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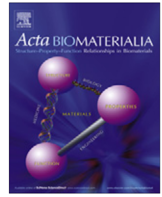

Fetal membrane patch and biomimetic adhesive coacervates as a sealant for fetoscopic defects

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ABSTRACT

Iatrogenic preterm premature rupture of membranes after fetoscopic procedures affects 10–47% of patients, secondary to the non-healing nature of membranes and the separation of layers during the entry. In this study we developed an in vitro model to mimic the uterine wall–fetal membrane interface using a water column with one end sealed with human fetal membranes and poultry breast, and a defect was created with an 11 French trocar. Further, a fetal membrane patch in conjunction with multiphase adhesive coacervates modeled after the sandcastle worm bioadhesive was tested for sealing of an iatrogenic defect. The sealant withstood an additional traction of 12 g for 30–60 min and turbulence of the water column without leakage of fluid or slippage. The adhesive is non-toxic when in direct contact with human fetal membranes in an organ culture setting. A fetal membrane patch with multiphase adhesive complex coacervates may help to seal the defect and prevent iatrogenic preterm premature rupture of the membranes.

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1. Introduction

Iatrogenic preterm premature rupture of the membranes (iPPROM) after a fetal intervention procedure is a major complication, affecting 10–47% of procedures [1–5]. iPPROM leads to an increased risk of preterm labor and worsens the perinatal mortality, undermining the true benefit of such interventions [6]. There are two possible explanations for the increased risk for iPPROM after invasive fetal procedures. One is the innate non-healing nature of the fetal membranes, as demonstrated in both in vivo and in vitro studies [7,8]. The other is that separation of the amnion from the chorio-decidual layers that occurs during the introduction of instrumentation into the uterine cavity can cause a persistent parting of membranes with subsequent leakage of amniotic fluid [9]. There have been several attempts to study sealants at the site of the fetal membrane defect, both in vitro and in vivo [10–12]. However, there is no ideal in vitro model to simulate the relationship of the uterine wall, the fetal membranes and the amniotic fluid environment. There is evidence to suggest that a decellularized fetal membrane scaffold can promote cellular proliferation at the defect site [13]; however, no method to introduce a fetal membrane patch through a narrow operative cannula and deliver it to the site of the defect has ever been described. Additionally, after the patch has been deployed, the challenge of fixation to the membranes and the uterine wall remains due to the dynamic nature of the amniotic fluid and uterine musculature. An underwater adhesive that would fix a tissue scaffold to the edges of the defect in place for the remainder of the pregnancy would be an ideal solution to the problem of iPPROM; however, no adhesive suitable for this task is available.

Development of medical adhesives for the wet interior of the body is both chemically and biologically challenging. The adhesive must be delivered, bonded and cured in the presence of moisture, must be non-toxic, and must not provoke a severe foreign body response. One approach to achieve underwater bonding is to study natural biological underwater adhesives, identify their key chemical features and copy that chemistry using non-toxic, biocompatible and cost-effective synthetic polymers. Numerous aquatic organisms produce working underwater adhesives as part of their

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aquatic lifestyle, to either position themselves in a suitable environment or to create a protective structure. The sandcastle worm, an intertidal marine polychaete (*Phragmatopoma californica*), produces a proteinaceous glue with which it joins together sand grains into a protective shell while fully submerged in seawater [14]. The proteins of the natural sandcastle glue are highly charged, with opposite charges segregated into different proteins [15]. The polyacidic and polybasic nature of the glue proteins suggests that complex coacervates – concentrated, phase-separated, associative polymer fluids – may be intermediates in natural bonding. Copying the side chain chemistry and molar ratios with synthetic poly(meth)acrylate copolymers resulted in adhesive complex coacervates that qualitatively replicated many of the features of the natural underwater adhesive [16]. Biodegradable versions [17] of the synthetic adhesive did not interfere with wound healing in a rat calvarial defect model [18]. Bond strengths and other material properties were improved by introducing additional polymer networks into the adhesive coacervates [19].

In this study, we aimed to create an in vitro model to simulate the anatomical relationship of the fetal membranes, uterine wall and surrounding amniotic fluid. Using such a model, we introduced an iatrogenic defect in a similar fashion to that used in clinical fetal interventions. Furthermore, we tested a technique to introduce a fetal membrane patch through a cannula to the site of a defect and test its sealing capacity, and evaluated the use of multiphase adhesive coacervates to adhere the fetal membrane patch to the defect. In addition, we examined the potential tissue cytotoxicity of the adhesive coacervates in an in vitro culture system.

2. Materials and methods

2.1. Creating an in vitro uterine model

The institutional review board of Baylor College of Medicine, Houston, TX (#H-26110) approved the collection of human fetal membranes for the study. We created an in vitro uterine model using a filleted poultry breast and human fetal membranes. Briefly, a 100 ml polypro cylinder (VWR International, West Chester PA) was cut at the base, and the cut end was lipped using heat. The cylinder was mounted on a stand. Fresh human fetal membranes were obtained from term vaginal deliveries and were transferred to the laboratory in a balanced salt solution (BSS). The fetal membranes were cut into 6 cm diameter patches and secured to the lipped end of the cylinder with the amnion facing towards the inside of the cylinder. A poultry breast was filleted to 1 cm thickness and pounded gently using a hammer to simulate the uterine wall musculature. A 6 cm diameter patch of poultry breast fillet was then wrapped over the fetal membranes on the cylinder and secured in place with a suture material. The column was filled using BSS.

2.2. Creating an iatrogenic defect

A defect in the fetal membrane through the poultry breast and the fetal membranes was created using an 18-gauge needle, followed by a guide wire (Cook® Urological Inc; Bloomington, IN, USA). Subsequently, an 11-French Teflon cannula (Cook® Medical Inc, Bloomington, IN, USA) was introduced over the guide wire using Seldinger's technique [20]. Then, the trocar was removed to leave the cannula in place. This entry method is identical to that used in most fetal intervention centers for fetal surgical procedures.

2.3. Technique to introduce the fetal membrane patch

Fetal membrane patches were supplied by Bio-Tissue, Inc. (Miami, FL) and processed in the same manner as described for human amniotic membrane currently used for ocular surface reconstruction [21]. Briefly, fetal membrane patches were placed on a nitrocellulose paper with the amniotic membrane facing up (for ease of handling). After being cut in a circular fashion to the desired size, they were lyophilized to reduce their thickness to facilitate their insertion into the cannula. Upon insertion, one edge of the membrane was removed from the paper and folded in half (Fig. 1a). The center of the patch was lifted from the paper, a 4-O Monocryl suture with a tapering needle (Ethicon Inc, San Angelo, TX) was passed through the center of the patch and a noose was tied (Fig. 1b). The remainder of the patch was removed from the paper (Fig. 1c). The needle was removed from the suture and the distal end was passed through a 9-French Teflon cannula while the self-check valve on the proximal end was removed using a knife. With gentle traction on the suture, the patch was retracted into the distal tip of the cannula (Fig. 1d). The original trocar that was an integral part of the 9F cannula was modified to serve as a blunt introducer. This blunt introducer was advanced from the proximal end of the cannula to abut the patch. Once the 11-French cannula had been introduced through the base of the in vitro model, the 9-French cannula containing the membrane patch was introduced through it. The column was filled to a height of 10 cm with BSS (Fig. 1e). The patch was introduced into the fluid column advancing the blunt introducer. Once free within the fluid medium, the patch was allowed to swell for 2 min – a timescale that had been established for maximum swelling based on prior experiments (Fig. 1f). Both cannulas were then withdrawn while keeping the suture and the patch in place. The suture was then withdrawn gently to position the patch in the defect so that the amnion faced the fluid medium mimicking the amniotic fluid while the chorion faced the poultry breast mimicking the uterine wall (Fig. 1g).

2.4. Optimization of the membrane patch size for sealing

Triplicates of lyophilized fetal membrane patches were created as mentioned above, with diameters ranging from 1 to 5 cm to determine the minimum size necessary to seal the iatrogenic defect in the above in vitro model. These were used to determine the sealing strength that could withstand the dislodgement of the plug. A 25 cm height of fluid in the column was chosen to mimic the average intra-uterine amniotic fluid pressure of 18 mm Hg that we had observed in patients with excess amounts of amniotic fluid (data not shown). We additionally applied 12 g of traction to the plug, and created turbulence in the fluid by shaking the column multiple times in all directions to mimic the in vivo fluid dynamics.

2.5. Adhesive complex coacervate formation

Polyethylene glycol diacrylate (PEG-dA, 760 Da, Aldrich) solutions were prepared in degassed, deionized water at the desired final concentration of 15 wt.%. Poly(acrylamide-co-aminopropyl methacrylamide) (MW 288 kDa, PDI 1.36) and poly (2-(methacryloyloxy)ethyl phosphate dopamine methacrylamide (MOEP-co-DMA, MW 64 kDa, PDI 2.8) were then dissolved in separate PEG-dA solutions at final concentrations of 5 wt.%. The poly (MOEP-co-DMA)–PEG-dA solution also contained a 0.2 M ratio of Ca^{2+} to phosphate sidechains and 1 wt.% nanosilica fillers (10 nm, Aerosil R 7200). The copolymer solutions were separately adjusted to pH 7.4 ± 0.2 with 6 M NaOH. The poly(acrylamide-co-aminopropyl methacrylamide)–PEG-dA solution was added dropwise, while stirring, to the poly(MOEP-co-DMA)–PEG-dA solution to a molar ratio of 0.6 amine sidechains to phosphate sidechains. Within a few minutes the complex coacervate settled out. The clear supernatant was removed.

The adhesive PEG-dA and nanosilica-filled coacervates were crosslinked through the *o*-DHP sidechains of the polyphosphate

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