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Development and testing of an absorbable spring for cranial expansion in rabbits

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ABSTRACT

Objective: Use of metal springs for treatment of craniosynostosis is gaining ground in the surgical armamentarium, as these springs simplify operative technique, help to avoid extended approaches, and thus minimize morbidity. Nevertheless, these devices have to be removed eventually. The purpose of this study was to perform cranial expansion with a fully integrated, biodegradable polymer spring in an animal model and to assess the efficacy of and histological reaction to this device.
Material and methods: This was an experimental, unblinded, prospective study. Twelve female New Zealand rabbits (*Oryctolagus cuniculus*) aged 6 weeks were randomly allocated to two groups. Control animals underwent linear craniectomy alone. Intervention animals underwent craniectomy with placement of a poly(lactic-co-glycolic acid)/polyisoprene (PLGA/PI) copolymer blend spring for cranial expansion transverse to the ostectomy. Expansion was measured radiographically over 12 weeks with amalgam markers. At the end of the experiment period, histological analysis was performed to quantify inflammatory reaction.
Results: The copolymer blend springs had a mean strength of 4.2N. In the intervention group, cranial expansion at the frontal markers was 9.6–11.67 mm (significantly greater than in controls). Histological analysis showed minor inflammatory reactions.
Conclusion: In this animal model, cranial expansion by linear craniectomy followed by bioabsorbable spring placement was feasible and well tolerated by adjacent tissues.

1. Introduction

In 1851, Virchow coined the term “craniosynostosis” and formulated the now-classic theory that bears his name (Virchow, 1851). Craniosynostosis has an incidence of approximately 1 in 2500 live births, and may be syndromic or isolated (Mooney et al., 1998; Ridgway and Weiner, 2004; Smartt et al., 2005; Ferreira et al., 2006; Kobus et al., 2007; Maltese et al., 2007; Di Rocco et al., 2009; Mackenzie et al., 2009; Kolar, 2011). It can cause intracranial hypertension, and, in syndromic cases, morbidity may be increased further due to exophthalmos, obstructive airway disease, and other comorbidities (Kapp-Simon et al., 2005; Di Rocco et al., 2009; Scott et al., 2009).

The main goals of craniosynostosis treatment are to expand the intracranial volume, to protect the eyes, to restore upper airway patency, and to improve cosmesis (Pearson et al., 2008; Scott et al., 2009).

The first procedure attempted for treatment of craniosynostosis was osteotomy of the affected sutures. Subsequent techniques included linear craniectomy, fronto-orbital or frontofacial advancement with or without fixation, and distraction osteogenesis (Lannelongue, 1890; Lane, 1892; Ingraham et al., 1948; Tessier, 1967; Tessier et al., 1967; Jane et al., 1978; Marchac et al., 1988; Persing and Luce, 1990; Persing and Jane, 1991; Burstein et al., 1994; Guimaraes-Ferreira et al., 2002). The hardware used for fixation or manipulation of the affected bone segments has

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included titanium plates, nylon and steel wire, and absorbable polymer implants. More recently, metal springs have been employed (Persing et al., 1986; Lauritzen et al., 1998; David et al., 2002; Guimaraes-Ferreira et al., 2002; Ferreira et al., 2006; Lauritzen et al., 2008; McIntosh et al., 2008).

Distraction osteogenesis with metal springs as a treatment for congenital cranial deformities yields outcomes comparable to those of established techniques (Persing et al., 1986; Lauritzen et al., 1998, 2008; David et al., 2002; Davis et al., 2009b). Springs combine the advantages of distraction with significant reductions in tissue elevation, dural manipulation, operative time, blood loss, and length of stay; furthermore, as they are exclusively internal, springs decrease the risk of infection and obviate the need for manual progressive distraction (Guimaraes-Ferreira et al., 2002, 2003; Lauritzen et al., 2008). Lauritzen et al. (1998) first reported the spring-based treatment of coronal craniosynostosis, and its use in other synostoses has followed (Lauritzen et al., 1998, 2008; David et al., 2002; Guimaraes-Ferreira et al., 2003; Windh et al., 2008; Davis et al., 2009b; Davis and Lauritzen, 2009). Briefly, after release of the affected suture, an omega-shaped stainless steel spring is implanted perpendicular to it. This imparts a linear force to the cranial bones, and rapid remodeling takes place over the following weeks (Gewalli et al., 2001; David et al., 2002; Guimaraes-Ferreira et al., 2003; Lauritzen et al., 2008; Pearson et al., 2008; Windh et al., 2008; Davis and Lauritzen, 2009; Davis et al., 2009b). Despite the improvement in craniosynostosis treatment provided by this technique, one disadvantage remains: the need for removal of the spring, which can be more complex than placement, as it is sometimes found completely embedded in bone, which can cause cerebrospinal fluid (CSF) leak and foreign body reaction (Stelnicki and Hoffman, 1998).

Bioabsorbable polymers have been used for osteosynthesis since the 1980s (Eitenmuller et al., 1987; Leenslag et al., 1987) and have become increasingly popular in the treatment of craniofacial anomalies, particularly in children (Eppley et al., 2004). These materials have properties such as inertia, strength, and elasticity comparable to those of metals such as titanium alloys (Dhol et al., 2008; Uckan et al., 2009), with the added advantage of not requiring removal; this makes them useful in any setting where leaving hardware in indefinitely or removing it would increase morbidity.

Within this context, the present study describes the development of a fully integrated, bioabsorbable spring device and its experimental use and efficacy testing for cranial expansion after linear craniectomy in rabbits.

2. Material and methods

2.1. Design

This was an experimental, open-label, prospective study.

2.2. Population and sample size calculation

The study sample comprised 12 female New Zealand rabbits (*Oryctolagus cuniculus*) aged 45 days (6 weeks).

In line with the previous literature, animals were divided into two groups: a control and an intervention group (Gewalli et al., 2001; Sanger et al., 2007; Davis et al., 2009a,b). Sample size was calculated with the open-source WinPepi software. The sample size required to demonstrate a 6-mm difference between markers over a 12-week study period, with a standard deviation of 1.7 mm and 80% statistical power, was determined as 12 animals (six animals per group).

Animals in the control group ($n = 6$) underwent sagittal ostectomy alone, whereas those in the intervention group ($n = 6$) underwent ostectomy and spring placement. Both groups were monitored radiographically over time.

To assess the proposed operative technique and to optimize radiographic assessment, a pilot study with two animals was conducted before the main experiment.

2.3. Implants

The spring implants used in the study intervention were manufactured from a bioabsorbable poly(lactic-co-glycolic acid)/polyisoprene (PLGA/PI) copolymer blend (Jahno et al., 2007; Marques, 2011) at the Biomaterials Laboratory, UFRGS School of Engineering (LABIOMAT, Porto Alegre, Brazil).

PLGA (84 mol%:16 mol% L-lactide/glycolide monomer ratio) was obtained from Purac Biomaterials (the Netherlands) and used as supplied, without any additional purification or processing. The pH as supplied was 7.2, thus obviating the need for neutralization (Marques, 2011).

PI was obtained from Mafer Ltda (Estância Velha, Brazil) as 60% centrifuged natural rubber latex. The pH as supplied was 10.0–11.2. Therefore, the material was neutralized with 2 M HCl solution to a pH range of 7.2–7.8. Before use, the polymer was completely dried and purified by reprecipitation from chloroform into methanol. After precipitation, the material was dried again (Marques, 2011). Chloroform and methanol (both 99.8%) were obtained from Synth (São Paulo, Brazil) and used as supplied.

The springs were manufactured as follows. Briefly, solid PLGA and PI were weighed separately. The materials, at a ratio of 60% PLGA: 40% PI by mass (51% PLGA: 49% PI by volume), were dissolved in chloroform by magnetic stirring. After homogenization, the polymer/solvent mixture was dried for 72 h at 40 °C for solvent evaporation. The resulting material was injection molded at 165 °C in a HAAKE MiniJet II system (Thermo Scientific) to form necked samples (width 4 mm, length 30 mm, thickness 2 mm). These specimens were molded in distilled water at 70 °C. For mechanical characterization, all specimens underwent compression testing in an Instron 3369 universal testing machine with a 2-kN load cell. The test was performed as per ISO standard 527-1 (British Standards Institution, 1996) at LABIOMAT.

2.4. Operative technique

All procedures involving animals were conducted at the HCPA Animal Experimentation Unit (UEA-HCPA). Ketamine (20 mg/kg IM), xylazine (1 mg/kg IM), and tramadol (5 mg/kg IM) were administered as preanesthesia. General anesthesia was induced and maintained with inhaled isoflurane via orotracheal cannula. After induction, the head of each animal was shaved and prepared with povidone–iodine, and the incision site infiltrated with bupivacaine 0.5% (2 mg/kg). A 3-cm midline skin incision was made and the scalp reflected. The periosteum was minimally mobilized to expose the sagittal and lambdoid sutures. Using a low-speed handpiece with 5-mm bur and an elevator, a 6 mm-wide midline linear craniectomy was performed, starting 10 mm anterior to the coronal suture and extending to the lambdoid suture. Dural manipulation was kept to a minimum. The same handpiece, with a 1.5-mm round bur, was then used to place amalgam markers at either side of the ostectomy, perpendicular to the coronal and lambdoid sutures, as shown in Fig. 1.

The springs were sterilized in a hydrogen peroxide plasma system (Sterrad 100, Johnson & Johnson) as per routine HCPA practice and shaped in hot saline solution (70 °C) for optimal strength and fit. The springs were implanted in an anteroposterior