POROUS NITINOL FOR ORTHOPAEDIC APPLICATIONS: EVALUATION OF SENSITIZATION POTENTIAL

INTRODUCTION:
Nitinol has been approved for many clinical applications including orthopaedic bone anchors, vena cava filters, cardiovascular endoprostheses, and orthodontic archwires. Other nitinol orthopaedic applications include osteosynthesis staples and scoliosis correction rods [1]. Nitinol biocompatibility results mainly from its tight intermetallic bounded structure, its chemically stable and homogeneous TiO₂ surface layer, and its corrosion resistance similar to other titanium alloys. More recently introduced, porous nitinol (PNT) is a homogeneous material with isotropic porosity forms and interconnected micropores. PNT possesses the capacity to trigger both fluid and cell capillarity without the need to exert external hydraulic forces. Therefore, this porous biomaterial may be conferred interesting long-term clinical applications such as bone or soft tissue attachment and regeneration provided it succeeds biocompatibility testing and corrosion resistance evaluation.

Similarly to solid nitinol, PNT is also composed of an important amount of nickel (46 at.% Ni) that plays an important role for chemical durability and phase stability. However, potential deleterious effects such as hypersensitivity to nickel and irritation must be carefully apprehended. In this study, we have therefore investigated porous nitinol extracts capacity to stimulate sensitization, irritation and acute systemic toxicity reactions using 3 different animal models. Animal care complied with the Canadian Council on Animal Care (CCAC) guidelines for care and use of experimental animals.

MATERIALS:
Biomaterials: Porous nitinol (Actipore™, Biorthex Inc., Montreal, QC, Canada) was produced by self-propagating high-temperature synthesis. The resulting PNT alloy (22±30±130-μm pores, 68% porosity) was then reduced in powder, porous nitinol (PNT) were placed in non-pyrogenic glass vessels and autoclaved at 121°C for 1h. After sterilization, NaCl (0.9%) was added to the mixture (5mL/g PNT) and placed in an incubator (37°C, 72h). In the acute systemic evaluation, animals received PNT extracts at 50.0 mL/kg (0.1 mL/s).

Controls: NaCl (0.9%) saline (and cottonseed oil for intracutaneous injection tests) only) solutions were used as blank negative controls. A 0.3-% w/v mixture of 2,4-dinitrochlorobenzene in aceton/ethanol (50% v/v) was also used as a positive control in the skin sensitization study.

METHODS:
Skin sensitization test: As an induction procedure, Cania porcellus guinea pigs received 0.5mL of PNT extracts applied on a pre-shaved skin surface (4-6cm²) with a sterile gauge patch on the surface. The animal trunk was then tightly wrapped in a rubber dam for 6h. An evaluation of irritancy was recorded both after 30 and 54h. The same treatment was performed on Day 30. An overall product irritancy (PI) value was calculated for each animal by subtracting the average irritation score provided it succeeds biocompatibility testing and corrosion resistance evaluation.

No intracutaneous irritation was induced either by PNT materials extracted in the saline solution. In the case of cottonseed oil extraction, both the PNT and blank solution obtained a negligible to slight irritation response (PII, Table 2). Nevertheless, the difference between PNT and blank solutions PII was 1.0 or less in both extraction media. Based on these results, PNT extracts in both saline and cottonseed oil solutions have met the requirements of the test criteria for biological responses in the intracutaneous reactivity assay.

No toxic symptoms or abnormal behavior such as convulsion, prostration or sign of biological reactivity were observed with any of the mice injected with PNT or blank controls. Animals from all groups gained normal body weight and appeared healthy at all times during the 72-h recovery period. Based on these results, PNT extracts in both saline and cottonseed oil solutions have met the requirements of the systemic injection test.

RESULTS:
PNT extracts and negative control solutions did not trigger irritation responses at any circumstance during the skin sensitization assay. Therefore, the overall irritation response was equivalent to zero (0) for both the PNT and solvent-exposed animals (Table 1). However, 80% of the animals in the positive control group responded with a score increase of 1 or more at the end of the challenge period (Table 1). Based on the above results, the PNT alloy extracts were found to be non-sensitizing under the conditions of this experiment.

TABLE 1: Overall product irritancy increase (Sensitization test).

<table>
<thead>
<tr>
<th>Materials</th>
<th>% Guinea pigs responding with a overall product irritancy (PI) increase ≥ 1</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>PNT extracts (n=20)</td>
<td>0</td>
<td>Negative</td>
</tr>
<tr>
<td>Neg. control (n=10)</td>
<td>0</td>
<td>Negative</td>
</tr>
<tr>
<td>Pos. control (n=5)</td>
<td>80</td>
<td>Positive</td>
</tr>
</tbody>
</table>

TABLE 2: Primary irritation index values (Intracutaneous test).

<table>
<thead>
<tr>
<th>Extracting Solution</th>
<th>Primary Irritation Index</th>
<th>Response Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>NaCl (0.9%) (n=180)</td>
<td>PNT 0.4 ± 0.23</td>
<td>0.0 ± 0.0 Negligible</td>
</tr>
<tr>
<td>Cottonseed Oil (n=180)</td>
<td>0.32 ± 0.16</td>
<td>Negl. to slight</td>
</tr>
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DISCUSSION:
The in vivo skin sensitization, intracutaneous, and systemic injection tests that have been performed in this study represented three important methods for biocompatibility evaluation. The Buehler patch test revealed no significant skin reactions such as erythema or swelling, therefore sensitization to PNT was considered negative. In the intracutaneous test, a negligible to slight irritation was only observed at some of the sites involving the PNT extracts in cottonseed oil, however it was not significantly different than that of the cottonseed oil negative solution itself. Finally, no toxic symptoms were either observed with mice during the acute systemic toxicity test. These results correlate very well with solid nitinol investigations, where no allergenic reactions such as swelling, erythema, oedema, eschar formation, and visible reaction were observed in the past [2]. A parallel long-term animal bone implantation is currently under investigation in our lab. It will help to confirm porous nitinol biocompatibility and safety as a long-term orthopaedic implant.

REFERENCE:

**Ste-Justine Hospital, Orthopaedics Dept., Montreal (QC) Canada

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