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Efficacy of Relaxin on functional recovery of post stroke patients

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Summary

Background. Relaxin is a peptide hormone that exerts specific effects on cardiovascular system and human brain, leading to the hypothesis that this hormone may play a protective role against CVD and integration and modulation of behavioral activation.
We aimed to demonstrate the efficacy of Relaxin on functional recovery of post-stroke patients.
Methods. Patients admitted within a Rehabilitation Unit suffering from stroke have been evaluated. Patients have been randomized to RLX (40 mcg/d) plus rehabilitation vs a control group that underwent only rehabilitation. A preliminary analysis of 36 patients at 20 and 40 days was made using the mRS for global function, the Functional Independent Measure (FIM) for daily activity and Trail Making Test (TMT) for cognitive function.
Results. Eighteen patients (age 72 (64-79), M 56%) randomized to RLX plus rehabilitation were compared to 18 patients (age 68 (64-78), M 50%) that underwent only rehabilitation. There was no difference between the two groups in terms of risk factors, stroke syndromes and etiology. At admission the two groups showed the same characteristics in terms of functional aspects (mRS, FIM; p ns) and cognitive function (TMT; p ns). After 20 days (T1) the treatment group (RLX+rehabilitation) showed no differences between the two groups (FIM 78 vs 69; p ns), while after 40 days (T2) patients treated with RLX+R showed an excellent recovery (FIM 96 vs 75; p0.001). In terms of cognitive function patients RLX+R revealed a better performance at T1 (TMT 3.5 vs 2; p 0.002) and still better at T2 (TMT 4 vs 2; p 0.001). These results have been confirmed in terms of global function both at T1 (mRS 2.5 vs 3; p0.001) and T2 (mRS 2 vs 3; p <0.001) .
Conclusion. Relaxin showed in this analysis a positive effects on stroke patient's recovery, thus offering the broad therapeutic potential role of RLX as new drug in post-stroke patients.

Key words

Stroke, rehabilitation, relaxin

Relaxin (RLX) belongs to the relaxin hormone family, which in humans includes 3 RLX molecules and 4 insulin-like peptides(1). Formerly known for its effects on reproduction and pregnancy(2), is actually proposed as a pleiotropic hormone for his multiple actions on numerous organs and systems, caused mainly by its property of inducing nitric oxide(NO) synthesis and release(3). It has been deeply studied on cardiovascular system where produces microvessels dilation(4), coronary blood

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flow increase (3), inhibition of platelet aggregation and, in ischemic tissues, neo-angiogenesys (5) and leucocytes migration(6). Those actions permit that RLX potently counteracts myocardial ischemic damages in experimental heart infarction (7). Recent studies on rat demonstated that RLX administration reduced the extension of the damaged tissue following experimental brain ischemia (8).

Furthermore RLX may also elicites direct actions on the central nervous system. In fact brain has an high concentration of RLX receptors (9) and an isoform of RLX has been discovered in the brain, where it has been postulated to act locally as a neurotrasmitter (10); furthermore RLX acting on circumventricular organs, stimulates water drinking and vasopressing release and appears to be involved in the regulation of behavioural processes (10) .

Based on the RLX properties on the vascular system and the brain functions, we aimed to evaluate the effect of oral administration of Relaxin in improving recovery of post-stroke patients during an admission in a rehabilitation Unit and compare the effects with patients undergoing only the rehabilitation setting.

Patients and Methods

Were recruited consecutive post-stroke patients admitted to our Clinical.

Eligibility criteria included: 1) clinical diagnosis of ischemic stroke within the previous three weeks 2) 18-85 years of age, 3) mRS at admission £3, 4) neither life-threatening major pathological conditions nor alcohol habit, 5) neither serious language disturbance nor poor compliance.

Eligible patients were randomly assigned to receive either RLX (40 mcg /die) plus rehabilitation (RLX+R) or rehabilitation (R).

To assess the stroke recovery we used the mRS for global function (11), the Functional Independent Measure (FIM) for daily activity(12), and the Trail Making Test (TMT) (13) for cognitive function, respectively at admission (T0), after 20 (T1) and 40 days (T2).

We used purified RLX ,extracted by porcine corpora lutea and prepared in a gastro-protected oral form. The trial was approved by the local ethical Committee. Patients or legally accepted surrogates provided informed consent prior to study entry.

Statistical Analysis

We performed the statistical analysis with the SPSS package for windows, and confidence interval analysis softwares. We used median values, interquartile ranges (IQR), and percentages (%). We compared groups for categorical variables, with the Chi Square test with Yate's correction or Fisher exact test when appropriate, and for continuous variables with the Mann and Withney U test.

Results

Eighteen patients (age 72 (64-79), M 56%) randomized to RLX +R were compared to 18 patients (age 68 (64-78), M 50%) that underwent only R. There was no differ-

ence between the two groups in terms of risk factors, stroke syndromes and etiology. At admission the two groups showed the same characteristics in terms of functional aspects (mRS, FIM; p ns) and cognitive function (TMT; p ns). After 20 days (T1) the treatment group (RLX+R) showed no differences between the two groups (FIM 78 vs 69; p ns), while after 40 days (T2) patients treated with RLX+R showed an excellent recovery (FIM 96 vs 75; p0.001). In terms of cognitive function patients RLX+R revealed a better performance at T1 (TMT 3.5 vs 2; p 0.002) and still better at T2 (TMT 4 vs 2; p 0.001). These results have been confirmed in terms of global function both at T1 (mRS 2.5 vs 3; p0.001) and T2 (mRS 2 vs 3; p <0.001) .

The treatment has been well accepted by the patients with good compliance; no negative side effects were registered.

Discussion

This is the first human study to test the effects of RLX on Stroke patients recovery. After 40 days-follow-up we noticed a positive effects of RLX+R on cognitive functions, motor functions and global recovery respect R group in post-stroke patients. The effects on cognitive functions is clear after 20 days and improved still after 40 days of administration. A positive trend can be noticed for functional activities (FIM) during the first period and become clear after 40 days. The positive effects are confirmed in terms of global function with an evident improvement of mRS score during the all observational time. No adverse side effects have been registered.

Evidences of our results and our studies on experimental ischemic diseases confirm that RLX must be considered as a novel therapeutic tool in human ischemic diseases, not only as a protective agent, but also as an efficacious therapeutic possibility to ameliorate and reduce the symptoms produced by the ischemic event. In fact the positive effects we described were found during the patients recovery, confirming our observation in rat and pig experimental myocardial infarction that RLX counteracts or reduces ischemic damages not only when given before but also after the occurrence of ischemia (14). Furthermore in a recent Pre-Relax AHF study, relaxin was associated with favourable relief of dyspnoea and other clinical outcomes, with acceptable safety, when given to patients with acute heart failure (15). It is possible that other actions of RLX, specific for the Central Nervous System and different from the vascular ones, may contributed to the clinical ameliorations described. Experimental evidence suggests that relaxin-3, a recently discovered member of the insulin superfamily, is an orexigenic hypothalamic neuropeptide(8). It is expressed at greatest levels in the central nervous system, and expression is localized to a distinct area called the nucleus incertus, situated in the caudoventral region of the pontine periventricular gray (9). Anatomical studies suggest that this nucleus is involved in a midbrain behavior control network that influences circuits regulating locomotion, attention, and learning processes(10) and that responds to stress-related neuroendocrine signals.

RLX has some other major advantages: it is a natural hormone targeting endogenous receptor/signal tranduction mechanisms; it has similar tertiary structure in many animal species and in humans, thus being poorly immunogenic. This highlights that, regardless the dose and delivery route, adverse side effects are indeed rare(14).

Table 1. Comparisons of the baseline characteristics between patients enrolled in either treatment. Data provided are number of patients (%) unless specified. *median (interquartile range). TACS: total anterior cerebral stroke, PACS: partial anterior cerebral stroke, POCS. posterior cerebral stroke and LACS: lacunar stroke syndrome. Statistics were performed with the Chi Square test (with Yates' correction or Fisher's exact test when appropriate). P values < 0.05 were considered as significant.

	RLX+R n=18	R n=18	p values
Demographics			
Age (years)*	72 (64-79)	68 (64-78)	ns
Male gender	10 (56)	9 (50)	ns
Medical history			
Arterial hypertension	14 (78)	9 (22)	ns
Diabetes mellitus	9 (50)	8 (44)	ns
Hypercholesterolemia	7 (39)	7 (39)	ns
Previous transient ischemic attack	6 (33)	2 (11)	ns
Prior ischemic heart disease	6 (33)	7 (39)	ns
Atrial fibrillation	4 (22)	4 (22)	ns
Cigarette smoking (currently)	8 (44)	3 (17)	ns
Stroke syndrome			
TACS	3 (17)	4 (22)	ns
PACS	7 (38)	6 (33)	ns
POCS	3 (17)	3 (17)	ns
LACS	5 (28)	5 (28)	ns
Presumed etiology			
Small-artery occlusion	6 (33)	6 (33)	ns
Large-vessel atherosclerosis	6 (33)	5 (28)	ns
Cardioembolism	6 (33)	7 (39)	ns
Other determined caused	0 (0)	0 (0)	ns
Undetermined causes	0 (0)	0 (0)	ns

In conclusion, our first analysis, confirms that RLX is a safety natural hormone as resulted in previos human studies and suggests his action on some brain processes, improving the motor and cognitive functions in post-stroke patients, when used in concomitant with physical exercise.

Many other studies need to be done to extend our results, expecially regarding different doses and lenght of treatment and also focusing on the best bio-availability upon oral administration ;for the near future we may hope that pharmaceutical studies may increase the possibility of availability of RLX for theapeutical applications also searching for the optimal RLX analogues easier to obtain and able to compete with the authentic hormone to its receptors.

Table 2. Comparisons of the outcome measures between patients enrolled in either treatment. *median (interquartile range). Comparison of mRS: modified Rankin Scale. FIM: Functional Indipendence Measure. TMT: Trail Making Test. Statistics were performed with the Mann and Withney U test. P values < 0.05 were considered as significant.

	RLX+R n=18	R n=18	p-values
mRS			
Baseline*	3 (2-4)	3.5 (3-4)	ns
T1*	2.5 (2-3)	3 (3-3)	0.001
T2*	2 (1.75-2)	3 (2-3)	<0.001
FIM			
Baseline*	53 (45-61)	59 (45-65)	ns
T1*	78 (70-85)	69 (54-81)	ns
T2*	96 (87-100)	75 (65-89)	0.001
TMT			
Baseline*	2.5 (1-3)	1.5 (1-3)	ns
T1*	3.5 (2.75-4)	2 (1-3)	0.002
T2*	4 (3-4)	2 (1-3)	0.001

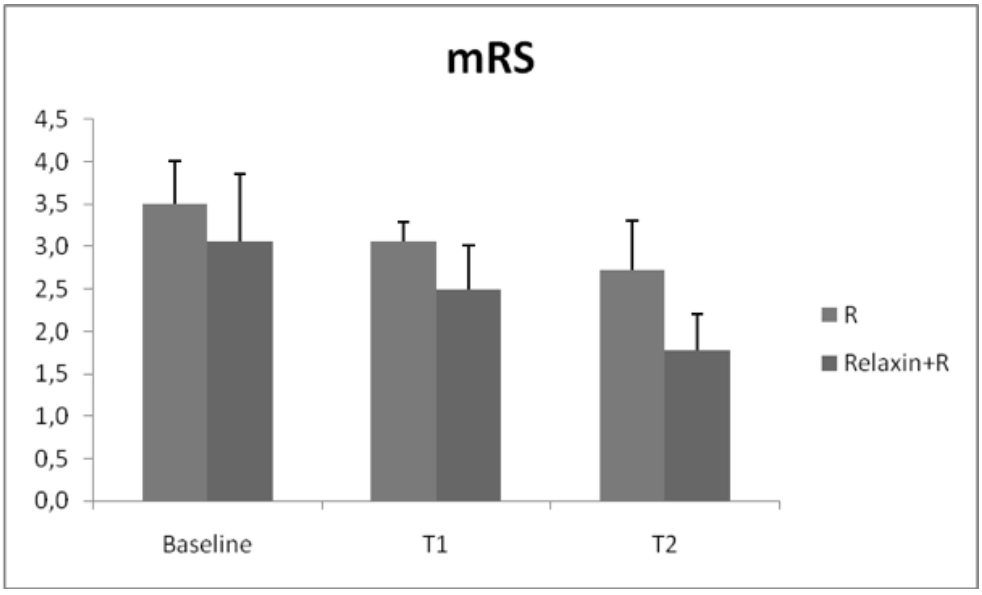

Figure 1. Comparisons of the outcome measures between patients enrolled in either treatment. Median (Standard Deviation). Comparison of mRs: modified Rankin Scale. R: rehabilitation

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