Journal of Cranio-Maxillo-Facial Surgery xxx (2018) 1–9

Contents lists available at ScienceDirect

Journal of Cranio-Maxillo-Facial Surgery

journal homepage: www.jcmfs.com

Preclinical randomized controlled trial of bilateral discectomy versus bilateral discopexy in Black Merino sheep temporomandibular joint: TEMPOJIMS – Phase 1- histologic, imaging and body weight results

David Faustino Ângelo [a, b, *], Pedro Morouço [b], Florencio Monje Gil [c], Lisete Mónico [d], Raúl González-Gárcia [c], Rita Sousa [a], Lia Neto [a], Inês Caldeira [a], Margaret Smith [e], Susan Smith [e], David Sanz [d], Fábio Abade dos Santos [f], Mário Pinho [f], Belmira Carrapiço [f], Sandra Cavaco [g], Carla Moura [b], Nuno Alves [b], Francisco Salvado [a], Christopher Little [e]

[a] Faculty of Medicine of Lisbon University, Av. Prof. Egas Moniz, 1649-035 Lisboa, Portugal
[b] Centre for Rapid and Sustainable Product Development, Polytechnic Institute of Leiria, Portugal, Rua de Portugal, Zona Industrial, Marinha Grande, 2430-028, Marinha Grande, Portugal
[c] Infanta Cristina Hospital, Faculty of Medicina, University of Extremadura, Av. Elvas, S/N, 06006 Badajoz, Spain
[d] Faculty of Medicine of Coimbra University, Portugal
[e] Kolling Institute, Institute of Bone and Joint Research, University of Sydney, Australia
[f] Faculty of Veterinary Medicine of Lisbon University, Portugal
[g] Instituto Nacional de Investigação Agrária e Veterinária (INIAVIP), Portugal

ARTICLE INFO

Article history:
Paper received 26 November 2017
Accepted 22 January 2018
Available online xxx

Keywords:
Preclinical study
TMJ discectomy
TMJ discopexy
TMJ imaging
TMJ histology
TMJ disc

ABSTRACT

Introduction: The role of temporomandibular joint (TMJ) surgery is not well defined due to a lack of quality randomized controlled clinical trials, comparing different TMJ surgical treatments with medical and placebo interventions. The temporomandibular joint interposal study (TEMPOJIMS) is a rigorous preclinical trial divided in 2 phases. In phase 1 the authors investigated the role of the TMJ disc and in phase 2 the authors evaluated 3 different interposal materials. The present work of TEMPOJIMS – phase 1, aims to evaluate histopathologic and imaging changes of bilateral discectomy and discopexy in Black Merino sheep TMJ, using a high-quality trial following the ARRIVE guidelines.

Material and methods: This randomized, blinded and controlled preclinical trial was conducted in 9 Black Merino sheep to investigate histopathologic (primary outcome), imaging and body weight (secondary outcomes) changes after bilateral discectomy, discopexy and sham surgery.

Results: Significant changes were noticed in discectomy group, both in imaging and histopathologic analyses. Body weight changes were most pronounced in the discectomy group in the first 4 months after surgery with recovery to baseline weight 6 months after surgery. Discopexy induced nonsignificant changes in histopathologic, imaging and body weight analyses.

Conclusions: This study reinforces the importance of developing an effective interposal material to substitute the TMJ disc and the need to explore the molecular mechanisms that underlie TMJ cartilage degeneration. The study design proposed in TEMPOJIMS represents an important progress towards future rigorous TMJ investigations.

* Corresponding author. Fax: +351 21 798 5110.
E-mail addresses: david.serrano.angelo@gmail.com (D.F. Ângelo), pedro.morouco@ipleiria.pt (P. Morouço), fmonje@oralmaxilofacial.com (F. Monje Gil), lisetemonico@gmail.com (L. Mónico), Raulmaxilo@gmail.com (R. González-Gárcia), ritafsousa1@gmail.com (R. Sousa), lia_neto@yahoo.com (L. Neto), maria_caldeira@hotmail.com (I. Caldeira), mobsmith@sydney.edu.au (M. Smith), susan.smith@sydney.edu.au (S. Smith), d.sanz@hotmail.com (D. Sanz), faas@outlook.pt (F. Abade dos Santos), mpinho@fmv.ulisboa.pt (M. Pinho), belmira@fmv.ulisboa.pt (B. Carrapiço), sandracavaco1@gmail.com (S. Cavaco), carla.moura@ipleiria.pt (C. Moura), nuno.alves@ipleiria.pt (N. Alves), fjsalvado2002@yahoo.com (F. Salvado), christopher.little@sydney.edu.au (C. Little).

https://doi.org/10.1016/j.jcms.2018.01.006
1010-5182/

Please cite this article in press as: Ângelo DF, et al., Preclinical randomized controlled trial of bilateral discectomy versus bilateral discopexy in Black Merino sheep temporomandibular joint: TEMPOJIMS – Phase 1- histologic, imaging and body weight results, Journal of Cranio-Maxillo-Facial Surgery (2018), https://doi.org/10.1016/j.jcms.2018.01.006

1. Introduction

In severe temporomandibular disorders (TMD) the standard treatment is mostly surgical (Dimitroulis, 2013). However, the role of temporomandibular joint (TMJ) surgery is not well defined (Dimitroulis, 2005) due to a lack of quality randomized controlled clinical trials, comparing TMJ surgical treatment with medical treatment and placebo (Reston and Turkelson, 2003; Souza et al., 2012). TMJ open surgical approaches for severe disorders include mostly discectomy or discopexy. In cases where nothing in the joint is salvageable, a total joint replacement may be necessary (Dimitroulis, 2013). Despite the large number of discectomy procedures performed annually, we are not aware of any rigorously performed, randomized, controlled trials that have investigated, in human or animal, the effectiveness of discectomy, compared with discopexy, bioengineered interposal material and sham surgical interventions. Previous studies stated a significant increase in TMJ osteoarthrosis (OA), following discectomy with and without replacement of the disc with an interpositional implant (93% and 100%, respectively). These authors presented a reduced incidence of OA (62%) when using discopexy. Still, this technique was associated with frequent relapse, requiring a secondary discectomy (Trumpy and Lyberg, 1995). These outcomes clearly demonstrate the importance of further studies to deeper understand the effects of surgery and progress for future development of interposal materials.

Most clinical trials use imaging to classify the TMJ degenerative process (Eriksson and Westesson, 2001). Computed tomography (CT) is a valuable tool to evaluate TMJ OA (Cordeiro et al., 2016) and it is used by most clinical studies to evaluate articular changes (Boman, 1947; Eriksson and Westesson, 1985; Hall, 1985; Kiehn and Desprez, 1962; Silver, 1984; Takaku et al., 1994; Tolvanen et al., 1988). Two important long-term follow-up clinical studies presented condylar flattening and sclerosis after discectomy, but these were not associated with TMJ symptoms (Eriksson and Westesson, 1985; Hall, 1985; Silver, 1984; Tolvanen et al., 1988). Opposingly, The *Desprez* group (1962) suggested an association of articular erosion with pain in the post-operative period (Kiehn and Desprez, 1962). While imaging modalities are key measures in clinical research, preclinical studies provide a unique chance to also obtain histologic pathology to better understand TMJ surgery-induced changes and improve knowledge for interposal materials research. Previous preclinical studies have evaluated histologic and imaging outcomes using study designs with a potential sources of bias (selection bias, measurement bias, non-randomization, non-blinded outcome assessment) increasing risk of errors in the results of the study, and in further conclusions (Block and Bouvier, 1990; Choukas et al., 1969; Hagandora and Almorza, 2012; Laurell et al., 1987; Macher et al., 1992; Ogi et al., 1996).

The Temporomandibular Joint Interposal Material Study (TEMPOJIMS) was planned with a rigorous pre-published design (Ângelo et al., 2017) according to the ARRIVE guidelines (Kilkenny et al., 2010). This first high-quality randomized preclinical study, performed in Black Merino sheep, was required to increase the translational power of further studies and to progress in future treatment options for patients undergoing surgery for TMJ disc replacement. TEMPOJIMS is divided into phase 1 and 2. Phase 1 was a randomized, blinded preclinical trial designed to investigate the TMJ imaging (CT), histopathologic, and body weight changes in sheep after bilateral discectomy, discopexy or sham surgery. Phase 2 uses the same design to test different bioengineering scaffolds to replace the TMJ disc in sheep. It is critical that all assessments are performed and classified independently by two professionals, from each area, who are blinded to intervention. In both phases the primary outcome was the histological grading of TMJ pathology. The main goal of the present investigation was to examine the effects of bilateral surgery over the phase 1 outcomes.

2. Material and methods

2.1. Study design

The rationale and protocol for the TEMPOJIMS preclinical trial are publicly available (Ângelo et al., 2017). An independent data and safety monitoring board unblinded preclinical results. The study was approved by the Portuguese National Authority for Animal Health registered with number 026618. The study design and organization respected the ARRIVE guidelines (Kilkenny et al., 2010).

2.2. Study population and sample

Relevant preclinical TMJ studies have been conducted in sheep (Ishimaru and Goss, 1992; Matsuura et al., 2006; Miyamoto et al., 1999; Ogi et al., 1996; Takaishi et al., 2007), and to decrease biological variability in TEMPOJIMS results, a specific purebred Black Merino sheep strain was used (Ângelo DF et., 2017). In 2016, our group performed an anatomic, biomechanical and histologic study of Black Merino sheep TMJ highlighting the potential of this animal to conduct preclinical trials in the TMJ domain (Angelo et al., 2016). The following eligibility criteria were used: certified *Black Merino* sheep, adult (aged between 2 and 5 years), female, and in good health condition (evaluation was performed by veterinaries, also confirming normal dentition).

2.3. Randomization

The randomization process was performed by a statistical group, not enrolled in the outcome assessments. Ten sheep were randomly allocated to the intervention group: bilateral sham surgery (n = 3), bilateral discectomy (n = 3), bilateral discopexy (n = 3), and backup group (n = 1). One backup sheep was planned to be used if death occurred due to anaesthesia, or other complication not related to surgical intervention. The allocation to each randomized group was performed preoperatively by sealed envelope.

2.4. Procedures

Ten eligible sheep were selected and baseline body weight was measured at days 11, 10, and 9 before surgery. Transportation to surgical facilities was performed 5 days before surgery to avoid animal stress and allow familiarization to the temporary accommodation. Head CT-scan was performed on the day of surgery taking advantage of pre-anaesthesia sedation (supplementary material doc 1). The surgical team was not blinded to treatment allocation given the type of intervention; however surgical team members were not involved in outcome assessment. Serious adverse events were defined as events that were fatal or life-threatening or persistent disability, or that resulted in death, over 10% weight loss per week, or clinically significant hazard or harm to the animal.

2.5. Intervention phase

2.5.1. Anaesthesia protocol

Fasting and water restriction were required 24 h before surgery. Sedation was performed with diazepam (0.5 mg/kg i.v.), followed by anaesthesia induction with ketamine (5 mg/kg i.v.). Oral intubation was performed and anaesthesia was maintained with isoflurane (1.5–2%). To guarantee animal analgesia, meloxicam

Please cite this article in press as: Ângelo DF, et al., Preclinical randomized controlled trial of bilateral discectomy versus bilateral discopexy in Black Merino sheep temporomandibular joint: TEMPOJIMS – Phase 1- histologic, imaging and body weight results, Journal of Cranio-Maxillo-Facial Surgery (2018), https://doi.org/10.1016/j.jcms.2018.01.006