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Efficacy of *Plantago major*, chlorhexidine 0.12% and sodium bicarbonate 5% solution in the treatment of oral mucositis in cancer patients with solid tumour: A feasibility randomised triple-blind phase III clinical trial

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ABSTRACT

Purpose: Oral mucositis is one of the most common adverse effects of chemotherapy and radiotherapy. The aim of this study was to compare the efficacy of *Plantago major* extract versus chlorhexidine 0.12% versus sodium bicarbonate 5% in the symptomatic treatment of chemotherapy-induced oral mucositis in solid tumour cancer patients.

Method: Multicentre randomised controlled trial estimated sample of 45 solid tumour patients with grade II-III mucositis. The participants were randomised to one of three treatments, consisting of sodium bicarbonate 5% aqueous solution together with: an additional dose of sodium bicarbonate 5% aqueous solution, *Plantago major* extract, or chlorhexidine 0.12%. The primary outcomes were severity of mucositis, pain intensity, oral intake capacity and quality of life. The independent variable was treatment group, and confounders included socio-demographic data, neutrophil count, chemotherapy drug and dose received.

Results: Of the 50 patients enrolled, 68% (n = 34) achieved grade 0 mucositis (none), with those using the double sodium bicarbonate rinse healing in five days on average (95% CI 3.9, 6.5) versus seven days (95% CI 5.3, 9,0) for the chlorhexidine group and seven days (95% CI 5.3, 8.5) for the *Plantago major* group. The pain experienced by the participants lessened over the 14 days of treatment, but differences in pain intensity between the three groups did not show statistical significance (p = 0.762).

Conclusions: Healing time was shorter with the double sodium bicarbonate solution compared to the other two rinses, but the differences were not significant. Our results suggest it may be time to reconsider the use of *Plantago major* extract in the management of oral mucositis.

1. Introduction

Oral mucositis is diagnosed in 40%–50% of cancer patients treated with chemotherapy. The condition may affect up to 80% of patients undergoing hematopoietic stem cell transplantation and 100% of patients receiving head and neck radiation therapy (Silverman, 2007; Sonis, 2011). The first symptoms appear 5–7 days after starting chemotherapy and typically last 7–14 days (even longer in some cases) before healing completely. Sonis ST has described the molecular mechanisms involved in chemoradiotherapy toxicity in cell tissue (Sonis, 2004a, 2004b). When an external factor causes cellular DNA damage, reducing capacity for cell renewal, the pathobiology of mucositis begins (Sonis, 1998). Multiple intrinsic and extrinsic factors determine the occurrence and severity of mucositis outbreaks (Facchini et al., 2012; Sabater-Recolons et al., 2006). The condition is associated with health problems such as risk of infection (Chen et al., 2011), pain (Marlow, 2005; Yamashita et al., 2002; Harris, 2006; Clarkson et al., 2010), decreased oral intake capacity (Jensen et al., 2010; Marazzi,

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2015; Nugent et al., 2013) and disrupted quality of life (QoL) (Cheng et al., 2007; Cheng, 2008; Kim et al., 2012; Kartin et al., 2014; Ni Riordain et al., 2011). In addition, the onset of mucositis can be dose-limiting, meaning the optimal treatment regimen cannot be administered (Ogata et al., 2016), and the treatment period is extended as a result, increasing the need for healthcare resources (Murphy, 2007; Vera-Llonch et al., 2007; Sonis et al., 2001; Elting et al., 2003).

Systematic reviews have examined the effectiveness of therapeutic interventions for oral mucositis (Mcguire et al., 2013; Saunders et al., 2013; Keefe et al., 2007). The latest clinical practice guidelines provided by the Mucositis Study Section of the Multinational Association of Supportive Care in Cancer and the International Society for Oral Oncology (MASCC/ISOO) (Lalla et al., 2014) list three prevention strategies: (1) the use of growth factors (keratinocyte growth factor-1 (KGF-1/palifermin)) (Raber-Durlacher et al., 2013); (2) the use of a low-intensity laser (low-level laser therapy: wavelength at 650 nm, power of 40 mW, and dose of 2 J/cm2); and (3) the application of cryotherapy for 30 min in patients treated with bolus 5-fluorouracil chemotherapy (Katrancı et al., 2012; Svanberg et al., 2012; Peterson et al., 2013). The available evidence is less conclusive on the active treatment of mucositis (Clarkson et al., 2010; Aghamohamamdi and Hosseinimehr, 2016). Growth factors should only be applied subcutaneously in the presence of neutropaenia, and low-intensity laser treatment is only beneficial for reducing the severity of mucositis (Clarkson et al., 2010; Mcguire et al., 2013).

Patients frequently use medicinal plants with anti-inflammatory, antiseptic, or emollient properties as an alternative to other drug solutions for treating mucositis (Aghamohamamdi and Hosseinimehr, 2016; Braga et al., 2015). Plantain or *Plantago* (*major*, *coronopus*, *media*, *lanceolata*, *alopex*) is used for its anti-inflammatory properties to treat oral diseases such as gingivitis and canker sores (Herold et al., 2003; Vizoso-Parra et al., 2000). It is usually administered as a mouthwash in the form of an infusion or extract. Studies examining *Plantago*'s ability to heal wounds have only evaluated the preclinical stages (Zubair et al., 2012). Several studies have described the medicinal effects of various *Plantago* species resulting from a decreasing inflammatory cascade process caused by nuclear factor (NF)-kappa B, nitric oxide (NO), cyclooxygenase-2 (Cox-2), and B4 leukotrienes (LB4) (Herold et al., 2003; Vizoso-Parra et al., 2000; Zubair et al., 2012; Rahimi et al., 2010). Some of these factors are relevant to mucositis development, but to date no randomised controlled trials have evaluated the clinical efficacy of this plant species in mucositis.

The objective of this randomised controlled trial is to evaluate the efficacy of a *Plantago major* extract mouthwash in the symptomatic treatment of oral mucositis in cancer patients with solid tumours, versus chlorhexidine 0.12% or an aqueous solution of 5% sodium bicarbonate, in terms of: (1) healing time, (2) pain, (3) oral intake and (4) quality of life.

2. Methods

2.1. Design and intervention

A randomised, controlled, phase III clinical trial (phase III RCT), with three parallel treatment groups: group A (control: regular practice in Catalan Institute of Oncology health care services) used sodium bicarbonate 5% aqueous solution and sodium bicarbonate 5% aqueous solution; group B (experimental) used sodium bicarbonate 5% aqueous solution plus *Plantago major* extract, (every 200 g of the *Plantago major* extract formula contained: *Plantago major* 5% [120 g]; potassium chlorate [8 g], sodium bicarbonate [6 g], Rodomiel [60 g] and Resorcinol [6 g]),[39]; and group C (experimental) used sodium bicarbonate 5% aqueous solution plus chlorhexidine 0.12%. Each participant was randomly assigned to one of the three groups for the treatment of a single mucositis outbreak. The proposed treatment was 14 days, based on models similar to those presented, and in accordance with physiology studies on the cell renewal process (Sonis, 2004a, 2004b). Patients received telephone follow-ups to ensure adherence during treatment.

2.2. Ethics statement

Our protocol was approved by Research Ethics Committee reference (Catalan Institute of Oncology, Catalonia; REF: AC-05-017) and registered with the European Union Drug Regulating Authorities Clinical Trials (REF: 2005-000689-38).

2.3. Setting and participants

Participants were recruited in three cancer centres in Spain over 36 months. The estimated sample size was 45 patients (15 per group), calculated assuming a two-day difference in duration of lesions (SD 2) (Cabrera-Jaime et al., 2006) and type I error 5%, using the 2000 Epicalc programme. We applied the following inclusion criteria: patients diagnosed with solid tumours and undergoing chemotherapy, over 18 years of age, of both sexes and all ethnicities, presenting grade II or III mucositis according to the World Health Organization (WHO) scale, and who gave informed consent. The exclusion criteria were: head and neck radiotherapy; haematological disorders; and treatment with growth factors, antibiotics, antivirals, antifungals or monoclonal drugs. All available and eligible patients were invited to participate. The criteria for withdrawal were: starting treatment with antibiotics, antifungals, antivirals or growth factors during the study period, along with voluntary withdrawal.

2.4. Sequence generation and allocation concealment

The pharmacy department randomised the patients into blocks of six using a computer programme. The medication was prepared in the central pharmacy office and sent, coded for subsequent administration, to the outpatient area. To ensure triple blinding, we used opaque containers of identical size and containing products of the same colour, associated with an indecipherable code that was not decoded until completion of statistical processing. This meant the principal investigator, care providers, the patients and statistician were all blinded to treatment allocation.

2.5. Data collection

The dependent variables were: mouthwash efficacy measured in days needed to reach grade 0 on the WHO mucositis scale; pain intensity, measured on a visual analogue scale (VAS); oral intake capacity (measured by asking participants whether they were able to tolerate solids and liquids or only liquids), and QoL, measured using the validated European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) (Version 3.0 Spanish). The independent variable was treatment group (A, B, C) and the confounding variables considered were the presence of dental prostheses, type and dose of chemotherapy, concomitant drug therapy, neutrophil count, weight, age, sex and ethnicity.

A clinical nurse at each centre was responsible for recruiting patients, dispensing mouthwashes, and offering education on managing mucositis. They also assessed and recorded the clinical data. All participants received a set of instructions, a diary to record signs and symptoms (pain, presence of sores, consumption of painkillers) and recommendations for correctly storing the mouthwashes. The instructions indicated that participants should rinse for 2 min with 8 ml from each product container every 6 h, with a 15-min interval between the two mouthwashes. The patient diary included a VAS for recording pain intensity. To assure adherence, patients were asked to attend weekly oral check-ups and return the mouthwash containers.

At baseline, the clinical nurse recorded the inclusion date,