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1 **Effects of combining modern recovery techniques with neurotrophic medication and**
2 **standard treatment in stroke patients**

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26

27 **Abstract**

28 Stroke is the main cause of disability after age 65, leaving survivors with sequels that require
29 care and recovery treatment lasting years. It is estimated that by the year 2030 this pathology
30 will be leading cause of mortality. To determine the efficacy of Lokomat training combined
31 with neurotrophic medication and balneo-physiotherapeutic treatment in rehabilitation of
32 post-stroke patients, a prospective study of 3 parallel groups was conducted: Group I (n = 22)
33 – Lokomat, balneo-physiotherapy, and Cerebrolysin; Group II (n = 18) – Lokomat associated
34 with balneo-physiotherapy; and Group III (n = 30) – balneo-physiotherapy alone (Control
35 group). Patients were evaluated physically, neurologically, and functionally, according to the
36 evolution of their motor deficiency, spasticity, functional independence and health-related
37 quality of life. Patient improvement is significantly better ($p < 0.05$) in the group with
38 associated therapies, especially during the first 6 months. Evolution was significantly better
39 in all groups at 12 months than initially ($p < 0.05$), for all studied parameters and with the best
40 effects in Group I (the three therapies combined). Association of Lokomat training with
41 neurotrophic factors and classic recovery techniques improves the rehabilitation process in
42 stroke patients.

43

44 **Keywords:** stroke; Lokomat; rehabilitation; neurotrophic medication; recovery.

45

46

47 **1. Introduction**

48 Stroke is a major health problem, not only due to the mortality rate, but also for its effects on
49 motor and cognitive ability, and on the quality of life of survivors and their family. Patients'
50 neurological handicaps are often severe and profound, expressed through many incapacities:
51 locomotion, communication, self-care, behaviour, physical independence, orientation, social
52 and economic integration (Fodor et al., 2018). The inability to move independently, along
53 with the regaining of speed (gait) in walking, are two determining factors of long-term
54 disability and alteration of daily-life functions (Mauritz, 2009).

55 Even with optimal care in specialized units, less than a third of patients having suffered a
56 stroke will ever fully recover (The Atlantis et al., 2004). Following a stroke, patients are
57 prescribed a complex and individualized recovery plan that is unlimited in time, begins in the
58 intensive care unit and later continues in a medical recovery clinic or at the patient's home.
59 Recovery treatment aims to give stroke-disabled patients the opportunity to maintain their
60 physical, intellectual, psychological and social functions at an optimal level (International
61 Classification of Functioning, Disability and Health, 2014). Recent clinical studies question
62 the use of multiple classes of drugs to treat disabilities resulting from stroke, findings
63 corroborated by physiotherapeutic and occupational approaches (Keskin et al., 2005).

64 Mainly due to the perspectives of application and theoretic importance, the last decade has
65 seen a step forward in neurotrophic factors which now occupy a leading position in scientific
66 research. To date, no specific schemes, medicines or definitive methods have emerged to
67 treat the consequences of a stroke (Uivaroşan et al., 2018). Rehabilitation and reintegration of
68 stroke patients should be undertaken with consideration for the type of disease that caused

69 the deficiency and focus on disability reduction and management. However, since the
70 recovery program is set up in function of diagnosis, the latter is critical (Fodor et al., 2018).
71 Though the post-stroke recovery program may evolve for improved results, its impact on
72 motor function remains modest, regardless of the method applied (Mauritz, 2000). One of the
73 most discussed features of gait recovery is that the patient must be as actively involved in the
74 rehabilitation program as possible. This ultimately request implies better learning of the
75 motor process, but it may also reduce the incidence of secondary complications such as
76 cardiovascular disease or osteoporosis. Inability to move is a long-term handicap and is
77 considered a key target in rehabilitation (Mauritz, 2000).

78 For the greatest possible improvement of motor function, we have studied the use of robotic
79 techniques and devices for gait recovery (Cho et al., 2018; Lunenburger et al., 2005) and a
80 number of therapeutic benefits have come to our attention: increased independence (Cho et
81 al., 2018; Dundar et al., 2014), improved walking (Simons et al., 2009), muscle tone
82 (Schwartz et al, 2009), walking speed, mobility, etc. (Schwartz et al, 2009; Tong et al., 2006).

83 Among the advantages of using medical robots are dynamic workout programs whose aim is
84 to improve patient condition by reproducing exercises otherwise performed by specialized
85 physical therapists and by quantifying the results. One of the robotic devices used to
86 rehabilitate walking is the Lokomat, a computer-controlled and electrically-driven orthosis
87 for walking, designed to assist training by means of a conveyor belt (Pohl et al., 2007). The
88 Lokomat supports the walking movement, using a physiological walking pattern to guide the
89 patient's legs, with body-weight support as an option. It provides all the benefits of a robotic
90 locomotor workout, training features, research and evaluation facilities, and hand-assisted

91 training. Study of the medical robot therapy useful in restoring gait showed that better
92 recovery is possible if the therapy is prompt, intense and prolonged (Cho et al., 2018;
93 Lunenburger et al., 2005). Some data have demonstrated that the potential of robotic
94 therapy is greater in the early stages following a stroke (Álvarez et al., 2000; Álvarez et al.,
95 2006; Zhang et al., 2017). Other researches have shown that, in certain cases, robotic
96 techniques may be more effective than conventional therapy (Hesse and Werner, 2009; Israel
97 et al., 2006; Peurala et al., 2009). However, there are some published papers mentioning that
98 walking behaviour with devices that maximize the level of motor support (such as Lokomat)
99 does not always produce positive results (Hidler et al., 2009; Maulden et al., 2005 ; Pohl et
100 al., 2007); moreover, some data show that the effects of using this type of device on walking
101 function, including the motor recovery after subacute stroke, still remain unclear (Cho et al.,
102 2018).

103 At present, the therapeutic approach for post-stroke rehabilitation involves use of multiple
104 therapies that act in different but complementary ways to identify treatment schemes that
105 transform disabilities into abilities. The advantages of robotic devices, along with the
106 benefits of neurotrophic medication and standard recovery procedures, led us to
107 hypothesize that a combination of these therapies could improve both functional recovery
108 and the quality of life. Thus, our aim was to study the effects of Lokomat use on stroke
109 victims when used: 1) in combination with both Cerebrolysin and recovery therapy, 2)
110 when associated only with classic recovery therapy.

111

112 **2. Materials and methods**

113 **2.1. Study design**

114 A comparative prospective study was conducted involving seventy Romanian patients
115 having suffered a stroke within the previous 6 months, and who were hospitalized for
116 post-stroke recovery at the Recovery Clinic Hospital of Băile Felix and at the Oradea
117 Neurology Hospital during the 2011-2014 period. Observation and treatment were
118 programed for 12 months, with initial evaluation, at 6 months and at 12 months. To
119 determine the efficacy of Lokomat training associated with neurotrophic medication and the
120 classic balneo-physiotherapeutic recovery treatment for stroke patients, we compared three
121 parallel groups: Group I (n = 22) – Lokomat combined with balneo-physiotherapy and
122 Cerebrolysin; Group II (n = 18) – Lokomat associated only with balneo-physiotherapy; and
123 Group III (n = 30) – balneo-physiotherapy alone (Control group). Patients who participated
124 in the study were distributed among the 3 groups considering the selection method for each
125 group along with to the patient's history, associated pathologies, clinical characteristics, and
126 the signed consent for training with Lokomat. Only hemodynamically stable patients with no
127 risks of vital importance were included in the study.

128 The patients were evaluated physically, neurologically and functionally, following the
129 evolution of pyramidal spasticity, functional independence and their health-related quality of
130 life. In the initial assessment, and in terms of the parameters evaluated, no statistically
131 significant differences between the groups ($p > 0.05$) were observed.

132 The study was approved by the Ethics Commission of the Council of the Medicine and
133 Pharmacy Faculty, University of Oradea, and conducted in accordance with the World
134 Medical Association Code of Ethics (Declaration of Helsinki, 1967). Each patient included in
135 the study signed an informed-consent form.

136 1.2. Drug/Medicinal Therapy

137 Cerebrolysin was administered as a chronic intermittent treatment in doses of 10
138 mL/day, 10 consecutive days per month, for one year. It was administered intravenously as
139 an infusion, diluted in a physiological saline solution. During the study, treatment with
140 medicines belonging to the following classes was allowed: antihypertensives, antidiabetics,
141 antibiotics, hydro-electrolytic and acid-base rebalancing, thrombolytic, and general stroke
142 treatment. Throughout the study, no treatment with different neuroprotectors was
143 administered, excepting diazepam, amantadine, cistoline or piracetam (which act
144 peripherally), or pentoxifylline, nicergoline, vinpocetine, ginkgo biloba or vincamine (which
145 determine blood vessel dilatation).

146 1.3. Recovery therapy

147 Recovery treatment, with established procedures, was performed for 14 (consecutive) days,
148 every 6 months and was strictly individualized, regardless of stroke type (thrombotic,
149 embolic, haemorrhagic), and took into account age, associated conditions, risk factors,
150 degree and form of motor deficiency, complications etc. Therapeutic means used were:

- 151 • *kinetherapy*, using a variety of postures, techniques and methods, types of exercises
152 and passive, active or active-passive exercises;
- 153 • *hydrokinetherapy* by immersing the patient in thermal water at 36-37°C in
154 collective pools, especially in swimming pools, under the strict supervision of a
155 physical therapist;
- 156 • *masotherapy*, using adapted and strictly individualized massage techniques,
157 performed either in the ward/salon or in a massage room;

- 158 • *electrotherapy* using low, medium or high frequency currents, depending on the level
159 of spasticity, on presence/existence of complications such as joint or
160 musculo-ligament retractions or associated pathology of the locomotor apparatus;
- 161 • *occupational therapy* for the performance of ADL by self-care, domestic,
162 professional and social care in relation to the patient's life stage;
- 163 • *thermotherapy*, in the form of dose III short waves, to reduce spasticity;
- 164 • *cryotherapy* in various forms, applied either to decrease spasticity or, in stage II, to
165 relieve lymphatic circulation;
- 166 • *contrasting therapy* in the form of alternating baths of the upper or lower limbs,
167 aimed to improve venous circulation;
- 168 • *psychotherapy* performed individually by a psychologist.

169 In all groups, kinetotherapy and massage were performed for all patients,
170 hydro-kinetotherapy was performed for over 50% of patients. Electrotherapy, with various
171 forms of low and high frequency currents, was applied to 72 - 74% of patients, and
172 occupational therapy was applied to 83 - 86% of patients. No significant differences ($p >$
173 0.05) concerning the rehabilitation treatments were observed between the studied groups.

174 **1.4. Lokomat training**

175 Lokomat is a robot assisted training / rehabilitation system consisting of a treadmill, a
176 dynamic body weight support system and robotic (motorized) orthoses that allow patients
177 with severe locomotor deficiency to train their walking using a physiological model of
178 walking. This device facilitates symmetrical walking patterns of hip and knee components
179 using an exoskeleton powered by programmable servomotors (Bae et al., 2014). During

180 training, patients are supported by harnesses to stay safe on the treadmill; they begin their
181 workout training using the body weight support system and the motorized orthosis.

182 Throughout the training, therapists can control the speed of walking, the angle of the knee
183 and hip joints, and the amount of physical support provided by the body weight support
184 system. Walking training sessions are kept at a demanding level; the speed of the treadmill
185 is set at the maximum that patients tolerate, the force of the acting mechanisms is adjusted,
186 and support for body weight is reduced as soon as the functionality of the patients accepts
187 and supports it. All patients in this study were trained at Lokomat while they were admitted
188 to the recovery clinic, as follows: 30 minutes/day, for 14 consecutive days, every 6 months.

189 **2.5. Spasticity assessment**

190 The adapted Ashworth scale, a standard scale showing resistance to/endurance of inactive
191 movement, was used to evaluate levels of pyramidal spasticity. The procedure offers the
192 examiner continuous observation of the endurance stage. A scale of severity degrees from 0
193 to 4 includes 5 muscle tone stages. The scale suggested by Bahanon adds level 1 + (Modified
194 Ashworth Scale, 2011).

195 **2.6. Motor deficiency evaluation – Barthel Index**

196 The Barthel Index, which tests 10 stages for using the 10 ADL for self-care was used to
197 evaluate motor deficiency. The index applies to all 10 assessed functions (Barthel Index
198 Scoring Form, 2011).

199 **2.7. Functional independence evaluation**

200 To evaluate functional independence, the FIM scale (Functional Independence Measure) was
201 used, a standard measuring system that contains 6 parameters. Functional independence is

202 presented on a decreasing scale in 7 stages, from 7 (totally independent) to 1 (totally
203 dependent) (Cavanagh et al., 2000). A high score indicates a healthy individual with no
204 dysfunctionalities.

205 **2.8. Quality of life evaluation**

206 To evaluate quality of life, the SS-QoL scale (Stroke Specific Quality of Life Scale) was
207 used, a standard scale to evaluate health as related to quality of life (HRQoL), particularly for
208 stroke patients. The evaluation was performed for three areas: 1) physical (energy, self-care,
209 mobility, extremity functionality, work, speech, sight), 2) mental (personality, mood,
210 thinking) and 3) social (social role, role of the family) (Williams^a et al., 1999; Williams^b et
211 al., 1999).

212 **2.9. Statistical analysis**

213 Statistics were analysed using SPSS Statistics 19. A sample calculation was performed,
214 considering a confidence level of 95% at $\alpha=0.05$ and a test power at $1-\beta=0.80$. Sample size
215 calculations were used to estimate the frequency in population along with the finite
216 population correction factor (FPC) (Chow et al., 2008). The following formula was used:

$$217 \quad n=N \cdot X/(X+N-1)$$

218 where $X= Z^2_{\alpha/2} \cdot p \cdot (1-p)/MOE^2$, and $Z^2_{\alpha/2}$ is the critical value of the normal distribution at
219 $\alpha/2$ (e.g. for a confidence level of 95%, α is 0.05 and the critical value is 1.96), MOE is the
220 margin of error, p is the sample proportion, and N is the population size. According to this
221 formula, the sample size should be higher or equal to 70.

222 Initially, over 300 patients were enrolled in this study, yet only 85 had a complete dataset,
223 among which 15 were incompatible with the requirements of our follow up study (they had

224 some medical boundaries). Thus, the current sample has 70 patients, divided into 3
225 subgroups.

226 Average parameter values, frequency ranges, standard deviations, statistical significance
227 tests using the ANOVA method and z-statistic were calculated. ANOVA with a post-hoc
228 analysis (Bonferroni) was used to analyze the differences among groups for evaluations,
229 where the compared data were expressed as an average, and z-statistic was used to evaluate
230 the spasticity, where the data compared were expressed as percentage. Statistical significance
231 was considered at $p < 0.05$. To assess the sensitivity to change of the measure, the statistical
232 effect size (ES) system was used. ES interpretation was compiled as: 1) small ES = 0.20; 2)
233 medium ES = 0.50; and 3) large ES = 0.80. This system is relevant in presenting the findings
234 of a quantitative study (an effect can be identified by a p-value, but this p-value cannot reveal
235 its magnitude) (Sullivan and Feinn, 2012). Calculation of the ES is performed by using the
236 following equation:

$$237 \text{ ES} = (m_1 - m_2)/s_1,$$

238 where m_1 is the average value of initial score, m_2 is the average score value after a determined
239 period, and s_1 is the standard deviation value of initial score.

240

241 **3. Results**

242 **3.1. Patient characteristics**

243 In terms of demographic and clinical characteristics, no statistically significant differences
244 were observed among the three groups (Table I).

245 **3.2. Motor deficiency evaluation - Barthel Index**

246 The Barthel Index evolution exhibits statistically significant difference among all groups as
247 assessed by one-way ANOVA ($F = 4.766$, $p = 0.012$ for BFT + Lokomat + Cerebrolysin and
248 $F = 5.741$, $p = 0.006$ for BFT+Lokomat group, and $F = 3.122$, $p = 0.049$ for BFT group).
249 ANOVA analysis revealed no consistent differences in the Barthel Index among the groups
250 at 6 or 12 months.

251 In the BFT + Lokomat + Cerebrolysin group, the motor deficiency disappeared in 9.09% of
252 patients in the first 6 months, and 9.09% in the next 6 months, while in patients with very
253 severe or severe deficiency, it became moderate or mild after 12 months, in 22.72% of
254 patients (13.63% for the first 6 months and 9.09% for the next 6 months). The Barthel Index
255 mean thus increased from 51.14 at the beginning to 59.77 at 6 months ($p = 0.232$) and to
256 65.91 at 12 months ($p = 0.009$). In the BFT + Lokomat group, the motor deficiency
257 disappeared in 5.56% of patients in the first 6 months, and 5.56% in the next 6 months, while
258 in patients with severe or very severe deficiency, it became moderate or mild after 12 months
259 in 16.67% of patients (11.12% in the first 6 months and 5.56% in the next 6 months), the
260 Barthel Index mean rising from 51.33 initially to 60.28 at 6 months ($p = 0.152$) and to 66.39
261 at 12 months ($p = 0.004$). In the BFT group, the motor deficiency disappeared in 6.67% of
262 patients in the first 6 months and in 3.33% in the next 6 months, while in patients with very
263 severe or severe initial deficiency it became moderate or mild after 12 months in 10.0% of
264 patients (6.67% in the first 6 months and 3.33% in the next 6 months), the Barthel Index mean
265 increasing from 50.50 at the beginning to 55.67 at 6 months ($p = 0.513$) and 59.83 at 12
266 months ($p = 0.044$). The best ES was recorded in the BFT + Lokomat + Cerebrolysin group

267 (Table II). ANOVA analysis revealed no consistent differences in the Barthel Index among
268 the groups at 6 or 12 months.

269 Since the Lokomat procedure led to good results, a risk analysis was performed in order to
270 assess if the observed improvements could be considered statistically significant. Thus, the
271 calculated values, both the risk ratio (RR) and odds ratio (OR) indicators were computed with
272 a confidence interval of 95%. Three different scenarios can be described: 1) when comparing
273 the BFT + Lokomat + Cerebrolysin group to the BFT group, 2) when comparing the BFT +
274 Lokomat group to the BFT group, and 3) the overall study (when were considered only two
275 groups: with or without the Lokomat procedure run on the patients). In the first and second
276 scenario, a protective risk factor (RR, OR<1) was obtained, yet with no statistic significance
277 ($p>0.05$). However, a significant risk factor was found (RR=0.66, 95% (0.5 ;0.88), OR=0.16,
278 95% (0.04; 0.64), $p=0.006<0.05$) when the entire group with the Lokomat procedure (with or
279 without Cerebrolysin) was compared to the group with only BFT. These results were
280 obtained by running a contingency table with the following proportions: 40% of the patients
281 with the Lokomat procedure + the BFT procedure ($N_1=40$ patients) had shown major
282 improvements, compared with the group of patients with only BFT procedure ($N_2=30$
283 patients), where only 10% showed improvements. The p value was obtained using a
284 Chi-square test for proportions, thus inferring that the Lokomat procedure provides a reliable
285 improvement for all patients.

286 **3.3. Spasticity assessment Aschworth Scale**

287 Data regarding the evolution of spasticity, measured with the Achworth scale are presented
288 in Table III. Regardless of the assessment, Z - statistical analysis showed that no significant

289 differences were observed ($p > 0.05$) between the groups with associated therapy related to
290 the BFT group.

291 At 12 months, the percentage of patients with a score ≥ 2 decreased by 31.82% in the BFT +
292 Lokomat + Cerebrolysin group (18.18% in the first 6 months, and 13.04% in the next 6
293 months) ($p = 0.016$), by 27.78% in the BFT + Lokomat group (16.67% in the first 6 months
294 and 11.11% in the next 6 months) ($p = 0.057$) and by 6.67% in the BFT group (in the first 6
295 months and 3.33% over the next 6 months) ($p = 0.595$).

296 **3.4. Functional independence evaluation – FIM Scale**

297 Evolution of the functional independence was statistically significant for all studied groups,
298 total FIM and for both domains of FIM scale, as determined by one-way ANOVA:

299 — total FIM: $F = 10.840$, $p < 0.001$ for BFT+Lokomat+Cerebrolysin; $F = 9.238$, $p <$
300 0.001 for BFT+Lokomat; $F = 12.958$, $p < 0.001$ for BFT group,

301 — motor score: $F = 15.217$, $p < 0.001$ for BFT+Lokomat+Cerebrolysin; $F = 7.930$, $p =$
302 0.001 for BFT+Lokomat; $F = 7.684$, $p = 0.001$ for BFT group, and

303 — cognitive score: $F = 4.737$ $p = 0.012$ for BFT+Lokomat+Cerebrolysin; $F = 5.259$, $p =$
304 0.008 for BFT+Lokomat; and $F = 4.770$, $p = 0.011$ for BFT group.

305 Compared to the baseline assessment, the FIM score for BFT+ Lokomat+Cerebrolysin group
306 increased from 87.68 to 99.09 at 6 months ($p = 0.016$) and at 12 months to 105.77 ($p < 0.001$);
307 the motor score increased from 60.36 to 68.77 at 6 months ($p = 0.002$) and at 12 months to
308 73.05 ($p < 0.001$); and the cognition score increased from 27.32 to 30.32 at 6 months ($p =$
309 0.300) and at 12 months to 105.77 ($p = 0.009$).

310 For the BFT + Lokomat group, compared to the baseline assessment, the FIM score increased
311 from 88.23 to 98.24 at 6 months ($p = 0.55$) and to 104.88 at 12 months ($p < 0.001$); the motor
312 score increased from 59.23 to 66.52 at 6 months ($p = 0.079$) and at 12 months to 70.94 ($p =$
313 0.001); and the cognition score increased from 29.00 to 31.72 at 6 months ($p = 0.242$) and at
314 12 months to 33.94 ($p = 0.001$).

315 In the BFT group the FIM score increased from 88.28 to 96.95 at 6 months ($p = 0.005$), and
316 to 100.85 at 12 months ($p < 0.001$); the motor score increased from 59.06 to 65.17 at 6
317 months ($p = 0.040$) and at 12 months to 67.68 ($p = 0.001$), while the cognition score
318 increased from 29.22 to 31.78 at 6 months ($p = 0.159$) and at 12 months to 33.17 ($p =$
319 0.009). ANOVA analysis revealed no significant differences in FIM score among the
320 groups at 6 and at 12 months, but the best ES was recorded for the group combining all
321 three associated therapies (Table IV).

322 **3.5. Quality of life evaluation - SS-QOL Scale**

323 ANOVA analysis showed a significant positive evolution for all three groups, across all three
324 areas of the SS-QOL Scale and total, as follows:

325 — physical score: $F = 11.549$, $p < 0.001$ for BFT+Lokomat+Cerebrolysin; $F = 6.318$, $p =$
326 0.004 for BFT+Lokomat; $F = 11.617$, $p < 0.001$ for BFT group,

327 — mental score: $F = 13.647$, $p < 0.001$ for BFT+Lokomat+Cerebrolysin; $F = 7.236$, $p =$
328 0.002 for BFT+Lokomat; and $F = 6.005$, $p = 0.004$ for BFT group,

329 — social score: $F = 8.813$, $p < 0.001$ for BFT+Lokomat+Cerebrolysin; $F = 8.031$, $p =$
330 0.001 for BFT+Lokomat; and $F = 10.724$, $p < 0.001$ for BFT group, and

331 — SS-SQL: $F = 21.217$, $p < 0.001$ for BFT+Lokomat+Cerebrolysin; $F = 11.358$, $p <$
332 0.001 for BFT+Lokomat; $F = 17.097$, $p < 0.001$ for BFT group.

333 As for the physical score, in the BFT + Lokomat + Cerebrolysin group, it increased from
334 106.18 to 118.41 at 6 months ($p = 0.024$) and to 127.50 at 12 months ($p < 0.001$). In the BFT
335 + Lokomat group, the score increased from 106.11 to 117.50 at 6 months ($p = 0.107$) and to
336 124.72 at 12 months ($p = 0.003$), while in the BFT group it increased from 106.03 to 115.90
337 at 6 months ($p = 0.100$) and to 121.67 at 12 months ($p < 0.001$).

338 In the mental domain, in the BFT + Lokomat + Cerebrolysin group the score increased from
339 23.77 to 28.18 at 6 months ($p = 0.024$) and to 32.27 at 12 months ($p < 0.001$). In the BFT +
340 Lokomat group, the score increased from 23.94 to 28.06 at 6 months ($p = 0.099$) and to 31.06
341 at 12 months ($p = 0.001$), while in the BFT group it increased from 23.67 to 25.70 at 6 months
342 ($p = 0.365$) and to 28.17 at 12 months ($p = 0.003$).

343 In the social domain, in the BFT + Lokomat + Cerebrolysin group the score increased from
344 16.18 to 18.14 at 6 months ($p = 0.039$) and to 19.36 at 12 months ($p < 0.001$). In the BFT +
345 Lokomat group, the score increased from 15.61 to 17.83 at 6 months ($p = 0.045$) and to 19.11
346 at 12 months ($p = 0.001$), while in the BFT group it increased from 16.10 to 17.63 at 6 months
347 ($p = 0.042$) and to 18.93 at 12 months ($p < 0.001$). The highest ES was obtained in the group
348 that combined all three therapies (Table V).

349 ANOVA analysis revealed a significant improvement at 6 months in the mental score of the
350 BFT + Lokomat + Cerebrolysin group versus the BFT group ($p = 0.024$). After 12 months,
351 the difference became significant in both groups with Lokomat versus BFT group ($p = 0.002$,
352 respectively $p = 0.015$). In addition, the SS-SQL total score was significantly higher at 12
353 months for the BFT + Lokomat + Cerebrolysin group than the BFT group ($p = 0.040$).

354

355 4. Discussion

356 Recovery from and assistance with neurological problems are long-term processes that may
357 sometimes last for the rest of the patient's life. Stroke patients often suffer from sequels such
358 as sensory impairments, perceptual deficiencies, balance deficiency, depression, aphasia,
359 dementia, paralysis and degeneration of cognitive functions, all of which may persist for
360 years (Brewer et al., 2013).

361 Even with optimal care in specialized units, less than a third of patients who have suffered a
362 stroke fully recover (The Atlnatis et al., 2004). Post-stroke recovery is made through a
363 complex and individualized plan, unlimited in time, that begins at the intensive care unit and
364 continues in a medical recovery clinic or at the patient's home. Rehabilitation aims to give
365 people with disabilities the opportunity to maintain their physical, intellectual, mental and
366 social functions at an optimal level (International Classification of Functioning, Disability
367 and Health, 2014). A meta-analysis shows that continuous rehabilitation efforts after
368 discharge, within the first year of stroke onset, reduces a patient's functional impairment
369 (Legg et al., 2004). As a result of recovery therapies, 80% of patients recover partially and
370 10% recover completely, while 10% remain in the vegetative stage (Sullivan et al., 1982).

371 In this study of stroke patients, the evolution of their motor deficiency, spasticity, functional
372 independence and quality of life were compared according to the specific therapies
373 associated with the classic recovery program. The recovery program aimed at improving the
374 functional status, reducing motor deficiency, diminishing patient dependency, preventing
375 and combatting complications, family and socio-professional reinsertion. An approach
376 combining Lokomat training, neuroprotection, and classic recovery therapy was attempted so

377 as to identify therapeutic regimens that could be applied in the first year following a stroke, in
378 order to increase functional independence and the patient's quality of life, as well as to
379 augment chances of complete rehabilitation.

380 Lokomat is a device successfully used for locomotor deficiency recovery, mainly used in
381 acute and sub-acute phases. Data from the literature concerning walking parameters, though
382 showing differing results, suggest the use of the Lokomat even for the patients' chronic
383 neurological and post-stroke impairments (Hidler et al., 2009; Hornby et al., 2008; Kelley et
384 al., 2013). A pilot case study conducted in 2014 showed that motor function, balance, muscle
385 force and gait, as well as cognition, mood and related strategies may all be successfully
386 improved by robot-assisted training (Calabrò et al., 2014).

387 The combination of Lokomat training, Cerebrolysin treatment and standard rehabilitation
388 therapy in post-stroke treatment has shown additional benefits for the rehabilitation of the
389 patients in this study. In terms of motor function, as assessed by measuring the Barthel Index,
390 the best results were obtained in the early stages of rehabilitation, when Lokomat treatment
391 was associated with classic recovery therapy and neurotrophic medication. The most
392 important benefits were improved walking independence, muscle tone, gait/walking speed
393 and mobility. In a study on 146 patients treated with Cerebrolysin, significant improvements
394 in the Barthel Index were observed at the end of the treatment period, with the effect lasting
395 for 3 months after the beginning of treatment (Ladurner et al., 2005).

396 Robotic assistance eliminates prolonged repetitive movements from post-stroke gait training
397 with a physical therapist (Mayr et al, 2007). This study shows that, by combining the three
398 therapies, the beneficial effects on the motor deficit of post stroke patients may be increased.

399 The spasticity that occurs post stroke, followed by superior motor neuron syndrome (lack of
400 coordination, agonist/antagonist contraction and exhaustion) (Francisco and McGuire, 2012)
401 was significantly reduced in all groups. The greatest decrease was recorded at the 6-month
402 evaluation in the group where robotic care was combined with both neurotrophic medication
403 and classic recovery treatment. A decrease in abnormal reflex rigidity following Lokomat
404 training has also been observed in other studies (Mirbagheri et al., 2005). Data from the
405 present study demonstrated that joining Lokomat with Cerebrolysin and classic recovery
406 resulted in a faster decrease in spasticity, as determined by the Achworth Index, in
407 post-stroke patient's recovery.

408 Functional independence, measured with the FIM scale in this study, evolved positively in all
409 three groups, showing significant improvement in the motor, cognition and overall scores,
410 consistent with other studies (Dundar et al 2007; Esclarín-Ruz et al., 2014; Mirbagheri et al.,
411 2005). In this case as well, the best effects were obtained by associating the three therapies.
412 These results show that the combination of the studied therapies induces an increase in
413 functional independence and a reduction of the time interval when the effects of therapy are
414 established.

415 The quality of life was also positively influenced, irrespective of the treatments applied, in all
416 three areas: physical, mental and social, with the greatest impact noted for the mental. The
417 evolution was significantly better in all groups, with the best results in the group that
418 included neurotrophic medication. This may be explained by the fact that, mentally, the
419 patient feels more comfortable when involved in several recovery activities, thus leading to a
420 favourable evolution in rehabilitation.

421 Rehabilitation of the post-stroke patients should include several therapeutic directions in
422 order to identify treatment regimens that can turn disabilities into abilities. In the present
423 study, a more correct and beneficial approach of neuroprotection and recovery was
424 attempted. This study is significant in that it monitors the effects obtained by associating
425 robotic training with classic recovery treatment and neurotrophic medication, administered
426 over time, for parameters that concern both physical and neurological evolution of patients in
427 post-stroke treatment for up to 12 months. Though favourable evidence emerged from the
428 benefits of Cerebrolysin (as a neurotrophic factor), combined with Lokomat treatment
429 (robotic orthosis for walking rehabilitation) and classic medical recovery, a thorough,
430 longer-term study involving several patients would definitely be useful to establish a more
431 precise therapeutic scheme with a role in early recovery of deficiencies and disabilities
432 occurring following a stroke.

433

434 **5. Conclusions**

435 The association of neurotrophic treatment, Lokomat training and classic recovery techniques
436 leads to improvements in motor deficiency, evolution of spasticity, functional independence,
437 and quality of life. All of these indices showed improvement in the Cerebrolysin + Lokomat
438 + BFT group compared to other therapies. The results of this study confirm the importance of
439 recovery treatment post stroke, as well as the importance of following a specific schedule in
440 order to achieve favourable results in improving patients' functional status.

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- 569
570

571 **List of figures**

572 **Figure 1.** Evolution of the patients with Achworth score ≥ 2 , depending on the therapy.

573 At 12 months, the percentage of patients with a score ≥ 2 illustrates a highly statistically

574 significant decrease ($p = 0.016$) for the BFT + Lokomat + Cerebrolysin group, weakly

575 significant ($p = 0.057$) for the BFT + Lokomat group and not significant ($p = 0.595$) for

576 the BFT group.

Aschworth >2

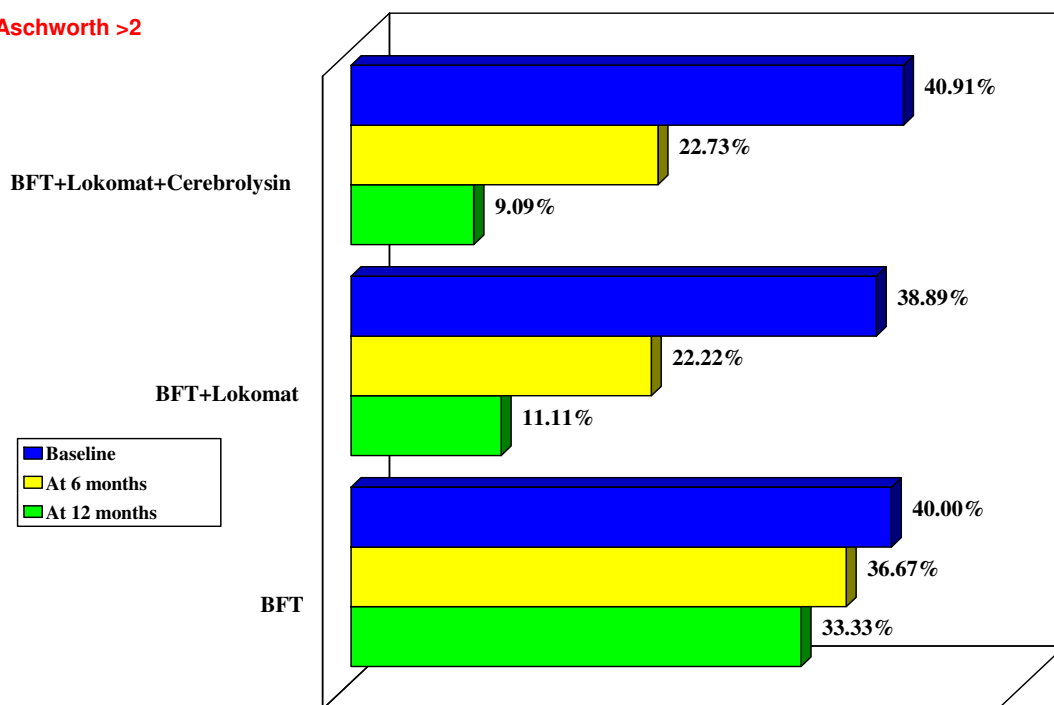


Fig. 1.

Table I. Demographic and clinical characteristics of patients

Characteristics	BFT+Cerebrolysin + Lokomat (n=22)		BFT+Lokomat (n=18)		Control group (n=30)	
	No.	%	No.	%	No.	%
Gender						
Females	3	13.64	3	16.67	14	46.67
Males	19	86.36	15	83.33	16	53.33
Age						
< 50 years	3	13.64	2	11.11	2	6.67
50-65 years	9	40.91	7	38.89	13	43.33
> 65 years	10	45.45	9	50.00	15	50.00
Average	62.91±6.13		63.67±6.63		64.12±7.25	
Diagnostic						
Ischemic stroke	16	72.73	13	72.22	20	66.67
Hemorrhagic stroke	6	27.27	5	27.78	10	33.33
Location of hemiplegia						
Global	12	54.55	10	55.56	17	56.67
Left	5	22.73	4	22.22	8	26.67
Right	7	31.82	6	33.33	9	30.00
Facio-brachial	8	36.36	7	38.89	11	36.67
Crural	2	9.09	1	5.56	2	6.67
Type of the motor deficiency						
Hemiparesis	15	68.18	12	66.67	21	70.00
Hemiplegia	7	31.82	6	33.33	9	30.00
Time since stroke occurred						
< 1 month	1	4.55	1	5.56	3	10.00
1-3 months	7	31.82	6	33.33	9	30.00
3-6 months	14	63.64	11	61.11	18	60.00
Average (months)	3.52±1.41		3.44±1.21		3.35±1.34	
Associated pathology						
Ischemic cardiomyopathy	13	59.09	12	66.67	19	63.33
Valvulopathy	2	9.09	2	11.11	3	10.00
Heart rhythm disturbances	2	9.09	1	5.56	2	6.67
Previous myocardial infarction	1	4.55	0	0.00	1	3.33
Total	18	81.82	15	83.33	25	83.33

Table II. Barthel Index evolution

Motor deficiency	No.	%	No.	%	ES	No.	%	ES
Evaluation	Baseline		At 6 months			At 12 months		
BFT+Lokomat+ Cerebrolysin								
Very severe	2	9.09	1	4.55	0.92	1	4.55	1.58
Severe	8	36.36	6	27.27		4	18.18	
Moderate	10	45.45	8	36.36		5	22.73	
Small	2	9.09	5	22.73		8	36.36	
Without deficiency	0	0.00	2	9.09		4	18.18	
Mean ± SEM	51.14±9.36		59.77±10.22				65.91±10.82*	
BFT+Lokomat								

Very severe	1	5.56	1	5.56		1	5.56	1.40
Severe	8	44.44	6	33.33		5	27.78	
Moderate	7	38.89	5	27.78		5	27.78	
Small	2	11.11	5	27.78		5	27.78	
Without deficiency	0	0.00	1	5.56		2	11.11	
Mean ± SEM	51.33±10.78		60.28±11.06		0.83	66.39±11.21*		
BFT								
Very severe	5	16.67	4	13.33		4	13.33	0.82
Severe	8	26.67	7	23.33		6	20.00	
Moderate	15	50.00	12	40.00		11	36.67	
Small	2	6.67	5	16.67		6	20.00	
Without deficiency	0	0.00	2	6.67		3	10.00	
Mean ± SEM	50.50±10.14		55.67±11.11		0.51	58.83±11.74*		

*Values are significantly different statistically for ANOVA compared to baseline evaluation (p < 0.05, 0.01, respectively).

Table III. Evolution of the Achworth Index

Spasticity	BFT+Lokomat+Cerebrolysin		BFT+Lokomat		BFT	
	No.	%	No.	%	No.	%
Baseline						
0	1	4.55	1	5.56	1	3.33
1	4	18.18	3	16.67	5	16.67
1+	8	36.36	7	38.89	12	40.00
2	3	13.64	3	16.67	6	20.00
3	4	18.18	2	11.11	3	10.00
4	2	9.09	2	11.11	3	10.00
At 6 months						
0	4	18.18	3	16.67	3	10.00
1	5	22.73	4	22.22	5	16.67
1+	8	36.36	7	38.89	11	36.67
2	1	4.55	2	11.11	4	13.33
3	3	13.64	1	5.56	4	13.33
4	1	4.55	1	5.56	3	10.00
At 12 months						
0	5	22.73	4	22.22	3	10.00
1	7	31.82	6	33.33	7	23.33
1+	8	36.36	6	33.33	10	33.33
2	0	0.00	0	0.00	4	13.33
3	1	4.55	1	5.56	3	10.00
4	1	4.55	1	5.56	3	10.00

0 - No increase in tonus; 1- Slight increase in tonus at the end or beginning of the motion arc; 1+ - Slight increase in tonus manifested in the middle of the motion arc; 2 - Marked increase in tonus for most of the movements; 3 - Considerable increase in tonus - difficult passive movements; 4 - Rigid affected part, rigid in flexion or extension.

Table IV. Evolution of the FIM score

BFT+Lokomat+Cerebrolysin (n=22)

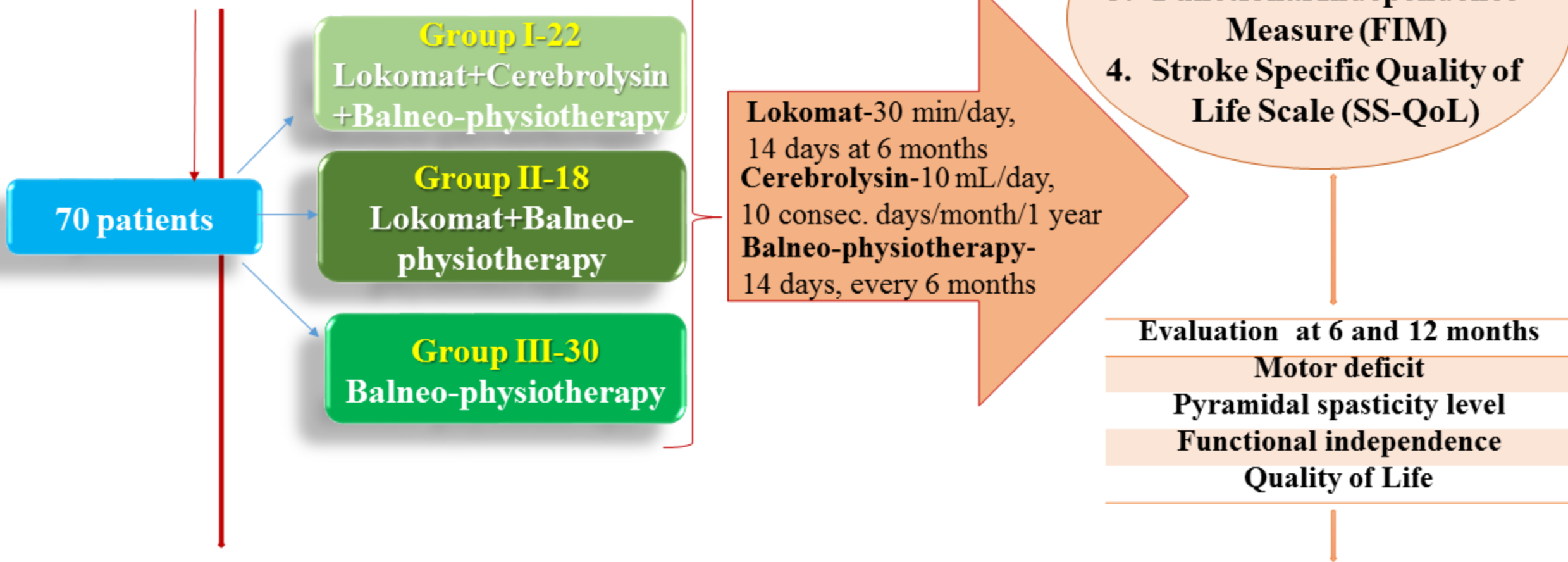
FIM domain	Baseline	At 6 months	ES 6 months	At 12 months	ES 12 months
Motor score	60.36±10.73	68.77±11.15*	0.78	73.05±11.94*	1.18
Cognition score	27.32±4.46	30.32±4.82	0.67	32.73±5.15*	1.21
Total score	87.68±11.32	99.09±12.46*	1.01	105.77±12.12*	1.60
BFT+Lokomat (n=18)					
Motor score	59.23±10.44	66.52±11.07	0.70	70.94±11.91*	1.12
Cognition score	29.00±4.47	31.72±4.51	0.61	33.94±4.39*	1.11
Total score	88.23±11.07	98.24±11.47	0.90	104.88±12.12*	1.50
BFT (n=30)					
Motor score	59.06±11.15	65.17±11.24*	0.55	67.68±11.67*	0.77
Cognition score	29.22±4.43	31.78±4.47	0.58	33.17±4.51*	0.89
Total score	88.28±11.21	96.95±11.47*	0.77	100.85±11.91*	1.12

*Values are significantly different statistically for ANOVA compared to baseline evaluation (p<0.05, 0.01, respectively).

Table V. Domain SS-QOL score evolution

Domain	BFT+Lokomat+Cerebrolysin (n=22)				
	Baseline	At 6 months	ES 6 months	At 12 months	ES 12 months
Physical	106.18±12.84	118.41±12.68*	0.95	127.50±13.12*	1.66
Mental	23.77±4.02	28.18±4.24*	1.10	32.27±4.28*	2.11
Social	16.18±2.08	18.14±2.31*	0.94	19.36±2.12*	1.53
Total	146.14±17.69	164.73±18.32*	1.05	179.14±18.64*	1.87
BFT+Lokomat (n=18)					
Physical	106.11±11.78	117.50±12.41	0.97	124.72±12.12*	1.58
Mental	23.94±4.16	28.06±4.81	0.99	31.06±4.78*	1.71
Social	15.61±2.43	17.83±2.12*	0.91	19.11±2.33*	1.44
Total	145.67±16.57	163.39±17.02*	1.07	174.89±17.17*	1.76
BFT (n=30)					
Physical	106.03±11.27	115.90±11.03	0.88	121.67±11.88*	1.39
Mental	23.67±2.67	25.70±3.42	0.76	28.17±3.11*	1.69
Social	16.10±2.20	17.63±2.38*	0.70	18.93±2.45*	1.29
Total	145.80±15.94	159.23±16.00*	0.84	168.77±16.44*	1.44

Rehabilitation after STROKE



The association of Lokomat training with neurotrophic factors and classic recovery techniques brings improvement in rehabilitation of stroke patients