Independent Measure, the "gold standard" of functional outcomes assessment in medical rehabilitation, and (3) to examine whether attention impairment, as indexed by UFOV, is amendable to pharmacological intervention with methylphenidate.

METHODS

Design

The study sample consisted of inpatients with a single-incident brain injury receiving rehabilitation at the Spaulding Rehabilitation Hospital Brain Injury Unit, in Boston, Massachusetts. Patients identified clinically as manifesting pervasive inattention in therapy and activities of daily living, not obviously secondary to other medical and neurological conditions, were routinely considered for treatment with methylphenidate.

A series of 16 consecutive patients were assessed using identical single-case methodology; a repeated measure, multiple baseline, AAB Single Case Experimental Design.[29] As part of their routine clinical assessment, baseline assessments were conducted twice before initiating methylphenidate.

Baseline testing was initiated across a period of 14 to 21 days to establish that the patient's performance was stable and to evaluate the impact of possible practice effects. Methylphenidate was then introduced at doses of 5 mg twice per day to 10 mg twice per day. Patients were reassessed on one further occasion, after two weeks from medication initiation. Since this assessment was introduced as part of the clinical process, there were variations in the timing of the follow up UFOV testing. As the present study reports on clinically gathered data, there was no attempt to control for the heterogeneity of the sample of patients, the time since injury, or the etiology and loci of the brain injury. Staff and patients were therefore not blinded to the treatment condition.

As the respondents were required to give meaningful responses, the injuries of most of the patients were either mild or moderate in severity. It was not the aim of this study to directly investigate the relationship between clinical and demographic information and the assessment of attention; this will be the subject of a future study. We classified severity of injury according to the Glasgow Coma Scale (GCS).[30] A score of 13 to 15 was rated as mild, 9 to 12 was rated as moderate, and eight or less was rated as severe on the GCS.

DRUG REGIMEN

Methylphenidate is an amphetamine-like central nervous system stimulant that is believed to act by releasing dopamine and norepinephrine from catecholaminergic neurons. More details of the pharmacology of methylphenidate can be found in previous studies.[24,31] Methylphenidate is a preferred medication for improving cognitive functioning because of its rapid onset of action and relative short half life; however, the complete mechanism by which methylphenidate exerts its effect remains unknown.[31]

ASSESSMENT MEASURES

Useful Field of View (UFOV)

Useful field of view is an area of the visual field in which visual information can be acquired and processed without eye and head movement[10] using a visual attention analyzer (Visual Resources, Inc., Chicago Ill). As detailed elsewhere,[7,32] the primary factors are the length of time that the display is visible, the difficulty of the central vision task, the eccentricity of the peripheral target, and the presence or absence of clutter in the field. Performance is expressed as a function of 3 variables: the minimum target duration required to perform the central discrimination task (Processing Speed Loss, PSL), the ability to divide attention between central and peripheral tasks successfully (Divided Attention Loss, DAL), and the ability to filter out distracting stimuli (Selective Attention Loss (SAL). Performance in each of the 3 subtests is scaled from 0 to 30.[10] In addition, performance in the 3 subtests is non-independent because speed of processing is relevant to all 3 tests, and attention abilities are relevant to subtests 2 and 3. Performance in the overall useful field of view task is a composite score expressed as percent reduction (0%-90%) of a maximum 30 degrees field size (maximum field size of the test apparatus screen at the viewing distance). These assessments have been shown to compensate for practice effects.[7]

Functional Independent Measures

The functional assessment instrument included is in the Uniform Data Set for Medical Rehabilitation. It is composed of 18 items that are rated on a seven-level scale representing gradations from dependent (1) to independent (7) func-

Table 1. Clinical Information for Each Patient*

Patient	Age/Sex	Cause of injury	Time since injury in days	Maximum dosage
#1	18/M	Anoxic	150	10 mg twice per day
#2	37/F	SAH	30	5 mg twice per day
#3	44/F	SAH	60	10 mg twice per day
#4	74/M	SAH	90	10 mg twice per day
#5	45/M	SAH	16	10 mg twice per day
#6	75/F	SAH	60	10 mg twice per day
#7	19/F	TBI	120	5 mg twice per day
#8	72/M	TBI	80	5 mg twice per day
#9	30/M	TBI	25	5 mg twice per day
#10	60/M	TBI	90	10 mg twice per day
#11	51/M	TBI	30	5 mg twice per day
#12	19/M	TBI	180	10 mg twice per day
#13	40/M	TBI	50	5 mg twice per day
#14	33/M	TBI	45	5 mg twice per da
#15	38/M	TBI	36	10 mg twice per day
#16	18/M	TBI	27	10 mg twice per day

*F indicates female; M, male; TBI, traumatic brain injury; and SAH, subarachnoid hemorrhage.

tion. The three subsets of Functional Independence Measure (FIM)[28] that were analyzed were the Activities of Daily Living subscale (FIM Activity Daily Living; FIM items 1-6), Mobility subscale (FIM Mobility; FIM items 9-13), and Cognition subscale (FIM Cognition; FIM items 14-18). The use of FIM as a measure of a patients' functional status has been validated in the literature.[33] These procedures have been previously described.[34]

STATISTICAL ANALYSIS

StatXact 5 used for statistical analyses.[35] In the presentation of data below, scores are presented for the following occasions: two baseline assessments and the assessment two weeks after initiation of maximum methylphenidate doses. Friedman's[36] non-parametric test was used to test for differences between the assessment scores at baseline-one, BL1, baseline-two, BL2, and after the administration of methylphenidate, ME. Post-hoc procedures were used to find specific differences between BL1, BL2, and ME scores. A conservative probability level of 0.01 was adopted.

RESULTS

Table 1 presents patient's demographic and clinical details. Of the 16 patients receiving treatment, 12 were males and 4 were females with an age range from 18 to 75 (mean = 42.06 ± 19.85). In terms of ethnicity, 12 (75%) were European-American, 2 (12.5%) Asians, one was Hispanic, and the other was African American. Ten (62.5%) were single and six (37.5%) were married. The Glasgow Coma Scale scores were available for only 6 patients. Six patients (37.5%) were on antiepileptic medications prescribed as a prophylactic. There was no statistical difference in scores of UFOV and FIM in those subjects who were taking medication for seizures and those who were not. The *P* value for all the tests was greater than 0.042. Also there

Table 2. Friedman's Test Results*

	Friedman's Test		Post hoc BL1 to BL2		BL1 to ME		BL2 to ME	
	Chi-square	*P* value	*t*	*P* value	*t*	*P* value	*t*	*P* value
Processing Speed Loss	24.75	0.000	0.201	0.842	8.000	0.000	8.660	0.000
Divided Attention Loss	22.06	0.000	0.936	0.357	7.490	0.000	6.554	0.000
Selective Attention Loss	31.388	0.000	1.414	0.168	34.649	0.000	33.232	0.000
FIM Cognition	17.294	0.000	0.849	0.403	4.669	0.000	5.515	0.000
FIM Activity of Daily Living	23.333	0.000	5.883	0.000	8.825	0.000	2.942	0.006
FIM Mobility	0.059	0.971	0.118	0.907	0.118	0.907	0.235	0.816

*BL1 indicates baseline 1; BL2, baseline 2; and ME, methylphenidate.

was no significant difference between males and females. All the *P* values were also greater than 0.058. The number of days since injury range from 16 to 180 (mean = 68.06 ± 47.76). There was no relationship between the indexes of UFOV and duration since injury. The time from baseline 1 to baseline 2 ranged from 7 to 16 days (mean = 8.94 ± 3.36).

Useful Field of View

Processing Speed Loss (PSL)

The Friedman's test disclosed significant reversal in the PSL after the introduction of the methylphenidate ($\chi^2 = 24.75$, $P < 0.001$). Post hoc contrasts confirmed that there was no significant change across the baseline periods ($t = 0.201$, $P = 0.842$). However, there was a highly significant increase from BL2 to methylphenidate ($t = 8.66$, $P < 0.001$). Case-by-case inspection revealed that all patients showed improvement over this time period. Figure 1 graphically shows the mean loss score for UFOV processing speed for the BL1 was 9.50 and 9.31 for the BL2. The mean loss score during methylphenidate was reduced to 1.19. There was a dramatic decrease in the PSL, almost a 90% decrease.

Divided Attention Loss (DAL)

Figure 1 shows DAL for 16 patients across all assessment occasions. There was a significant difference between the occasions ($\chi^2 = 22.06$, $P < 0.001$). Post hoc contrasts confirmed no significant changes across the baseline period, but highlighted a significant increase after methylphenidate was introduced; BL2 to methylphenidate ($t = 6.55$, $P < 0.001$). Indeed, all 16 patients showed a decrease in DAL from BL2 to methylphenidate.

Selective Attention Loss (SAL)

Figure 1 shows stable baseline but increased selective attention upon intervention with methylphenidate. There was a significant difference between the levels of occasion ($\chi^2 = 31.39$, $P < 0.001$). Post hoc contrasts confirmed no significant changes across the baselines period ($t = 1.41$, $P < 0.168$) and highlighted a significant increase after methylphenidate was introduced (BL2 to methylphenidate; $t = 33.23$, $P < 0.001$). Indeed, all 16 patients showed a decrease in SAL from BL2 to methylphenidate.

Functional Independent Measures

There were general improvements in the functional independence measures. Table 2 shows the detailed results of the comparisons. Figure 2 displays the relative improvement in Cognition and Activity of Daily Living subscale and no improvement in Mobility subscale.

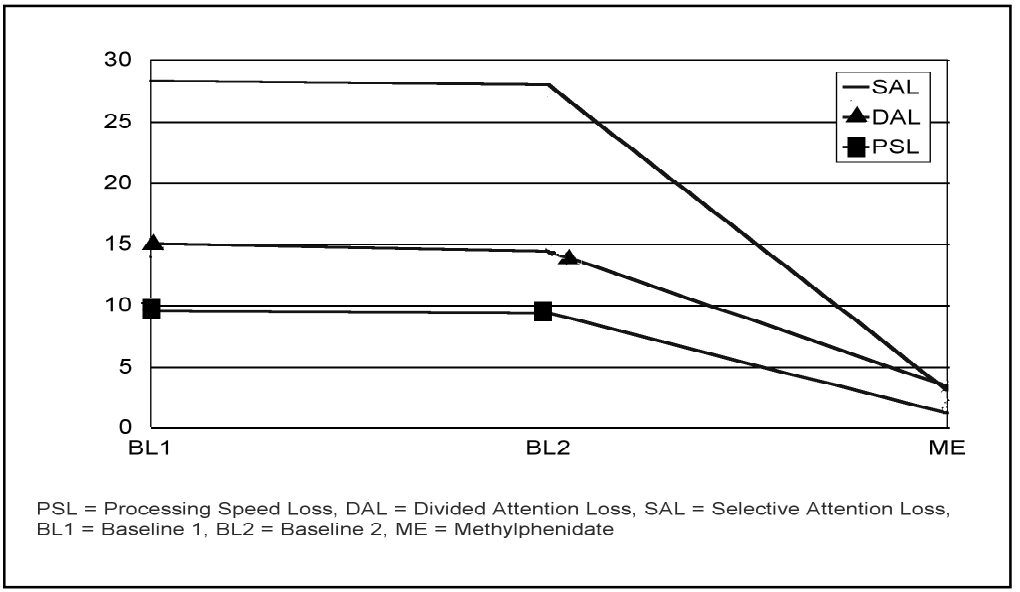

Figure 1. Useful Field of View—Indexes of attention across assessment occasions.

FIM Cognition

The Friedman's test did disclose significant difference for FIM Cognition subscale ($\chi^2 = 17.294$, $P < 0.001$). Post hoc contrasts confirmed that there were no significant changes across the baseline periods ($t = 0.849$, $P = 0.403$). However, there was highly significant increase in FIM Cognition score from BL2 to methylphenidate ($t = 5.515$, $P = < 0.001$). Case-by-case inspection revealed that 80% of the patients showed improvement.

FIM Activity of Daily Living

Friedman's test did disclose significant differences for FIM Activity of Daily Living ($\chi^2 = 23.333$, $P < 0.001$). Post hoc contrasts showed that the two baseline measures were not stable ($t = 5.883$, $P < 0.001$). There was a significant increase in the FIM Activity of Daily Living score from BL2 to methylphenidate ($t = 2.942$, $P < 0.006$), suggesting that pharmacological intervention did have a significant impact on the patients' activity of daily living. However, in the light of unstable baseline, such increment cannot be solely attributed to the drug intervention.

FIM Mobility

Friedman' test did not disclose main effects of occasion for FIM Mobility ($\chi^2 = 0.059$, $P = 0.971$). Post hoc contrasts confirmed that there were no significant changes across the baseline periods ($t = 0.118$, $P = 0.907$). Also, there was no significant increase in FIM Mobility score from BL2 to methylphenidate ($t = 0.235$, $P = 0.816$), suggesting the drug did not impact the indexes of Mobility.

DISCUSSION

As there is growing literature stressing the importance of accurately determining patients' level of cognitive functioning and its role in appropriate rehabilitation and long-term management, rehabilitation specialists often need a rapid and reliable way of checking whether patients are suffering from attention impairment; and if so, determining how severe is this impairment.[13,37] UFOV has been specifically

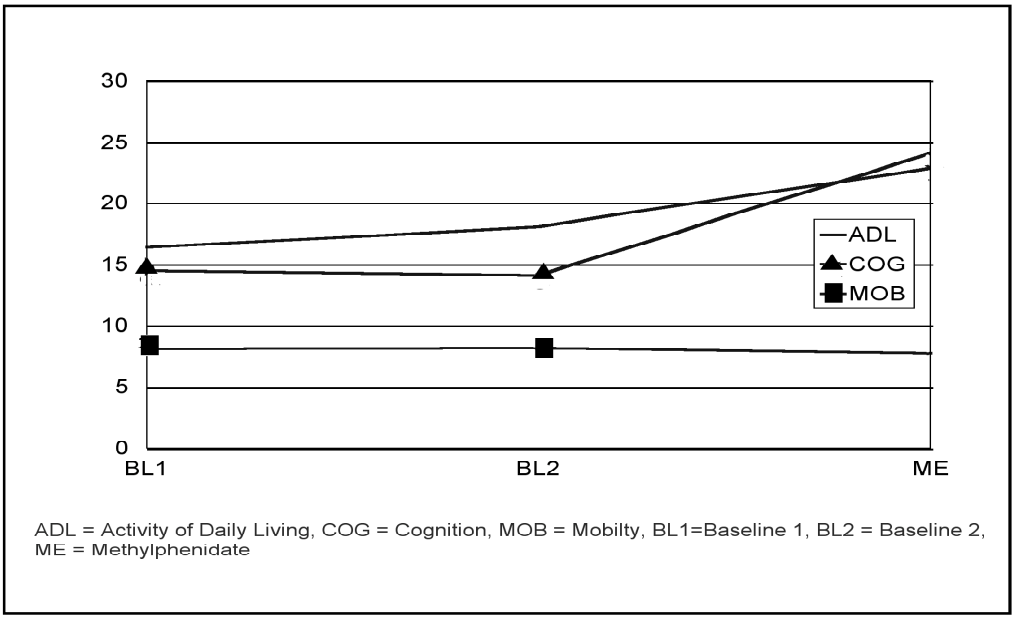

Figure 2. Functional Independence Measures—Indexes of attention across assessment occasions.

devised to measure how people detect information within their radial visual field under conditions that simulate the visual clutter of the real world. Specifically, the useful field of view is a measure that detects decline in visual sensory function, slowed visual processing speed, and impaired visual attention skills. In a previous study,[38] we were able to demonstrate that the UFOV could be used by patients with ABI, and the score on this test could provide information that was partially accessed by neuropsychological examinations. This study did indicate that a good deal of the variance for length of stay was accessed by the divided attention task of the UFOV.

One principal aim of the present study was to examine whether the UFOV could provide useful information concerning the effect of methylphenidate, introduced during the clinical care of patients in an acquired brain injury unit. The variations between UFOV score before and after treatment with methylphenidate were used as one of several clinical measurements of the impact of the medication. All 16 consecutive patients treated with methylphenidate for alleviation of attention responded favorably to low doses of methylphenidate (5 mg to 10 mg twice per day). The patients were of both sexes, with differing etiology and loci of brain injury. The time since initial injury varied between approximately two weeks to three months. It is most unlikely that the changes simply reflected spontaneous recovery since two consecutive baseline measurements were shown to be statistically stable. The result thus collaborate some clinical indication that medications that release catecholamine may relieve symptoms of hypoattention.[3]

As this study applied a new assessment measure, an essential part of this study is also to determine the usefulness of UFOV in an ABI population. In the absence of a gold standard, the usefulness of this assessment measure is established by assessing the degree to which the scale correlates with other existing measure of related or unrelated enti-

ties.[39] In a previous study, we determined that the UFOV was correlated with visual attention measures determined with neuropsychological testing and that this visual attention ability is correlated with length of stay at the rehabilitation unit.[40] An alternative measure of the utility of a measurement is 'pharmacological validation' in which changes are observed during drug intervention. If the score fluctuates as a consequence of the intervention, a change in the criterion variable is the essence of such validation. The rational of pharmacological validation has been detailed elsewhere.[26,41] At face value, the scores of the UFOV significantly increased with low doses of methylphenidate, a compound presumed to trigger neurotransmission in centers involved in arousal and attention. While others have suggested that there is no significant practice effect with repeated testing with the UFOV,[7-9] their data were collected on a geriatric population that did not involve brain injury. It was therefore important for our clinical evaluation as well as for the evaluation of these data that we could demonstrate neither a practice effect nor healing process that was occurring before the introduction of the medication. It is important that no changes in score were noted with repeated testing with the UFOV. Albeit indirectly, the present findings lend credence to the view that UFOV is likely to detect attention deficits in ABI that is emendable to a pharmacological agent. It was postulated that the mechanism underlying these associations is catecholaminergic circuitry, activation of which is thought to be involved in goal directed behavior. Reduced efficiency in the functioning of this circuitry, arising either from focal structural damage to relevant neuronal pathways or from disruption to the synthesis, release, or metabolism of catecholaminergic itself, would impact on the functioning of the entire system and thus have observable effects at the three levels of attention described.

As we have noted in previous work that the UFOV scores do correlate with the patient's length of stay, we postulate that any medication that improved the abilities measured with the UFOV would in fact improve at least some of the measures of progress at the rehabilitation unit. As the FIM is the standard measurement tool at our unit, we were able to compare the changes before and after the introduction of methylphenidate. Therefore, the second intent of this study was to examine whether pharmacological influences on attention as indexed with UFOV would coincide with improvements in the patients functional performance. The data from this study showed an improvement in functional abilities in both FIM cognition as well as the FIM Activity of Daily Living. With the FIM Cognition scores, there was a reasonably stable baseline such that we could determine that the change in the FIM Cognition scores was correlated with the introduction of the medication and changes in the UFOV scores. Just as with FIM cognition, it appears that methylphenidate did impact activity of daily living, namely eating, grooming, bathing, transferring, and dressing. However, as the baseline scores were not stable, the influence on attention cannot be solely attributed to pharmacological intervention. It is possible that the patients were experiencing spontaneous recovery, though the data do suggest that the rate of recovery may have been accelerated by the introduction of the medication. Future studies are needed to clarify the effect of the medication on the patients' FIM Activity of Daily Living.

Methylphenidate did not raise the score of mobility despite stable baselines. It is beyond the scope of this paper to assess the reasons why the FIM

Mobility scores did not change in a similar fashion as the FIM Cognition and FIM Activity of Daily Living. It is possible that there was motor tract involvement or deconditioning that resulted in a more layered involvement of recovery. It could be argued that the level of strength needed to increase ambulation may need to be in place before a significant recovery of FIM Mobility could be achieved, while such a change in the muscular system would not need to be as significant for the FIM Activity Daily Living and certainly not for the cognitive tasks. To analyze this, it would have been instructive to assess the motor as well as the cardiovascular ability of each individual, as well as any other pertinent comorbidity that might have affected the capacity of the patient to engage in ambulation. Further studies are required to isolate these.

A major caveat in interpreting the findings is that the treatment was not given in a blinded manner. While the UFOV is given in a standardized way and is scored automatically by computer, the open design of these results leave room for differences in demand characteristics on the part of the staff who collected the data. It does seem unlikely, however, that this limitation could account for the improvements in their entirety. The validity and use of this single case type of trial is well-documented.[42] The single case design model appears to be the intervention of choice, with its great flexibility and tailored approach to each individual case. Although the present assessment measure may have been influenced by both the researchers' and patients' expectations, such "demand characteristics" of the treatment may have motivated patients to perform better. Notwithstanding this view, these patients were selected (before drug treatment) for being poor in attention. The objective computerized scoring for UFOV in each case reduces scope for inadvertent distortion of the data by the researchers. Nevertheless, it is clearly important that this study's findings be more rigorously evaluated via a double blind, randomized and controlled trial.

SUMMARY

This study demonstrates that, with a clinical population of patients with ABI the UFOV test can provide assessment of attention, which seems able to capture and to quantify the effects of the introduction of methylphenidate. These data seem to further support our previous work suggesting that the UFOV test may be an efficient and important tool for the measurement of a cognitive variable critical for the recovery of patients with ABI.

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