

Analgesics Assessment in Rat MIA Model Using the Bioseb Automated Dynamic Weight Bearing System



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1 INTRODUCTION

Osteoarthritis (OA) is a complex, multi-factorial joint disease affecting both the cartilage and the subchondral bone and is often accompanied by chronic joint pain and stiffness. Among several experimental models of OA, the rat mono-iodo-acetate (MIA)-induced osteoarthritic joint pain model has been recognized as one of the most translatable joint pain models. Weight bearing assessment has been extensively used to measure joint pain in this model. In the present study, we compare effects of analgesics in this model using the BioSeb dynamic weight bearing assessment system.

2 METHODS

Model induction: Monoarthritic joint pain is induced in rat by a single intra-articular injection of MIA (3mg/25uL, Day 0) into the right hind knee joint.

DWB Joint Pain Assessment: Joint pain is measured as the deficit in weight bearing by the MIA-injected limb using the BioSeb Dynamic Weight Bearing (DWB) system. The system consists of an arena box with a pressure-sensitive sensor mat on the bottom and an attached high-resolution camera on the top. The rat can move freely inside the arena box. The system automatically calculates the weight borne by each limb and the tail (**Figure 1**). DWB data are calculated by normalizing as percent of total body weight borne by each limb and tail. A two-minute recording is usually done for each rat and analysis is done off-line using the BioSeb software.

Effects of analgesics on MIA-induced joint pain were evaluated after single dosing as well as after dosing for 3-4 days with the analgesics. Weight bearing assessments were performed at various time points following MIA injection between Day 1 to Day 28 post-MIA.

4 CONCLUSIONS

Present results show that DWB system can objectively measure joint pain in the rat MIA model. The late phase of the model seems insensitive to NSAIDs mimicking clinical situation where effectiveness of NSAIDs gradually declines as OA progresses. Results also suggest possible usefulness of the weak opioid tramadol as an analgesic in NSAID-refractory OA pain in clinic.

3 RESULTS

Weight Bearing Pattern in MIA Rat

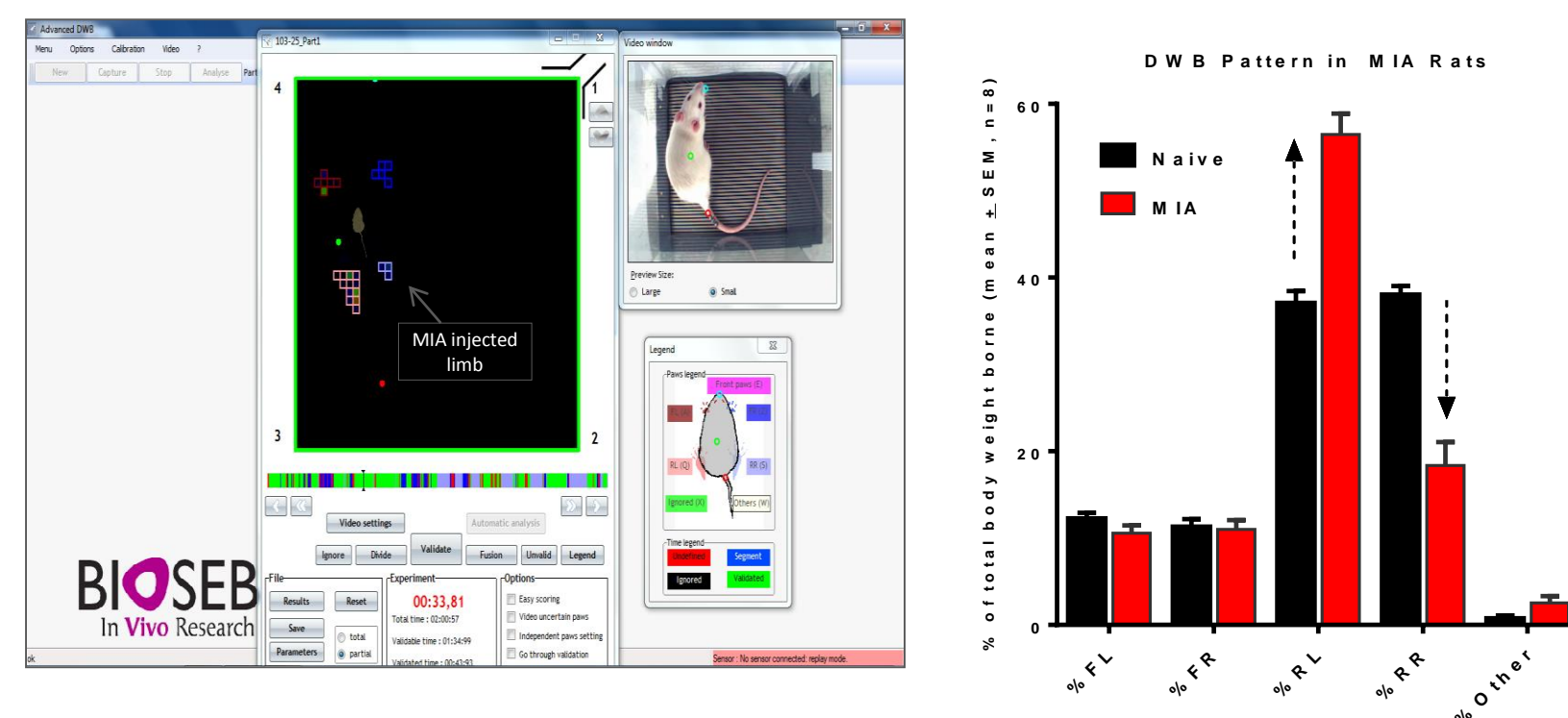


Figure 1: Left panel: Data capture and Analysis procedure using the BioSeb™ DWB system. Right panel: DWB pattern in control Naive and MIA-injected rats. Following MIA injection into the right hind knee joint, there is decreased weight bearing on the ipsilateral side which is mostly compensated by increase in weight bearing by the contra-lateral left hind limb. FL: front left, FR: front right, RL: rear left, RR: rear right, Other: mainly tail.

DWB Time-course and Effects of Dexamethasone

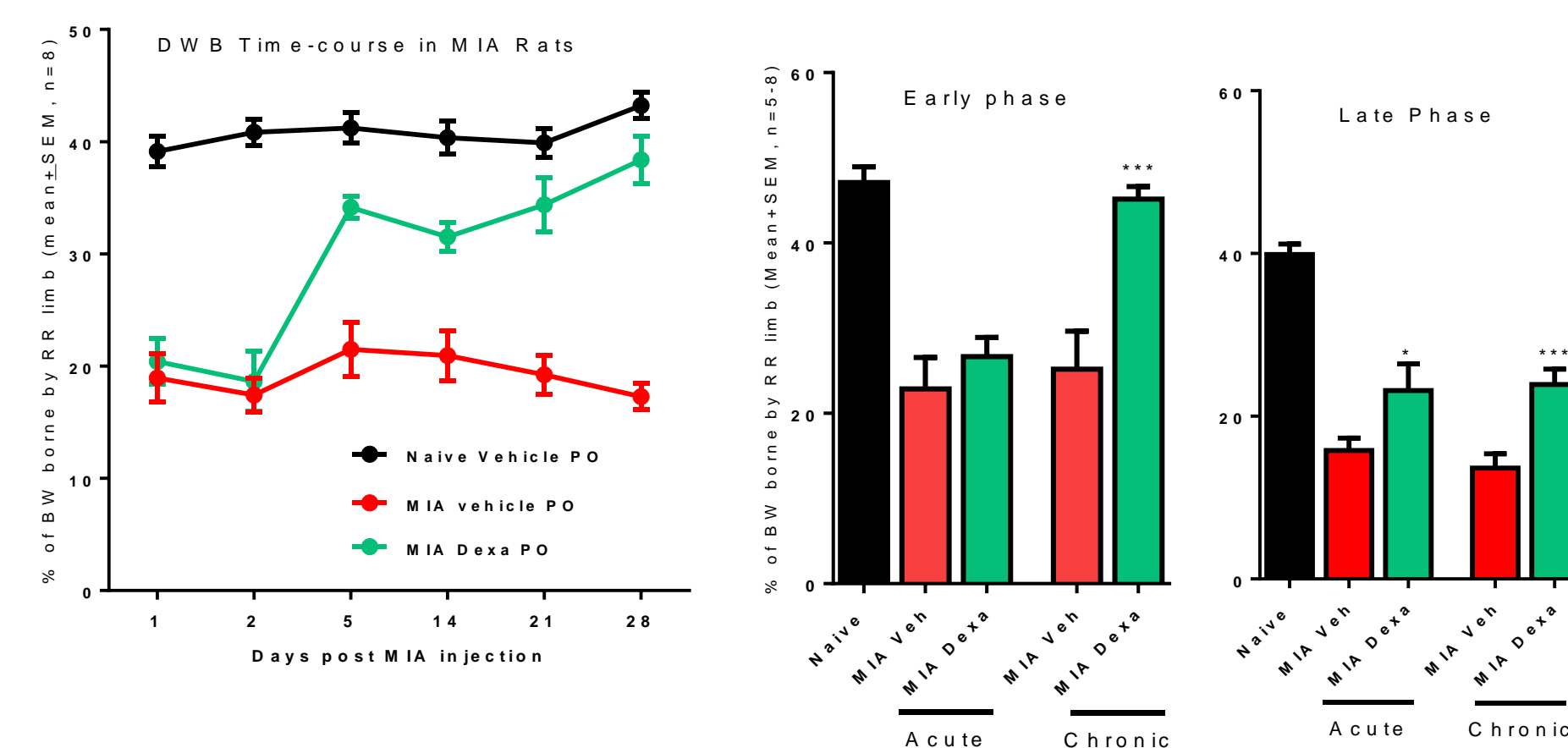


Figure 2: Left panel: DWB time-course in MIA rats and effects of dexamethasone. The window of weight bearing persisted from Day 1 to 28. Once daily oral gavage with 0.3 mg/kg of dexamethasone (Dexa) from Day 2-28 gradually prevented weight bearing deficits in MIA rats. Right two panels: Effects of dexamethasone in early (Day 2-4) and late (Day 22-24) phase of the MIA model. Dexamethasone had effects in both phases although efficacy was slightly lower in the late phase.

Effects of NSAIDs

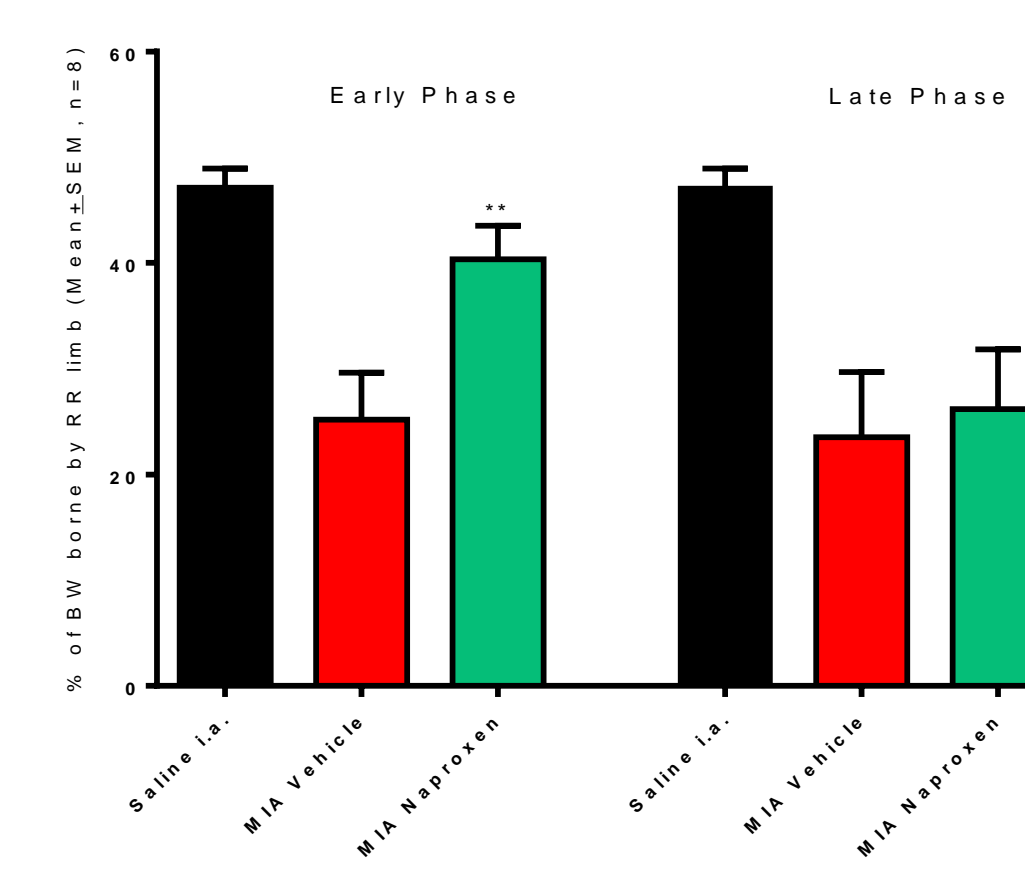


Figure 3: NSAID, naproxen (30 mg/kg, twice daily oral gavage for 3 days) was effective only in the early phase (Day 2-4) of the MIA model while no effects were observed in the late phase (Day 22-24). No acute effects were observed for naproxen.

Effects of Tramadol

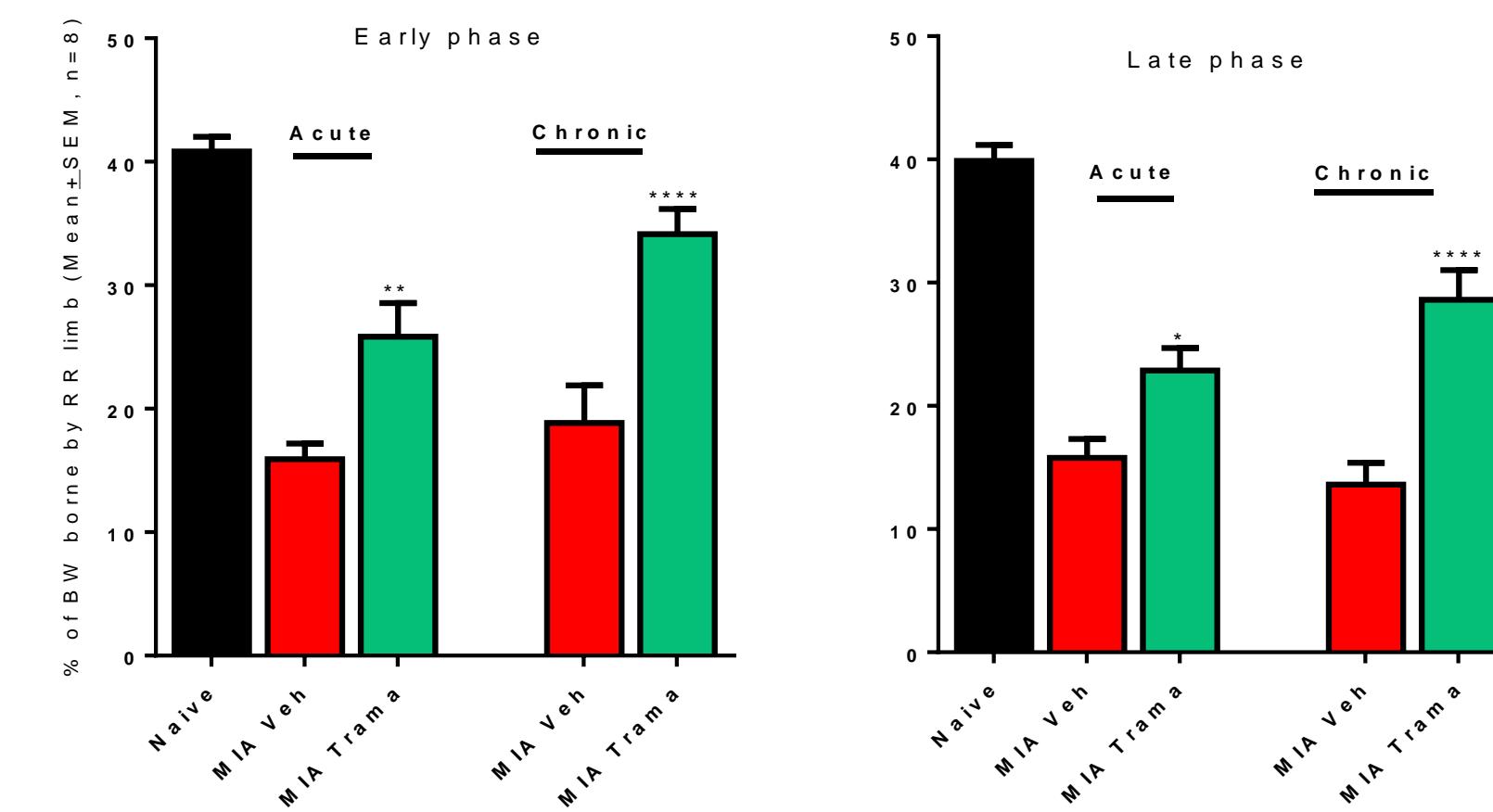


Figure 4: Tramadol (60 mg/kg, once daily oral gavage) significantly reversed the weight bearing deficits in both early (Day 2-4) and late phase (Day 22-24) of the rat MIA model following a single dosing and following 3 days of dosing. Efficacy was higher following repeated administrations.