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Dimethyl sulfoxide but not indomethacin is efficient for healing in hydrofluoric acid eye burns

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ABSTRACT

Introduction: In this study, we aimed to investigate the effect of indomethacin and dimethyl sulfoxide (DMSO), well-known antioxidant and anti-inflammatory agents, to heal eye burns induced with hydrofluoric acid in rabbits.

Methods: After general anesthesia, the right eye of 72 male New Zealand rabbits were burned by instillation of 2% hydrofluoric acid for 60 s. Following this, the eyes were irrigated with 500 cc normal saline. The rabbits were then divided into four groups of 18 rabbits each. Group D was instilled dimethyl sulfoxide 40%, Group I indomethacin 0.1%, and Group DI dimethyl sulfoxide together with indomethacin for 2, 7, and 14 treatment days, respectively. Group C received no instilled drug as control. Treatment efficacies were evaluated as clinical (corneal haziness, conjunctival status, conjunctivitis, corneal erosion area, and intraocular pressure) and histopathological (inflammatory cell infiltration, vascularization, stromal thickness, reepithelization, proliferating cell nuclear antigen [PCNA], apoptosis, and inducible nitric oxide synthases [iNOS]).

Results: In terms of corneal haziness and erosion area at days 7 and 14, group D showed the best result statistically as compared to the other groups. This group also showed the best result statistically for reepithelization rate, stromal thickness, and inflammatory cell end at day 14 as compared to the other groups.

Conclusions: Dimethyl sulfoxide (40%) was efficient to induce reepithelization on mild hydrofluoric acid eye burns, whereas 0.1% indomethacin both alone and along with DMSO poorly induced reepithelization and exacerbated inflammation. Thus, 40% DMSO could be used for the treatment of corneal disorders.

1. Introduction

Hydrofluoric acid (HF) burns are becoming increasingly common with its wide use in industrial and domestic areas. Although remarkable studies have been performed regarding dermal burn, there is little information regarding the ideal treatment of HF acid eye burns. Compared with other acids, HF acid results in more extensive injury in ocular tissue because of the corrosive hydrogen ions and toxic fluoride ions that can penetrate deep into tissue, causing subsequent liquefaction necrosis [1–3]. The failure of proper corneal repair following

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such severe chemical burn often causes loss of vision [4]. The main strategies in controlling these injuries include immediate irrigation to reduce further damage, decrease inflammation, and promote healing and re-epithelialization to prevent ulceration and perforation [5,6]. For each of these steps, many studies have been performed to evaluate the efficacy of different medications for severe ocular HF acid burns [1,3,7,8].

In degenerative and inflammatory conditions such as chemical eye burns, toxic free radicals are generated by lipid peroxidation, which decrease antioxidant protection activity of the body. In particular, polymorphonuclear leukocytes (PMNLs) release collagenase, and their respiratory bursts form free oxygen radicals that could cause further tissue damage. In such cases, to prevent permanent damage to the eye tissue, several researchers have reported that natural antioxidants and anti-inflammatory drug combinations play a major role in treatment [9–14].

Dimethyl sulfoxide (DMSO) is a drug characterized by anti-inflammatory and analgesic, weak bacteriostatic, anticoagulant, and anti-ischemic effects and has the ability to remove free radicals [9,15,16]. It has been used in the treatment of ophthalmological diseases [17–21]. Administration of 50% DMSO combined with dexamethasone in the treatment of chronic superficial keratitis (CSK) in dogs has been reported to be much more effective than the administration of dexamethasone alone by reducing the inflammatory process [17]. In particular, long-term administration (10 months) of DMSO in the treatment of CSK has been reported to reduce the formation of inflammatory products and cause no side effects on the corneal epithelium [18]. DMSO accelerated the healing of corneal ulceration in rabbits [19] and reduced neovascularization in the treatment of CSK [21]. Moreover, the useful effects of DMSO in cases of alkali corneal burn in rabbits were demonstrated by Skrypuch et al. [21].

Topical indomethacin, which is a nonsteroidal anti-inflammatory drug, is widely used in the prevention of inflammation of the eye [22]. It was also used for alkali eye burn [5,23]. One study reported that indomethacin showed results similar to steroids or more effective results than steroids in acute corneal alkali burns when used alone or in combination with an antioxidant [5].

Studies related to the usage of antioxidants and indomethacin in chemical eye burns have generally focused on alkali burns [5,23,24]. The hypothesis of the present study was that the combination of DMSO and indomethacin might be effective in healing experimental HF acid eye burn in rabbits because exogenous antioxidants and indomethacin are highly effective in acute alkali eye burns. Therefore, this study was planned to investigate the efficacies of DMSO and indomethacin on the experimental HF acid eye burn model.

2. Methods

2.1. Animals

The study was conducted on a total of 72 male New Zealand rabbits (weighing 2–2.5 kg); they were allocated to four groups of 18 rabbits each and were housed individually and fed *ad libitum*. Each group was then divided into three subgroups with six animals each at 2, 7, and 14 days. This study was performed in compliance with national and international laws and guidelines on animal handling, and the experimental protocol was approved by the Animal Ethical Committee of University of Selçuk (approval number: 2010/15).

2.2. Drugs

In this study, 40% DMSO (99.9%, Merck, USA), 0.1% indomethacin (İndocolir® 5 mL, Abdi-İbrahim, Turkey) alone, and their combinations were used. To prevent possible infections, topical tobramycin (Tobrased® 3%, Bilim, Turkey) and dipyrone (Devalgine® 0,5 g/mL, Vetaş, Turkey) were used as analgesic agents in all groups, respectively. For general anesthesia, 2% xylazine hydrochloride (Rompun®, Bayer, Turkey) and 10% ketamine hydrochloride (Ketasol®, Interhas, Turkey) were used.

2.3. Experimental corneal acidic burn model

After routine examinations, by using the experimental procedure of Beiran et al. [1], under general anesthesia of xylazine (10 mg/kg) and ketamine (30 mg/kg), the right eye of each rabbit was exposed to 0.05 mL of 2% HF (38–40% Merck, USA) for 60 s followed by flushing with 500 mL 0.9% isotonic saline, followed by 14 mg/kg dipyrone given intramuscularly prior to corneal burn. Dipyrone was continued every 6 h for 2 days.

DMSO, 175 mg/kg/day, was applied in 4 drops, 4 times a day, according to the therapeutic index of 100–200 mg/kg/day [25] in the first group (D). Indomethacin was applied in 4 drops, 4 times a day in the second group (I). DMSO and indomethacin were applied together, as was administered in the first and second groups, respectively, in the third group (DI). The control group was not given any treatment as the fourth control group (C). Another control group using hydroxypropyl-β-cyclodextrin, HCL, and pure water as carriers of indomethacin was not included in the study because there was no information about the percentage of carriers. This lack of information might cause endless alternatives of different preparations to be formed, which would not be the same as that used in the original commercial preparation of Indocolir® % 0.1, 5 ml-Abdi-Ibrahim, Turkey, thus leading to incorrect and irrelevant results.

2.4. Clinical examination

Intraocular pressure (IOP) was measured with a rebound tonometer (Tonovet, Icare, Finland) prior to experiment (0) and on the 2nd, 7th, and 14th day in all groups. Burn-induced eyes were examined with a hand type slit-lamp (Heine HSL 150, Germany) on 2nd, 7th, and 14th day, both prior to and after staining with 1% fluorescein strips, and the images were photographed with a digital camera (Sony DSC-HX 1, Japan). Clinically, corneal haziness and conjunctival status in all groups were evaluated using a scoring method developed by Beiran et al. [1]. Conjunctivitis was also evaluated depending on the severity of inflammation by assigning a score between 0 and 4 (Table 5).

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