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Letter to the Editor

Wounded tissues and neurotoxicity of polyglutamate

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ABSTRACT

A recent paper in your journal presenting a novel wound dressing material drew our attention. We notice with caution several mistakes regarding the part of the vivo study for wound dressing application in the literature. The specific ones are listed and explained in the letter to editor. In addition, we raise the concern about the potential neurotoxicity of degradation products of poly(glutamic acid).

While reading with great interest the article by Tsao et al. (2011), we noticed some flaws. In order to quantitatively evaluate the effectiveness of the dressing material, the authors used the equation: wound closure = $(L_o - L_f)/L_o \times 100\%$ to measure the wound closure rate. L_o and L_f are the length of the originally created wound, and the length of the wound postoperative for a specific time interval, respectively. Judging from the representative photographs in Fig. 6(a), the length of the wound did not change visibly within the first 3 days. However, the data in the following histogram (as presented in Fig. 6(b)) demonstrated a sharp alteration of wound closure rate at the postoperative day 3 with the exception for the control group. The two results were clearly inconsistent. As the wound healing event progressing to 7 and 14 days, the length of the wound gradually shortened as seen in Fig. 6(a), so that the wound closure rate as calculated by the above-mentioned equation should increase as time passed by. In contrast, the results given in the histogram demonstrated a regressive wound closure rate.

Aside from the contradiction between the digital photographs and the wound closure rates, we doubted the appropriateness of using the length of the wound to calculate wound closure rates. Although a linear full thickness wound was surgically created on the dorsal area of the animal, the contraction of peripheral tissue led to a quadrangular shaped wound. Thus, it is hard to describe the wound healing by simply measuring the length of the wound. As depicted in Fig. 6(a), within the initial three to seven days, the length of the wound did not change too much, but the wound shrank visibly. An alternative wound area measurement (wound closure = $(A_o - A_f)/A_o \times 100\%$) was more rigorous in terms of illustration of the wound contraction (Balakrishnan, Mohanty, Fernandez, Mohanan, & Jayakrishnan, 2006; Balakrishnan, Mohanty, Umashankar, & Jayakrishnan, 2005; Kim et al., 2005; Sung et al., 2010).

In addition, we would like to make a few comments regarding the degradation products of poly(glutamic acid). Glutamate is the predominant excitatory neurotransmitter in mammals (Fonnum, 1984). It has been recognized that glutamate can cause toxicity in the nervous system and contribute to the pathogenesis of several neurodegenerative diseases (Coyle & Puttfarcken, 1993; Sheldon & Robinson, 2007). For example, glutamate can modify the structure of amyloid β peptide through cyclization. The resulting peptide is nondegradable by most aminopeptidases leading to its accumulation and aggregation, thus taking part in the Alzheimer pathology (Perez-Garmendia et al., 2010). It is true that under the protection of the blood brain barrier, the products of chitosan/γ-poly(glutamic acid) dressing materials are not thought to readily exert hazardous effects to the nervous system. Nevertheless, polyglutamate is not exempt from serious suspects of neurotoxicity, due to the possibility that they could enter the brain when the blood brain barrier is not fully formed, or when the blood brain barrier is injured.

In conclusion, the major flaw in the Tsao et al.'s article on the polyglutamate chitosan polyelectrolyte complexes is the omission of any warning about neurotoxicity.

References

Balakrishnan, B., Mohanty, M., Fernandez, A. C., Mohanan, P. V. & Jayakrishnan, A. (2006). Evaluation of the effect of incorporation of dibutyryl cyclic adenosine monophosphate in an in situ-forming hydrogel wound dressing based on oxidized alginate and gelatin. *Biomaterials*, *27*(8), 1355–1361.

Balakrishnan, B., Mohanty, M., Umashankar, P. R. & Jayakrishnan, A. (2005). Evaluation of an in situ forming hydrogel wound dressing based on oxidized alginate and gelatin. *Biomaterials*, *26*(32), 6335–6342.

Coyle, J. T. & Puttfarcken, P. (1993). Oxidative stress, glutamate, and neurodegenerative disorders. *Science*, *262*(5134), 689–695.

Fonnum, F. (1984). Glutamate: A neurotransmitter in mammalian brain. *Journal of Neurochemistry*, *42*(1), 1–11.

Kim, M. S., Hong, K. D., Shin, H. W., Kim, S. H., Kim, S. H., Lee, M. S., et al. (2005). Preparation of porcine small intestinal submucosa sponge and their application as a wound dressing in full-thickness skin defect of rat. *International Journal of Biological Macromolecules*, *36*(1–2), 54–60.

Perez-Garmendia, R., Ibarra-Bracamontes, V., Vasilevko, V., Luna-Munoz, J., Mena, R., Govezensky, T., et al. (2010). Anti-11[E]-pyroglutamate-modified amyloid beta antibodies cross-react with other pathological A<beta> species: Relevance for immunotherapy. *Journal of Neuroimmunology*, *229*(1–2), 248–255.

Sheldon, A. L. & Robinson, M. B. (2007). The role of glutamate transporters in neurodegenerative diseases and potential opportunities for intervention. *Neurochemistry international*, *51*(6–7), 333–355.

Sung, J. H., Hwang, M. R., Kim, J. O., Lee, J. H., Il Kim, Y., Kim, J. H., et al. (2010). Gel characterisation and in vivo evaluation of minocycline-loaded wound dressing with enhanced wound healing using polyvinyl alcohol and chitosan. *International Journal of Pharmaceutics*, *392*(1–2), 232–240.

0144-8617/$ – see front matter.
doi:10.1016/j.carbpol.2011.05.068

Tsao, C. T., Chang, C. H., Lin, Y. Y., Wu, M. F., Wang, J. L., Young, T. H., et al. (2011). Evaluation of chitosan/y-poly(glutamic acid) polyelectrolyte complex for wound dressing materials. *Carbohydrate Polymers*, *84*(2), 812–819.

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