Spinal Cord (2011) 49, 484

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LETTER TO THE EDITOR

Reply to Gallieni *et al.* and Silver

Spinal Cord (2011) **49**, 484; doi:10.1038/sc.2010.136; published online 5 October 2010

The letters by Gallieni *et al.*[1] and Silver[2] regarding our paper[3] both provided interesting insights into heterotopic ossification (HO) post spinal cord injury (SCI). It is a pleasure to be able to respond to thoughtful responses. We agree with the comments of Gallieni *et al.*[1] on the possible mechanism of warfarin treatment in preventing HO post SCI. The authors suggest that the positive effect of warfarin may be in response to its block on osteocalcin. Other studies have shown that warfarin's inhibition of osteocalcin leads to abnormal mineralization of bone matrix.[4–6] Further, these studies suggest the effect of warfarin to be even more potent during embryonic stages of bone development. Hence, though warfarin may not directly impair mineralization of bone matrix, it has a potential role in disrupting the formation of mineral crystals on collagen microfibrils involved in bone development.

We also agree with the authors' comment that there is an increased risk of cardiovascular calcification due to warfarin; however, this is a complex relationship.[1] This risk has been shown to occur in certain individuals with specific genetic variations in their carboxylation enzymes.[7] As cited by the letter of Gallieni *et al.*[1] and our article,[3] this may lead to increased risk of hemorrhage.

Our review of the literature was based upon our well-defined methodology.[8] The fact that warfarin appeared to have a protective effect in a retrospective study suggests that it has potential as a treatment; we agree that more research is needed before it can be considered as a treatment.[3]

Silver[2] provided evidence for an association between delayed passive movement (after time for contracture formation), microtrauma and HO development. In a pre-post study, Daud *et al.*[9] found that occurrence of HO was associated with the interval between admission to the SCI center and the initiation of passive movement therapy, $P<0.005$. A delay of 7 or more days of passive movement therapy post SCI was associated with an increased probability of HO development. Izumi[10] in a study of paralyzed rabbits found passive movements following immobilization of a paralyzed rabbit resulted in heterotopic bone formation. Hence, it is clear that there is an association between delayed passive movements of paralyzed joints and the development of HO post SCI; it is arguable whether that is enough to constitute a causative relationship but the evidence provided makes a compelling case.

Conflict of interest

The authors declare no conflict of interest.

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