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Mussel-mimetic tissue adhesive for fetal membrane repair: An ex vivo evaluation

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ABSTRACT

Iatrogenic preterm prelabor rupture of membranes (iPPROM) remains the main complication after invasive interventions into the intrauterine cavity. Here, the proteolytic stability of mussel-mimetic tissue adhesive (mussel glue) and its sealing behavior on punctured fetal membranes are evaluated. The proteolytic degradation of mussel glue and fibrin glue were compared in vitro. Critical pressures of punctured and sealed fetal membranes were determined under close to physiological conditions using a custom-made inflation device. An inverse finite element procedure was applied to estimate mechanical parameters of mussel glue. Mussel glue was insensitive whereas fibrin glue was sensitive towards proteolytic degradation. Mussel glue sealed 3.7 mm fetal membrane defect up to 60 mbar (45 mm Hg) when applied under wet conditions, whereas fibrin glue needed dry membrane surfaces for reliable sealing. The mussel glue can be represented by a neo-Hookean material model with elastic coefficient C_1 = 9.63 kPa. Ex-vivo-tested mussel glue sealed fetal membranes and resisted pressures achieved during uterine contractions. Together with good stability in proteolytic environments, this makes mussel glue a promising sealing material for future applications.

1. Introduction

With advances in fetal diagnosis, the number of performed invasive interventions into the uterine cavity is increasing. Despite improvements in such procedures, even small-diameter fetoscopic access sites do not heal, and thus iatrogenic preterm prelabor rupture of fetal membranes (iPPROM) remains the main risk after fetoscopic procedures [1].

During the last decade several strategies to prevent iPPROM have been evaluated. Among such strategies were attempts to stimulate biological repair. Although some repair was observed in rabbit models [2,3], healing in sheep and rhesus monkeys was relatively limited [4,5]. It appears that dislocation of amnion and chorion as well as reattachment of fetal membranes (FMs) to the decidua rather than healing lead to sealing of the membrane defects [6]. Due to poor in vivo functionality and stability of materials, prophylactic plugging strategies have not advanced into clinical practice. Major limitations include lack of stable integration of scaffold materials, inability of biocompatible glues to bond to wet surfaces and susceptibility of naturally derived materials towards proteolytic degradation. Such shortcomings of materials generally lead to the instable plugging of the defect and subsequently to leakage shortly after application [7]. As FMs are temporary tissues and their repair mechanisms have recently been described as rather inefficient, the use of gluing materials that are not prone to in vivo remodelling might be envisaged, resulting in sealants that simply act as physical barriers to amniotic fluid.

Recently, star PEG-based polymers have been developed, which are either functionalized with the unusual amino acid 3,4 dihydroxyphenylalanine (DOPA) or catechol-presenting analogues thereof [8,9]. By conversion of catechol groups under oxidative conditions, highly reactive quinones are formed [10] that allow strong adherence of the polymer on wet surfaces and gel formation in a saline environment. A catechol functionalized PEG polymer mimic of mussel glue has been employed in a murine model of pancreatic islet transplantation in which absence of an inflammatory response, long term in vivo stability and good tissue integration were demonstrated [11]. In a recent in vitro study, the same mussel-mimetic tissue adhesive (“mussel glue”) has been described to be a non-cytotoxic sealant material that tightly adheres to FM [12].

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