HOW TO ASSESS MODELS OF OXALIPLATIN INDUCED PERIPHERAL NEUROTOXICITY. A NEUROPHYSIOLOGICAL TRANSLATIONAL APPROACH

Alberti P.[1,2,3], *Fumagalli G.* [1,3], *Monza L.*[1,3,4], *Cavaletti G.* [1,3]

Affiliations: 1) Experimental Neurology Unit, University of Milano-Bicocca 2) PhD programme in Neuroscience, University of Milano-Bicocca 3) Milan Center for Neuroscience, Milan 4) PhD program in Translational and Molecular Medicine, DIMET, University of Milano-Bicocca

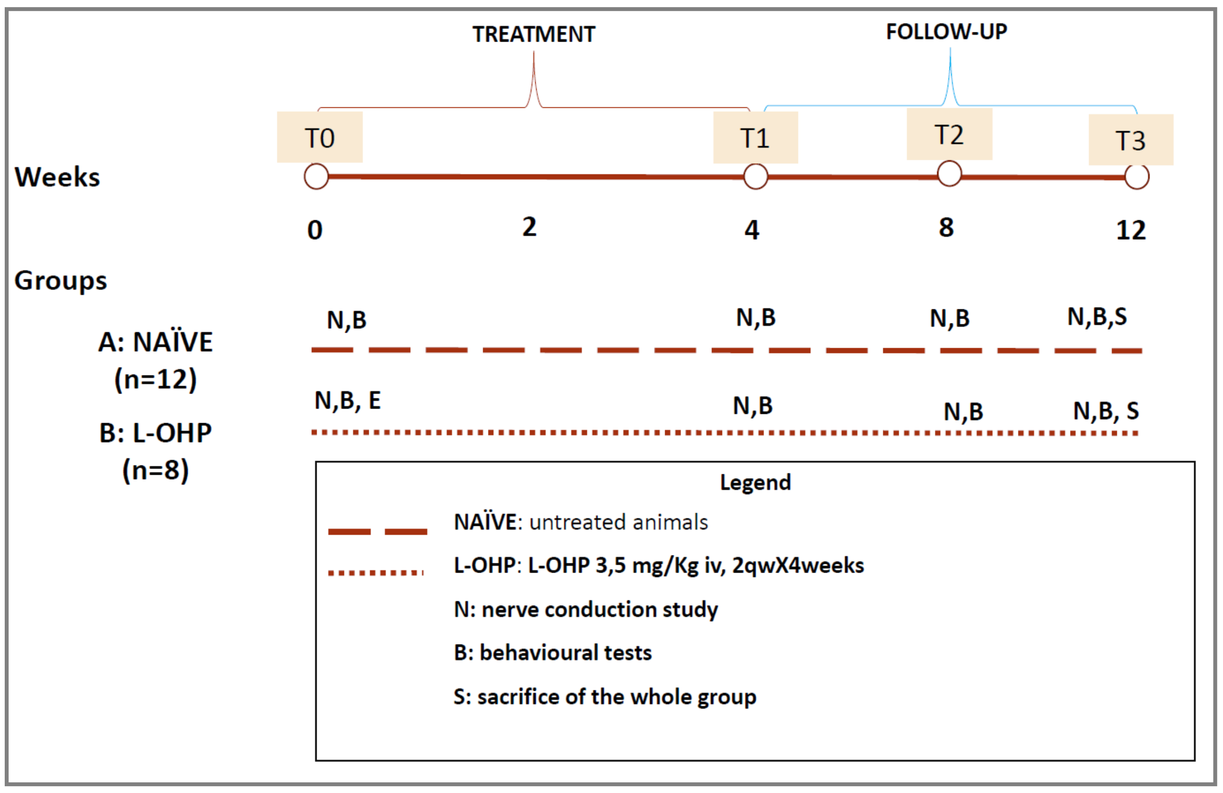
INTRODUCTION

Oxaliplatin (L-OHP) Induced Peripheral Neurotoxicity (OIPN) burdens a large cancer survivor population. No cure is available and accurate “human” readouts are necessary in animal models. Our aim was to set up a standardized neurophysiological protocol in animals, similar to clinical practice, in order to achieve a comparable situation both at “bench” as well as “bed” side.

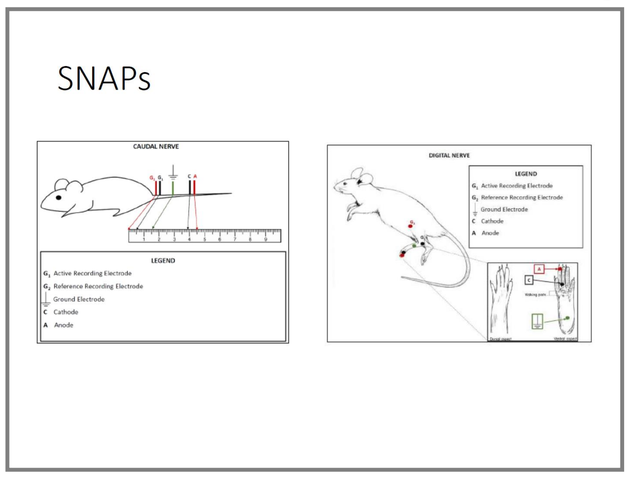
MATERIALS AND METHODS

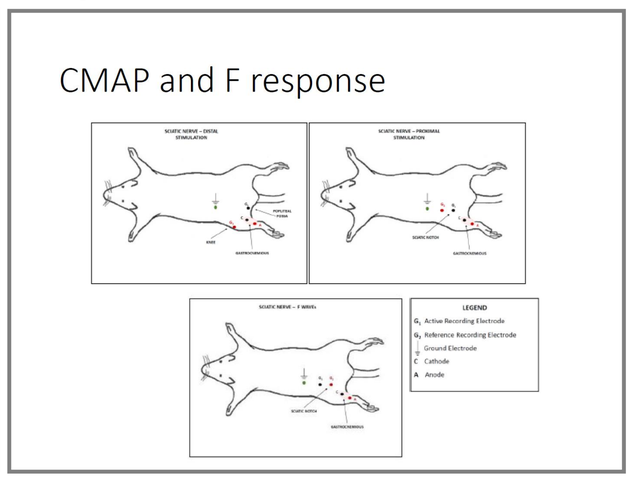
Twenty male BALB/C mice were tested. Animals were divided as follows: GROUP A (n=12), control arm; group B (n=8), treatment arm. GROUP B was treated with L-OHP (3.5 mg/kg) twice weekly for four weeks. Nerve conduction studies were performed before treatment (T0), after last L-OHP administration (T1) and 4 (T2) and 8 weeks (T3) after treatment completion. These recordings were obtained: sensory nerve conduction study of caudal and digital nerves, motor nerve conduction study and F waves of sciatic nerve. All recordings were performed under standard conditions in a temperature-controlled room; deep isoflurane anesthesia was administered.

Study Design

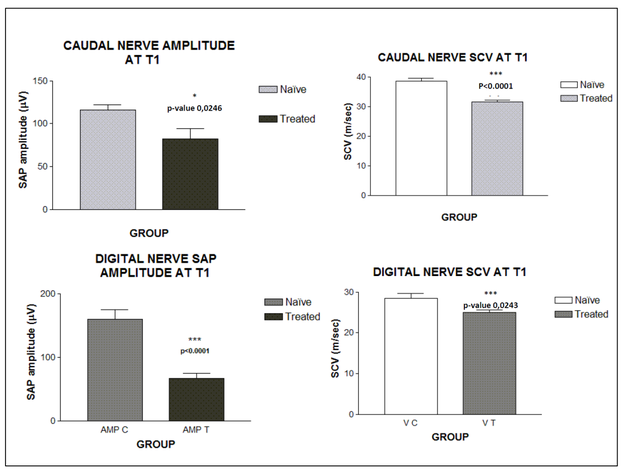


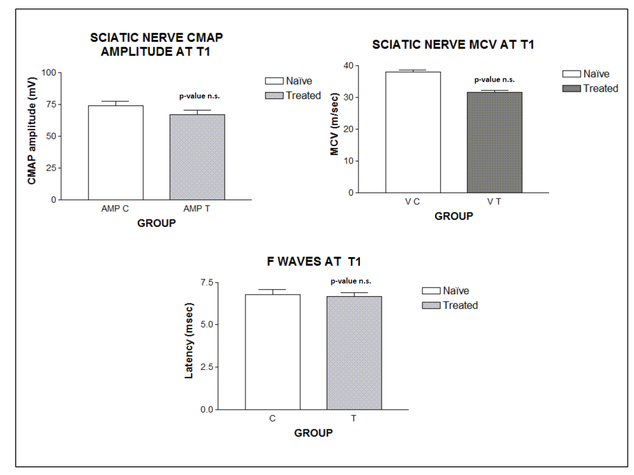
Recording setup

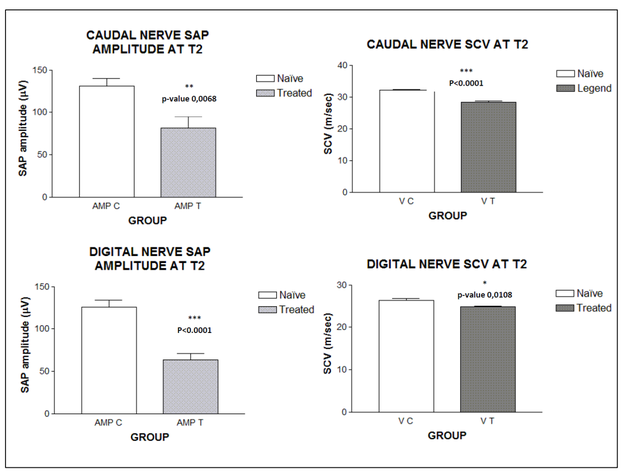


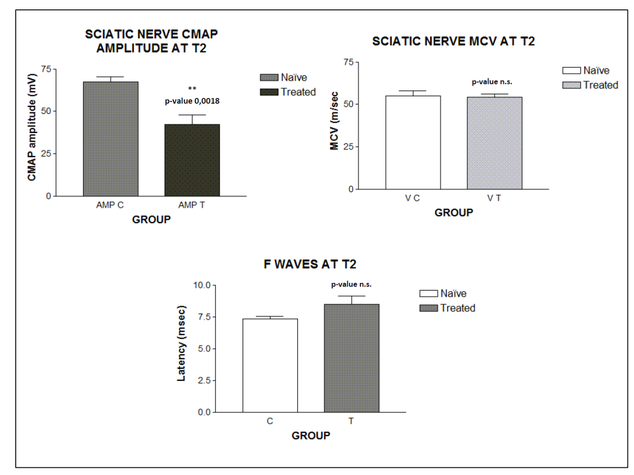


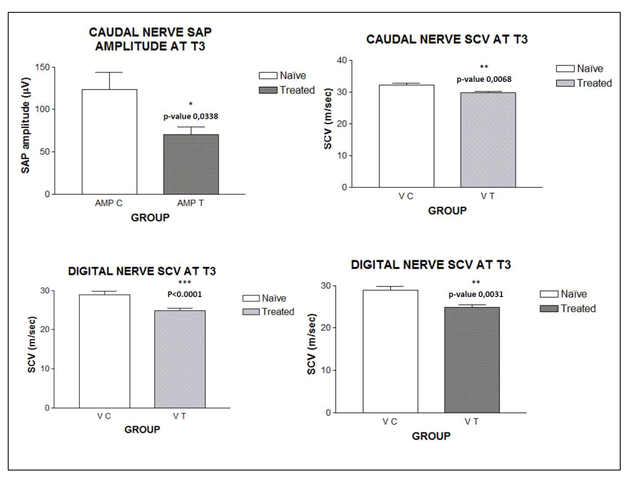
RESULTS

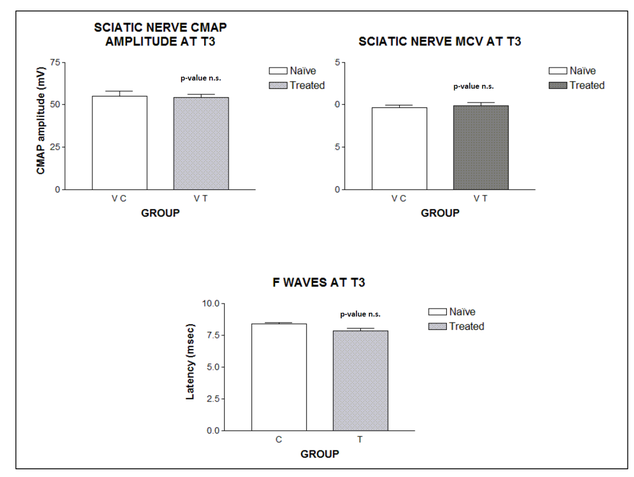












DISCUSSION

All variables were easily obtained following our protocol. The key issue was recording **amplitude for sensory nerves**, being OIPN a mainly sensory length-dependent axonal neuropathy/neuronopathy. At T1 data are consistent with findings known from clinical practice. Data at T2 were even more consistent with OIPN clinical natural history: sensory alterations were more pronounced, according to the well-established “coasting phenomenon”(i.e. after chemotherapy patients show a mild neurological deterioration for a few months); a mild alteration of motor parameters was also seen: deterioration of CMAP amplitude in lower limbs can also be seen in patients. Data at T3 were consistent with a partial recovery: no motor neurophysiological dysfunctions was still present, residual sensory damage was detected; this was similar to what is known from clinical experience.

Our “bench” data were perfectly matching what is commonly observed at the “bed side”; our model was able to catch also “long term toxicity” phenomena. Our algorithm for neurophysiological testing in animals could be now proposed to promptly transfer preclinical data to CIPN preventive clinical trials.

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