



Alcoholic Polyneuropathy: Clinical Assessment of Treatment Outcomes Following Therapy with Nucleotides and Vitamin B₁₂

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Abstract

The purpose of this study was to evaluate the clinical action of the combination of cytidine monophosphate (CMP), uridine triphosphate (UTP), and hydroxocobalamin in the treatment of patients presenting alcoholic polyneuropathy. Patients received a 6-day intramuscular treatment of: CMP 5.0mg; UTP 3.0mg; hydroxocobalamin 2.0mg; lidocaine 20mg, followed by a 30-day treatment period of thrice daily oral ingestion of: CMP 2.5mg; uridine triphosphate UTP 1.5mg; hydroxocobalamin 1.0mg. Efficacy assessments included a 100mm pain VAS, paresthesia testing, motor coordination evaluation, vibration perception testing, and 1-10 point overall condition questionnaire. Safety assessments included vital signs and adverse event monitoring throughout the study. A total of 120 patients were included in the study. The number of symptomatic patients at Assessment 4 was significantly lower in relation to pretreatment for pain ($p=0.0009$), paresthesia ($p<0.0001$), altered vibration perception ($p=0.0004$), and altered motor coordination ($p=0.002$). VAS score reduction at Assessment 4 was found to be statistically significant ($p<0.0001$), with improvement in overall condition assessment scores performed by the patients and the physician ($p<0.0001$ for both). Adverse events were observed among 27 patients, and were overall mild or moderate in severity, short-lasting, did not lead to study withdrawal. Based on the results observed in our study, we conclude that the combination of CMP, UTP, and vitamin B₁₂ was safe and effective in the treatment of patients presenting alcoholic polyneuropathy. Treatment with the intramuscular injection form followed by oral treatment reduced pain in relation to pretreatment values, increased vitamin B₁₂ levels and improved motor coordination among affected patients.

Keywords: Alcoholic Polyneuropathy, Uridine, Cytidine, Vitamin B₁₂

Introduction

Alcohol abuse and alcohol dependence are very prevalent conditions in the general population. Alcohol abuse is defined by alterations in control of alcohol consumption, alcohol consumption despite adverse consequences, and distortion in thought patterns, especially denial. These symptoms can be either continuous or periodic (APA, 2000). Alcohol dependence is clinically manifested as continuous use of alcohol despite significant problems associated to alcohol consumption, in addition to increased tolerance to alcohol, abstinence symptoms, and physical manifestations including blackouts or memory lapses after drinking episodes, sleep alterations, and tremors. Alcohol dependence is a chronic disease, associated with malnutrition, trauma, and a wide variety of nervous system dysfunctions, including alcoholic polyneuropathy (Sosenko et al., 1991).

Alcoholic polyneuropathy is a progressive disorder that involves the sensory, motor, and autonomic nerves (Sosenko et al., 1991), distinguishable from beriberi neuropathy by the marked sensory component and significant neuropathic pain (Koike et al., 2001). The most frequent symptoms include numbness, paresthesia, disesthesia with burning sensation, pain, weakness, muscle cramps and gait ataxia. Neurological evaluation frequently reveals loss of tendon reflexes, alterations in tactile perception and vibration perception, weakness and decreased muscle coordination (Kemppainen et al., 1982; Sosenko et al., 1991). The pathophysiology of alcoholic polyneuropathy is thought to be twofold, combining the toxic effect of alcohol with nutritional deficiency caused by long-term heavy alcohol consumption (Koike et al., 2003; Koike & Sobue, 2006; Koike et al., 2012).

In this study, we evaluated the treatment outcomes following administration of a combination of uridine triphosphate (UTP),

cytidine monophosphate (CMP), and vitamin B₁₂ in the treatment of patients with alcoholic polyneuropathy. The pyrimidine nucleotides cytidine and uridine have shown beneficial effects in several preclinical studies of peripheral neuropathies of various origins. Beneficial effects have been reported in animal studies following experimentally induced crush injury, with accelerated nerve and muscle fiber regeneration (Wattig et al., 1991; Wattig et al., 1992a; Wattig et al., 1992b). Results of further preclinical investigations have indicated increased nerve conduction velocity, increased levels of neuritic protein neurofilaments, increased axon myelin surface area and thickness, and increased levels of neuronal cell membrane phospholipids phosphatidylcholine and phosphatidylethanolamine following nucleotide administration (Wurtman et al., 2006).

Previously reported clinical findings of cytidine and uridine administration have indicated reduction in pain intensity following treatment in combination with vitamin B₁₂. The painful conditions that have been investigated in clinical trial settings with this combination include lumbar and cervical pain, diabetic neuropathy, traumatic-compressive lesions, and acute, non-traumatic pain (Lauretti et al., 2004; Lauretti et al., 2005; Mibielli et al., 2010; Müller 2002a; Müller 2002b; Serra et al., 1972).

The human body requires an exogenous source of vitamin B₁₂ in order to maintain a variety of processes vital to health and maintenance – among which are cell reproduction and growth, and nucleoprotein and myelin synthesis (Gubler 1984, p. 245; Wilson 1998, p. 481). In the nervous system, vitamin B₁₂ plays a role in nerve metabolism via the remethylation of homocysteine to methionine for de novo synthesis of s-adenosylmethionine (*Chemistry and Biochemistry of B12* 1999; Oh & Brown 2003; Schjonsby 1989). In deficiency states, neurological damage is caused by a disruption of myelin formation that is thought to result from alterations to reactions beginning with s-adenosylmethionine (Carmel 2000).

Vitamin B₁₂ absorption depends on five factors – dietary ingestion, the acid-pepsin complex in the stomach that releases cobalamin from its binding proteins, pancreatic proteins that release cobalamin from the R factor bond, and secretion of intrinsic factor by gastric parietal cells in order to bind cobalamin, and finally, the presence of cobalamin and intrinsic factor receptors in the ileum (Allen et al., 1993). Vitamin B₁₂ deficiency can be caused by numerous factors, usually some combination of inadequate ingestion and absorption (Carmel 2000). Deficiency can lead to neurological alterations and megaloblastic anemia; the neurological symptoms of this deficiency are thought to be linked to the absence of s-adenosylmethionine formation (Green & Kinsella 1995).

Objectives

The primary study objective was to evaluate the clinical action of the combination of CMP, UTP, and hydroxocobalamin in the treatment of patients presenting alcoholic polyneuropathy. Secondary study objectives included assessment of the combination of CMP, UTP, and hydroxocobalamin in the treatment of patients presenting alcoholic polyneuropathy, using clinical, physical, and laboratory endpoints, as well as adverse events assessment.

Material & Methods

The study was performed at UNIFESO university medical facilities in Rio de Janeiro, Brazil. The study was submitted to and approved by the institution's ethical committee (approval no. 593-2011). Eligible subjects included patients of both genders, between the ages of 18 and 65, with a clinical presentation of alcoholic polyneuropathy. Given that there are no established diagnostic criteria for alcoholic neuropathy, after confirmation of alcoholism (per ICD-10 / DSM-IV criteria), we also based on history of alcoholism, history of symptom progression, physical exam (assessing for pain, paresthesia, motor coordination changes, and changes in vibration perception on the lower limbs).

Female patients performed a urine pregnancy test prior to inclusion and were required to maintain adequate birth control throughout the study period. All patients who agreed to participate gave written informed consent, and were not to consume alcohol during the treatment period.

After screening and pretreatment evaluations, 120 patients received a 6-day intramuscular treatment (administered by the investigating physician) consisting of: cytidine monophosphate (CMP) 5.0mg; uridine triphosphate (UTP) 3.0mg; hydroxocobalamin 2.0mg; and lidocaine 20mg (for local pain relief). This was followed by a 30-day treatment period of thrice daily oral ingestion of: cytidine monophosphate (CMP) 2.5mg; uridine triphosphate (UTP) 1.5mg; hydroxocobalamin 1.0mg.

A total of 4 study assessments were performed: Assessment 1 (pretreatment), Assessment 2 (following 3 days of intramuscular treatment), and Assessments 3 (following 6 days of intramuscular treatment) and 4 (at the end of the 30 day oral treatment period). At each assessment, a medical history was taken, along with physical and laboratory exams. Use of concomitant medications and occurrence of adverse events were monitored throughout the study.

Efficacy assessments included a 100mm pain VAS (visual analog pain scale), paresthesia assessment (using the two-point test), the finger-to-nose test to evaluate motor coordination, and the vibration perception test (performed on the lower limbs using a tuning fork). At each assessment, the patient and the investigating physician evaluated the patient's overall condition on a scale of 1-10 points. At Assessment 4, patients also answered a question regarding their willingness to continue treatment on a scale of 1-10. Safety assessments took into account vital signs at each assessment and occurrence, severity, and duration of any adverse effects, including changes in laboratory tests. These assessments were adopted based on previous clinical studies of alcoholic polyneuropathy (Peters et al. 2006; Woelk et al., 1998).

Results were statistically analyzed using the software GraphPad Prism 5.0. Overall clinical efficacy and tolerability were analyzed via comparison of the results of each assessment in relation to pretreatment values. For categorical variables, we used the χ^2 or Fisher's test, while continuous variables were analyzed using the repeated measures ANOVA or Student's T test.

Results

A total of 120 patients were included in the study. The demographic data and pretreatment characteristics of the study population are summarized in Table 1. It is important to note that all patients reported consumption of at least two alcoholic drinks per day. Table 2 summarizes the specific symptoms reported at each study visit. The number of patients presenting each symptom at the final study assessment was significantly lower in relation to pretreatment for pain ($p=0.0009$), paresthesia ($p<0.0001$), altered vibration perception ($p=0.0004$), and altered motor coordination ($p=0.002$).

At Pretreatment, mean serum B₁₂ levels were 186.7pg/mL. After 3 days of intramuscular treatment (Assessment 2), mean serum B₁₂ levels increased to 214.3pg/mL. Mean serum B₁₂ levels at Assessments 3 and 4 were 265.7 and 503.1pg/mL, respectively. The increase in serum vitamin B₁₂ level from Pretreatment to Assessment 4 was statistically significant ($p<0.0001$; Fig. 1).

Figure 2 summarizes the results of the motor coordination test. At Pretreatment, 14 (11.67%) of the patients presented altered motor function. At Assessment 4, this number dropped to 4 patients (3.3%). The vibration perception test was repeated 3 times, and ranked by the investigating physician as 0 (no perception), 1 (altered perception), or 2 (normal perception). Table 3 summarizes the results of the vibration perception tests performed during the study.

Among the patients presenting pain, mean pretreatment VAS value was 46.78mm. At Assessment 3, mean VAS value was 40.12mm;

while at Assessment 4, mean VAS value decreased to 23.79mm. VAS score reduction from pretreatment to Assessment 4 was found to be statistically significant ($p < 0.0001$) (Figure 3).

There was a statistically significant improvement in the scores of the patient's overall condition assessments performed by the patients and the investigating physician from Pretreatment to Assessment 4 ($p < 0.0001$ for both evaluations) (Figure 4).

A total of 27 patients presented with adverse effects, which are summarized in Table 4. The majority of the AEs were mild or moderate in severity, short-lasting, and none caused withdrawal from the study. Table 5 summarizes the safety assessments performed throughout the study.

Discussion

During the treatment period, we observed clinical improvement in the study subjects as evidenced by the VAS and overall condition assessments performed at each study visit. There were significant reductions in the number of patients presenting pain, paresthesia, altered motor coordination, and vibration perception at end of treatment in relation to pretreatment observations.

The nucleotides may have played a role in the pain reduction experienced among the treated subjects. Although the nucleotides do not exert any direct analgesic or anti-inflammatory action, they may contribute to symptomatic improvement in conditions in which peripheral nerves are affected. The neuroregenerative capacity of the pyrimidine nucleotides has been demonstrated in animal models of nerve damage, revealing that both axons and myelin sheaths of regenerating nerve and muscle fibers are favorably influenced by nucleotide administration, with improvements in nerve fiber conduction velocity (Wattig et al., 1991; Wattig et al., 1992a; Wattig et al., 1992b). Clinical benefits of nucleotide administration have been demonstrated in cases of diabetic neuropathy and polyneuropathy as well as neuropathic

pain syndrome (Gallai et al., 1992; Müller 2002a; Müller 2002b).

The combination of uridine, cytidine, and vitamin B₁₂ has been employed with favorable results in the clinical trial setting in the treatment of a variety of pain syndromes of neural origin, including chronic neuropathic lumbar pain (Lauretti et al., 2005), pain following neurological surgical procedures (Lauretti et al., 2004), neural compression-induced neuralgias (Goldberg et al., 2009), peripheral neuropathies (Serra et al., 1972), as well as pain and paresthesia in anemic patients (Nunes et al., 2008). Further studies may support additional indications in addition to contribution to a better understanding of the interaction between the nucleotides and Vitamin B₁₂ in painful conditions.

Vitamin B₁₂ and other B vitamins have been confirmed to exhibit antinociceptive effects that are not associated with vitamin deficiency, in both animal models and in clinical trials (Mauro et al., 2000). On the other hand, B₁₂ deficiency may lead to neurological alterations; sub-acute degeneration of dorsal and lateral spinal columns is the most common manifestation. The latter condition would arise as a result of defective myelin formation (Gomes et al. 2006; Wang et al. 2005).

Vitamin B₁₂ has been shown to experimentally inhibit thermal hyperalgesia whether administered alone or in combination with vitamins B₁ and B₆ (Wang et al., 2005). Administration of vitamin B₁₂ resulted in a dose-dependent reduction of tactile allodynia induced by spinal nerve ligation in the rat (Granados-Soto et al., 2004). Patients with mechanical or irritative lumbago and who did not exhibit nutritional deficiency were treated with vitamin B₁₂, resulting in significant improvement in pain and related disability, along with a reduction in paracetamol consumption (Mauro et al., 2000). This effect has been attributed to the effect of vitamin B₁₂ on axonal conduction (Wang et al., 2005). In the treatment of patients presenting with diabetic polyneuropathy, treatment with vitamin B₁₂ led to a reduction in pain and paresthesia along with significant

improvement of ulnar motor and median nerve conduction velocities (Kuwabara et al. 1999).

Conclusion

Based on the results observed in our study, we conclude that the combination of uridine,

cytidine, and vitamin B₁₂ was safe and effective in the treatment of patients presenting alcoholic polyneuropathy. Treatment with the intramuscular injection form followed by oral treatment reduced pain in relation to pretreatment values, increased vitamin B₁₂ levels and improved motor coordination among affected patients.

Figures and Tables

Table 1: Pretreatment and Demographic Characteristics

Variable	Results
Gender	
Male	89
Female	31
Age (years)	46.58 (± 4.93)
Height (cm)	169.8 (± 6.7)
Ethnicity	
Black	36
Caucasian	42
Mulatto	42
Marital status	
Divorced	30
Married	52
Single	27
Widowed	11
Overall diet	
Good	0
Moderate	23

Poor	97
Alcohol consumption	
≤2 drinks / day	0
> 2 drinks / day	120
Variable	Results
Cigarette smoking	
Non-smoker	22
< 10 cigarettes / day	44
≥ 10 cigarettes / day	54
Manual labor	
Light	28
Moderate	34
Heavy	58
Physical exercise	
Regular (at least 1x / week)	0
Irregular	22
None	98

Data are *n* or means (\pm)SD

Table 2: Symptoms Recorded at Assessments 1, 3, and 4 (A1, A3, A4)

	Pain			Paresthesia			Alterations in vibration perception			Alterations in motor coordination		
	A1	A3	A4	A1	A3	A4	A1	A3	A4	A1	A3	A4
Yes	120	114	102	47	32	22	34	29	14	18	13	2
No	0	1	8	43	83	90	86	86	106	102	102	110

Data are *n*

Table 3: Results of the Vibration Perception Test recorded at Assessments 1, 3, and 4 (A1, A3, A4)

Scores	Assessment 1			Assessment 3			Assessment 4		
	Test 1	Test 2	Test 3	Test 1	Test 2	Test 3	Test 1	Test 2	Test 3
0	0	1	1	0	0	0	0	0	0
1	31	37	41	32	31	32	22	15	17
2	89	82	78	83	84	83	90	97	95

Data are *n***Table 4: Adverse Events**

Adverse Events	Severity	# of Subjects Affected
Abdominal distension	Moderate	1
Abdominal distension	Mild	1
Agitation	Moderate	1
Anxiety	Mild	1
Breast pain	Moderate	1
Constipation	Moderate	2
Adverse Events	Severity	# of Subjects Affected
Cough	Moderate	1
Diarrhea	Moderate	1
Diarrhea	Mild	1
Epigastralgia	Mild	1
Epigastralgia	Moderate	1
Erythema at injection site	Moderate	1
Flatulence	Moderate	1
Headache	Moderate	4

Adverse Events	Severity	# of Subjects Affected
Headache	Severe	1
Headache	Mild	2
Heartburn	Moderate	1
Hemorrhoids	Moderate	1
Hyperemia at injection site	Moderate	1
Increased uric acid	Mild	1
Insomnia	Severe	4
Irritability at injection site	Moderate	1
Loss of appetite	Moderate	4
Muscle cramp	Severe	1
Nausea	Mild	6
Nausea	Moderate	7
Pain at injection site	Moderate	5
Pyrosis	Moderate	2
Vomiting	Moderate	2
Vomiting	Severe	1

Data are *n*

Table 5: Safety Assessments

Parameters	Results	Change from pretreatment
Weight (kg)		No (p=0.184)
A1	64.6 (\pm 10.68)	
A2	64.18 (\pm 10.45)	
A3	64.17 (\pm 10.19)	
A4	64.71 (\pm 9.27)	

Parameters	Results	Change from pretreatment
BMI		No (p=0.254)
A1	22.33 (± 2.94)	
A2	22.21 (± 2.85)	
A3	22.19 (± 2.77)	
A4	22.33 (± 2.41)	
Systolic Blood Pressure (mmHg)		Yes (p=0.0006)
A1	127.7 (± 5.61)	
A2	127.4 (± 5.61)	
A3	127.2 (± 5.72)	
A4	126.5 (± 5.03)	
Diastolic Blood Pressure (mmHg)		Yes (p=0.0283)
A1	84.93 (± 7.74)	
A2	84.69 (± 7.92)	
A3	84.17 (± 8.24)	
A4	84.27 (± 7.81)	
Pulse (bpm)		No (p=0.0892)
A1	71.08 (± 4.67)	
A2	70.51 (± 4.51)	
A3	70.40 (± 4.5)	
A4	70.59 (± 4.33)	

Parameters	Results	Change from pretreatment
Respiratory rate (ipm)		No (p=0.355)
A1	17.83 (\pm 7.78)	
A2	17.94 (\pm 7.52)	
A3	16.86 (\pm 2.12)	
A4	17.13 (\pm 4.63)	

Data are means (\pm SD)

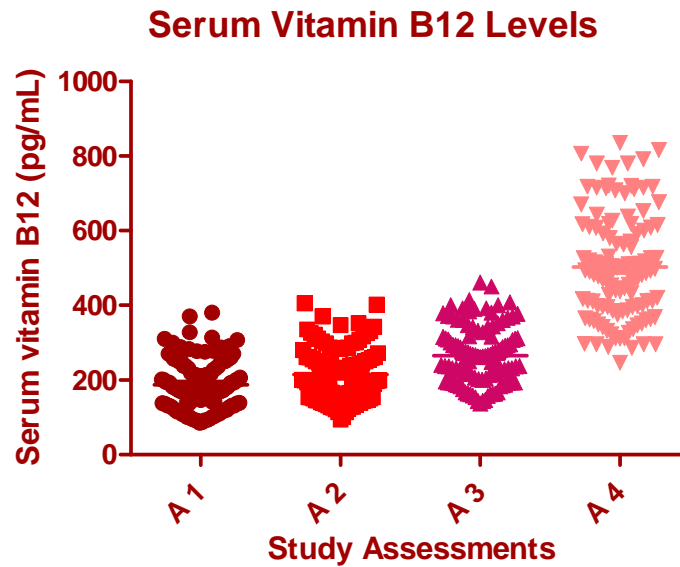


Figure 1: Serum Vitamin B12 Levels At Assessments 1, 2, 3, and 4

Figure 1 shows a statistically significant increase in serum vitamin B₁₂ level from Pretreatment to Assessment 4 (p<0.0001)

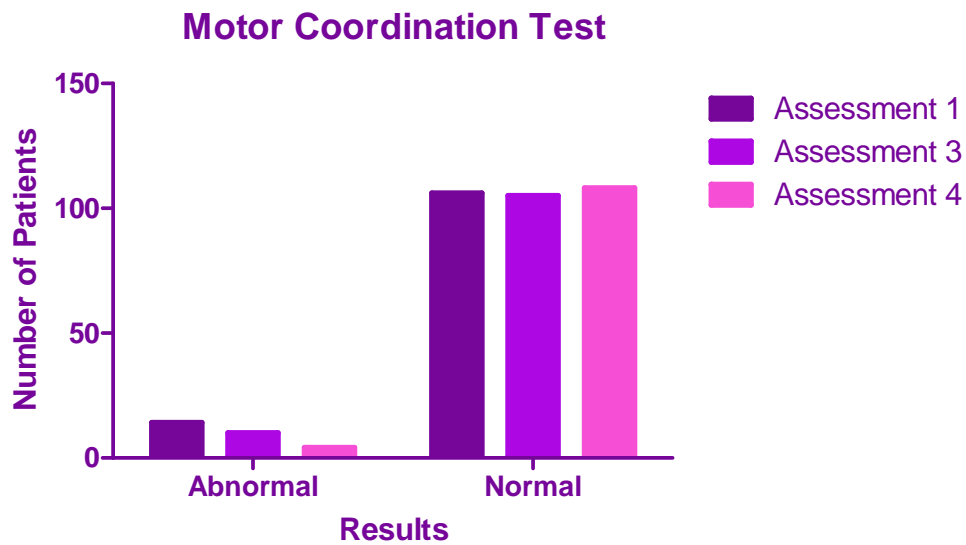


Figure 2: Results of the Motor Coordination Test at Assessments 1, 3, and 4

Figure 2 summarizes the results of the motor coordination test performed at each study Assessment, displaying the number of

patients with normal or abnormal results at each assessment.

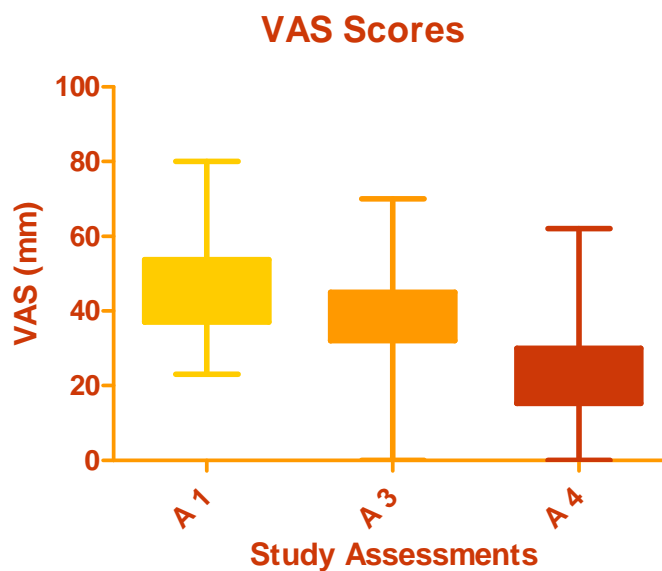
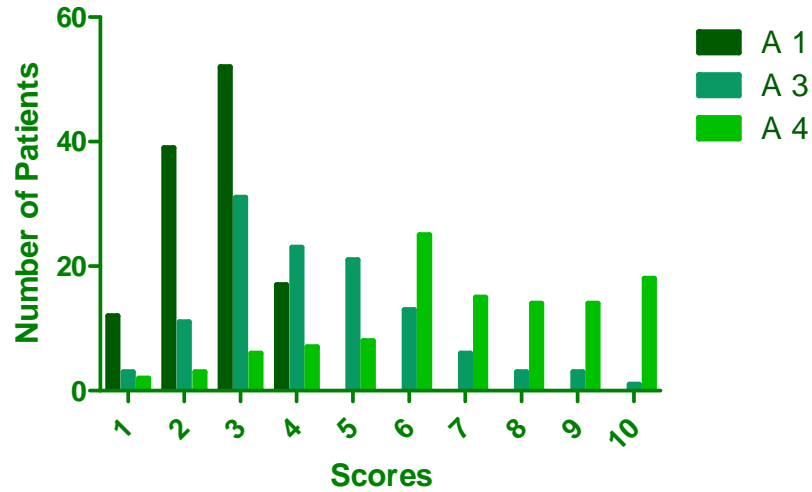


Figure 3: Visual Analog Pain Scale Scores at Assessments 1, 3, and 4

Figure 3 shows significant VAS score reduction from pretreatment to Assessment 4 ($p < 0.0001$).

Patient's Assessment of Overall Condition (Patient Scores)



Patient's Assessment of Overall Condition (Physician Scores)

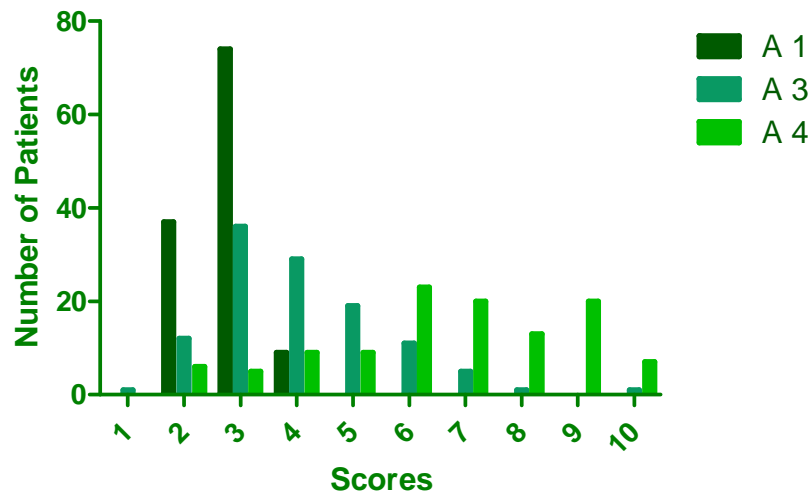


Figure 4: Assessment of Overall Condition Scores (as evaluated by the patient and physician)

Figure 4 shows the improvement in scores of the patient's overall condition assessments performed by the patients and the investigating physician from Pretreatment to Assessment 4 ($p < 0.0001$ for both evaluations).

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