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A novel microneedle array for the treatment of hydrocephalus

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Abstract

We present a microfabricated 10 by 10 array of microneedles for the treatment of a neurological disease called communicating hydrocephalus. Together with the previously reported microvalve array, the current implantable microneedle array completes the microfabricated arachnoid granulations (MAGs) that mimic the function of normal arachnoid granulations (AGs). The microneedle array was designed to enable the fixation of the MAGs through dura mater membrane in the brain and thus provide a conduit for the flow of cerebrospinal fluid (CSF). Cone-shaped microneedles with hollow channels were fabricated using a series of microfabrication techniques: SU-8 photolithography for tapered geometry, reactive ion etching for sharpening the microneedles, 248 nm deep UV excimer laser machining for creating through-hole inside the microneedles, and metal sputtering for improved rigidity. Puncture tests were conducted using porcine dura mater and the results showed that the fabricated microneedle array is strong enough to pierce the dura mater. The *in-vitro* biocompatibility test result showed that none of the 100 outlets of the microneedles exposed to the bloodstream were clogged significantly by blood cells. We believe that these test results demonstrate the potential use of the microneedle array as a new treatment of hydrocephalus.

Index terms

communicating hydrocephalus; cerebrospinal fluid; dura mater; microneedle; microfabrication

I. INTRODUCTION

Cerebrospinal fluid (CSF) is a colorless body fluid containing small quantities of glucose and proteins [1]. It is believed that CSF is produced in the ependyma of the choroid plexus at a relatively constant rate of 0.3 ~ 0.5 ml/min, circulates through the ventricular system and spinal cord, and is absorbed into superior sagittal sinus (SSS) through arachnoid granulations (AGs) located in dura mater membrane as shown in Figure 1 (a) [1, 2]. One of the major roles of CSF is to protect the brain and maintain the pressure within the intracranial space [3]. Hydrocephalus is an abnormal accumulation of CSF in the brain, which can lead to brain swelling and central nervous problems. The disease can be characterized as either communicating or non-communicating hydrocephalus, depending on the cause of the blockage [4]. The more common communicating hydrocephalus is caused

by deficient AGs, which are natural one-way valves that regulate the CSF flow from subarachnoid space (SAS) to SSS [5, 6]. Figure 1 (b) shows an infant suffering from severe communicating hydrocephalus.

A typical treatment for communicating hydrocephalus is a surgical implantation of a shunt system (Fig. 1c), which consists of a ventricular catheter, a check valve, and a distal catheter [7–10]. Although this shunt system has been principally adopted for the treatment of hydrocephalus for many years, it still suffers from many problems such as high failure rate, inaccurate shunting, inconvenience, and high cost. The failure rate of the shunt systems is as high as 40% in one year and 50% in two years [11]. The device failure stems from occlusion of the shunt lumen and mechanical failure such as fracture of the distal tubing, disconnection of shunt components, migration of the intraventricular catheter after initial insertion, and misplacement of ventricular & distal catheters [12]. Other problems include over- and under-drainage, loculation (isolated segments of ventricle), and abdominal complications (loculated intra-abdominal fluid collection) [13]. These problems that require additional treatments incur significant monetary loss as well.

In order to address such problems in current treatment of hydrocephalus, we proposed an innovative approach, that is, to develop and implant a small microchip device that mimics the normal arachnoid granulation. This microfabricated arachnoid granulations (MAGs) consist of a 10 by 10 array of dome-shaped microvalves and a 10 by 10 array of hollow microneedles (Fig. 2). We have previously developed a passive microvalve array for the regulation of the CSF flow between the SAS and the SSS just like normally functioning AG [14, 15]. In order to implant the microvalve array on the dura mater and create channels for the flow of CSF through the membrane, a microneedle array needs to be coupled with the microvalve array.

Various microneedle arrays made of silicon, metals or polymers have been developed for biomedical applications. Xu et al. (2007) reported on an array of polymer microneedles with pyramid-shaped tips and titanium shield for transdermal drug or nanoparticle delivery [16]. Roxhed et al. (2007) presented ultrasharp hollow silicon microneedles for efficient transdermal drug delivery [17]. Choi *et al.* (2007) reported on a three-dimensional MEMS microfluidic perfusion system with a SU-8 microneedle array for thick brain slice cultures [18]. Wang et al. (2009) presented a hollow polymer microneedle array for drug delivery that was fabricated by a photolithography process combined with replica molding technique [19]. Choi *et al.* (2010) demonstrated a polymethylmethacrylate (PMMA) microneedle array with electrical functionality for electroporating skin's epidermal cells to increase their transfection by DNA vaccines [20]. Although these microneedles have been successfully applied to specific applications, they do not meet the requirements for the current application, namely presence of hollow microchannels as conduits for CSF flow, ability to be integrated with a microvalve array, sharpness and rigidity for surgical implantation into dura mater, and biocompatibility for long-term performance.

This paper presents the design, fabrication, and testing of a 10 by 10 array of hollow microneedles for the treatment of communicating hydrocephalus. The microneedle array presented here was designed to be able to puncture human dura mater and provide a conduit

for CSF flow. It was also designed to be assembled with a dome-shaped microvalve array we have previously developed [15]. The microneedle was made of SU-8 and coated with Titanium and Parylene C for mechanical strength and biocompatibility, respectively. Hollow channels with two different diameters were made through the microneedles using 248nm KrF excimer laser machining. The selected laser parameters which yields optimized ablated surface quality were decided by extensive parametric characterization work [21]. The smaller channel was made off center for CSF flow and the larger channel was made for the assembly with microvalve array. Puncture test was performed using porcine dura mater which is very similar to human dura mater. Lastly, *in-vitro* haemocompatibility test using human blood was performed to check the channel blockage from platelet adhesions.

II. MATERIALS AND METHODS

Design Optimization

Figure 2b shows the design of a microneedle array. In order to provide multiplicity, 10 by 10 array of microneedles were designed on a 200 μm thick base with an area of $5 \times 5 \text{ mm}^2$. The height and bottom diameter of the conical-shaped microneedle are 500 and 120 μm , respectively. The distance between two adjacent cone centers is 400 μm . This long conical-shaped needle was designed to have a sharp tip in order to be able to puncture human dura mater about 300 μm thick. In order to deliver CSF to the sagittal sinua, microfluidic channel system inside the microneedles were designed to have a combination of a small channel in the needle and a large channel in the base. The large channels were designed to be 250 μm in diameter and 150 μm in height to accommodate microvalves. The diameter of the small channel was selected to ensure that pressure drop across the channel is minimized leaving most of the pressure drop across SAS and SSS applied to the microvalves. In order to determine the channel diameter minimizing the pressure drop through the channel, three dimensional numerical simulations using Comsol Multiphysics were performed to calculate and visualize the pressure drop through the channel inside the microneedle. We have previously conducted a three dimensional numerical simulation for the microvalve [15]. Therefore, the needle with a small channel was added to the previous geometry. Three multiphysics modules of Solid Stress-Strain, Moving Mesh, and Incompressible Navier-Stokes were coupled in the simulation. All boundary conditions (BCs) necessary to determine a solution are shown in Fig. 6a: 1 is an inlet with an applied pressure, 2~11 are walls with a no slip condition, 12 is an outlet with zero pressure. The BCs of the microvalve remains the same as described in Figure 6a [15].

Fabrication of Microneedle

In order to fabricate a 10 by 10 array of microneedles, there are four main fabrication processes: photolithography for tapered SU-8 geometries, RIE (Reactive Ion Etching) for sharpening microneedles, excimer laser machining for creating hollow channels inside the microneedles, and metal (Ti) & Parylene deposition for improved mechanical strength and biocompatibility. Figure 3 shows the fabrication process flow for an array of microneedles.

First, a Cr mask with a 10 by 10 array of circle patterns on a $4 \times 4 \text{ in}^2$ glass plate was prepared. Dextrin (Sigma-Aldrich, MO, USA) solution (dextrin: DI water=1 g: 10 g) was

then spin-coated on the Cr mask at 2000 rpm for 20 sec and baked at 120°C for 2 min. This dextrin layer was used for easy release of the microneedle array from the Cr mask plate. To form the base, SU-8 2035 (Microchem, MA, USA) was spin-coated at 500 rpm for 40 sec for a thickness of 200 μm and baked at 65°C for 10 min followed by 95°C for 50 min. It was exposed to UV light for 17.7 sec with a UV intensity of 21.2 mW/cm² and then baked at 65°C for 5 min followed by 95°C for 30 min. To form tapered microstructures, SU-8 2150 (Microchem, MA, USA) was spin-coated at 1000 rpm for 30 sec for a thickness of 550 μm and baked at 65°C for 5 min followed by 125°C for 4 hrs. It was exposed to UV light upside down from the glass side for 235.8 sec and then baked at 65°C for 1 min followed by 95°C for 2 hrs. Then, it was developed with SU-8 developer (Microchem, MA, USA) and rinsed with IPA (Isopropyl alcohol). The 10 by 10 array of tapered microstructures was separated from the mask plate by dissolving dextrin layer in water. The 10 by 10 array of tapered microstructures with different diameters were fabricated. The diameters of circles patterned on the Cr plate were 50, 60, 80, and 100 μm . The bottom diameters of the tapered microstructures were larger than the original patterns on Cr plate due to the scattered light, but the top diameter of tapered microstructures were smaller than those of the Cr pattern. The height of all of the needles was 550 μm .

The tapered microneedles were then sharpened by RIE (VITA; Femto Science Inc., Korea). Optimal process conditions were as follows: gas composition CHF₃ (20 sccm), O₂ (180 sccm); pressure = 900~1500 mTorr; and power = RF 100 W. The next process was KrF excimer laser machining (RAPID X250; Resonetics Co. Ltd, NH, USA) to generate a microfluidic channel inside the microneedle. The excimer laser ablation was done in two steps to form a big channel inside the base and a small channel inside the cone-shaped body. First a 20 μm diameter laser beam was used to generate small channels from the backside which were off-center and perpendicular to the cone shape and then, a 250 μm diameter laser beam was used to generate the larger channels. The reason for machining from the backside is that it is easy to align the microneedle with a laser beam on the flat side and much less debris is produced at the needle outlet by etching from the backside.

The final process is the metal deposition on the SU-8 microneedle surface using the DC sputter system (T-M Vacuum Product, Inc., NJ, USA). The preferred metal is either Ni or Ti due to its biocompatibility and high strength. 1 μm thick Ti layer was deposited under the following conditions: argon: 40 sccm and 30 mTorr, power: DC 50 W, target temperature: room temperature, cycle: 5 min deposition & 5 min cooling, and total run time: 1 hr 30 min. And then, 1 μm thick Parylene C layer was deposited on the microneedle to enhance the biocompatibility of the microneedle and to facilitate the bonding between the microneedle and the microvalve arrays.

Dura Puncture Test

Figure 4 shows two puncture methods of gradual and impact insertions into porcine dura mater. A device designed for gradual insertion consists of a movable microneedle array holder as a moving part, a fixed cap system to apply tension to the dura mater in order to mimic the *in-vivo* condition of dura mater in the brain, and a 1-axis stage driven by a micrometer (No. 263M, The L.S. STARRETT Co., Athol, MA, USA). The microneedle

array was placed on the small chuck with circular shape. To fix it on the chuck, dextrin solution was used as a temporarily adhesive. Porcine dura mater was fixed using a cap system. The horizontal movement of the microneedle on the 1-axis stage was controlled by rotating the knob of the micrometer, which has a minimum resolution of 10 μm . The microneedle array was incrementally moved up to 1100 μm inside the holder after contacting the microneedle array with the dura mater under microscope. For impact insertion method, dura mater was fixed using the cap system and the microneedle array was put and fixed on the holder. Impact movements toward dura mater were vertically generated by a finger snap. After gradual and impact insertions of the microneedle array, the backside of dura mater was investigated under optical microscope to verify the piercing by the microneedles. Then the microneedle was detached from the dura mater and was observed to see if there was any deformation due to the puncture test.

***In-vitro* Haemocompatibility Test**

Commercially available human blood (LAMPIRE Biological Laboratories Inc., PA, USA) containing an anti-coagulant K2 EDTA was used in *in-vitro* haemocompatibility test. It must be noted that the platelet adhesion was not hindered by the anti-coagulant. The test was performed in the tissue-culture incubator to maintain blood cell viability during the test. As shown in Figure 5, two chambers were designed to simulate the real volumes of SAS and SSS. Whole blood using a 12 ml syringe was injected into Chamber 1 ($1 \times 1 \times 5 \text{ cm}^3$), and saline solution using a 20 ml syringe was injected into chamber 2 ($5 \times 5 \times 5 \text{ cm}^3$). Since a syringe pump with two different sized syringes infused two solutions into two respective chambers, a pressure difference (1700 Pa at 0.333 ml/min) between chamber 1 and chamber 2 was achieved. This pressure made a continuous forward flow from chamber 2 to chamber 1. The microneedle array was placed between two chambers and the needle outlets were placed in the opposite direction of blood flow during the test to minimize the platelet adhesion. The needle array was incubated to react with blood for 1 hr. After the test, the microneedle array was taken out of the experimental set-up. Platelets adhered to the microneedle were investigated under optical microscope. Then, the microneedle was rinsed with phosphate buffered saline (PBS) several times to remove non-adherent platelets. Platelets adhered on the microneedles were investigated again under optical microscope. Platelets around the outlets of the microneedles were investigated in details under the scanning electron microscope (SEM). For the SEM sample, the microneedle array was dried and coated with platinum.

III. RESULTS AND DISCUSSION

Optimal Microneedle Design

Figure 6 shows three dimensional simulation results conducted to predict the pressure drop through the microvalve and microneedle. Channel diameters of 30 and 40 μm were analyzed at a fixed pressure differential of 1500 Pa. When the channel diameter was 30 μm , the pressure drop across the channel was around 600 Pa (Fig. 6b). This pressure drop was approximately 40% of the total pressure drop and therefore affected the valve performance significantly. However, if the channel diameter is 40 μm , the pressure drop across the channel becomes less than 100 Pa, which is little less than 8% of the total pressure drop

(Fig. 6c). Larger channels could cause significant loss of the microneedle tip. Therefore, the channel diameter of the microneedle was chosen to be 40 μm .

Microfabricated Microneedle Array

Figure 7 shows the tapered SU-8 microstructures (left images). They were different in size from the original patterns in Cr masks which were designed to have bottom diameters of 50, 60, 80, and 100 μm with constant spacing of 400 μm . Microstructures with diameters of less than 50 μm collapsed due to high aspect ratio. The heights of all tapered microstructures were around 550 μm . The bottom diameters of the tapered microstructures were larger than the Cr patterned diameters, and the top diameters were smaller. The tapered high aspect ratio microstructures were created by a non-uniform UV dose between top and bottom of the SU-8 resist. Due to light scattering effects, the bottom section was overexposed and the top section was relatively underexposed. The sidewalls of the tapered microstructures were fairly smooth, and the tapered angles of the microstructures were approximately 86–87°.

Sharp microneedles produced by RIE process are also shown in Figure 7 (right images). The etch time for each tapered microstructure with diameters of 50, 60, 80, and 100 μm depended on the etch rate at given conditions. The optimal etch times for sharpening the microneedle while maintaining its height at about 500 μm were 6 min, 6 min 15 sec, 8 min 10 sec, and 9 min 20 sec, respectively for the above-listed diameters. When the etch time exceeded these values, the needle height decreased significantly. Figure 8 shows SEM images of excimer laser machined microneedle array. The microneedle array was placed and fixed upside down into a hole drilled on a metal chuck prior to laser machining. This metal holder protected the microneedles during the laser ablation process and also made it easier to focus the laser beam on the top surface. The small channels were drilled first and then the big channel was processed. Both of them were processed using mask projection technique with suitable demagnification and pattern size on mask. The through-hole microchannels are located on the side of microneedles as designed for maintaining sharp tip for puncturing the dura mater. The small microchannel was about 30 μm in diameter on the microneedle surface (Fig. 8a). Since the excimer laser drilled holes are tapered, the microchannels are expected to have a larger diameter at the base. The larger hole was about 250 μm in diameter and 150 μm in depth (Fig. 8b). This hole was designed to be housing for PDMS/Parylene microvalve array as shown in Figure 8c.

Dura Puncture Test

Both tapered microneedles and sharpened microneedles with an original diameter of 50 μm were used in the puncture tests using porcine dura mater. The tapered microneedle was moved up to 580 μm toward the dura mater after coming into contact with the membrane. The dura mater was not punctured by the tapered microstructure array, and the tapered microneedles were not deformed by the experiment. This result showed that the tapered microneedle is rigid but not sharp enough to puncture through dura mater. In the puncture test with sharpened microneedle array, the movement of the microneedle array was increased up to 590 μm toward the dura mater after contact with the membrane. Sharpened SU-8 microneedles were not able to puncture the dura mater, either. The microneedles were bent during the experiment due to insufficient rigidity (data not included). These results showed

that the tapered microstructures require increased sharpness and the sharpened microneedles need higher rigidity. In order to enhance the rigidity of the sharpened microneedles, we deposited a thin Ti layer on the sharpened microneedles using DC sputtering. The metal layer was deposited at relatively low temperature and thus any thermal deformation of SU-8 microneedles due to thermal stress was prevented. A 1 μm thick Ti layer was coated on the SU-8 needle followed by 1 μm thick Parylene coating. Figure 9 shows the results of the puncture tests with metal/Parylene-coated needles. Most of the microneedles were not deformed. However, the incremental movement of the microneedle array toward the dura mater resulted in only 6 out of 100 microneedles piercing through the dura mater as shown in Figure 9a and 9b. This problem can be attributable to the elastic characteristic of the dura mater. When the needle was pushed into the dura mater gradually, the dura mater was stretched instead of being pierced. In order to overcome this problem, impact insertion method, commonly used in the installation of neural probes, was adopted. Generally, they use a pressure gun to implant a metal needle array into the brain [22]. However, this technique is not feasible for our application in which the device needs to be implanted inside the brain. So we attempted to create impact by finger snap. The result showed that about a third of the microneedles penetrated the dura mater (Fig. 9c and 9d). The microneedles were inspected after the experiment and they were not deformed. The puncture technique still needs to be further improved for higher success rate.

***In-vitro* Haemocompatibility Test**

Figure 10 shows the results of the *in-vitro* haemocompatibility test under dynamic condition. Figure 10a is a microscopic image of the top view of the needle right after the test. Many red blood cells were found on the needle surface. Figure 10b shows the microneedle after rinsing with PBS several times. Most red blood cells were removed by rinsing. Figure 10c is the microscopic images of the side view of the microneedle array. Figure 10d is the SEM image of a microneedle. Arrows point to cells remaining on the surface. They were observed as single cells (triangular arrow) or aggregated (circular arrow) cells. The single cells are 2 and 4 μm in diameter comparable to a human platelet size. Rather than red and white blood cells which are much bigger, these cells must be platelets. Single platelets tend to spread out and look non-circular. After spreading out on the surface, they started to aggregate and then formed linear patterns. Despite the presence of platelets, the outlets of the needles were not blocked by platelet adhesion. This is probably due to two reasons: One is that the microneedles were placed in the blood streams such that the outlets are not directly exposed to the incoming blood flow. In this way, platelets had less chance of contacting the outlet. The other reason is that hydrophobic Parylene surface is not favorable to protein adsorption resulting in reduced cell adhesion [23, 24].

IV. CONCLUSION

We have presented the design, fabrication, and testing of a 10 by 10 array of microneedles for the treatment of a neurological disease called hydrocephalus. The microneedle array was designed for piercing the human dura mater that has 300 μm thickness and thereby providing a CSF conduit without impeding the function of the microvalves as microfabricated arachnoid granulations. The array was fabricated using a combination of four main

techniques: photolithography for tapered SU-8 needle fabrication, RIE etching for needle sharpening, 248nm KrF deep UV excimer laser machining for through-hole creation in micron level resolution, and Ti & Parylene coating for improved mechanical strength and biocompatibility. Puncture tests were conducted using porcine dura mater under tension. The incremental insertion method caused elastic deformation of the dura mater resulting in few pierced needles, while the impact insertion method led to a promising puncture result. Biocompatibility test was additionally performed using human blood in order to simulate the CSF dynamics. No significant platelet adhesion was observed at the outlets of microneedles. Combined with the previously reported microvalve array, the current implantable microneedle array completes the microfabricated arachnoid granulations (MAGs) that mimic the function of normal arachnoid granulations (AGs). We believe that the microneedle array presented here demonstrates great potential for the treatment of communicating hydrocephalus.

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Figure 1.

(a) Cerebrospinal (CSF) fluid flow (arrows) and arachnoid granulations (AGs) in the dura mater membrane of the brain [15], (b) photo of an infant with hydrocephalus (from Wikipedia), and (c) schematic of a current treatment called ventriculo-peritoneal (VP) shunt (<http://drarunlnaik.com>).

Figure 2.

(a) A photograph of a small microchip that mimics arachnoid granulation, (b) the microfabricated arachnoid granulation (MAG) mimics the function of AG, and (b) 10 by 10 array of microneedles and microvalves.

Figure 3. Microneedle array fabrication processes: (a) fabrication process for tapered SU-8 microstructures and (b) reactive ion etching, excimer laser machining, and coating processes.

Figure 4.

Two puncture methods for piercing dura mater: (a) gradual insertion using a device which can create the incremental movement controlled by a micrometer, and (b) impact insertion using finger snap.

Figure 5.

Experimental setup for biocompatibility testing in the incubator. This setup consists of syringe pump, pressure sensor, system with blood & saline chambers, and two syringes with different size.

Figure 6.

3-D Comsol simulation of pressure drop through microchannel: (a) boundary conditions, (b) pressure distribution result for microchannel diameter of 30 μm at $P_{\text{in}} = 1500$ Pa, and (c) pressure distribution result for microchannel diameter of 40 μm at $P_{\text{in}} = 1500$ Pa.

Figure 7. Fabricated 10×10 array of tapered SU-8 microstructures (left images) and sharp microneedles after RIE process (right images); Cr patterned circle diameters of (a) 50 μm, (b) 60 μm, (c) 80 μm, and (d) 100 μm.

Figure 8.

SEM images of microneedles with microchannels made by KrF excimer laser: (a) top side of a microneedle array with small microchannels, (b) bottom side of a microneedle array with large microchannels, and (c) optical microscope image of a previously developed microvalve array that will be assembled with a microneedle array.

Figure 9.

Puncture test results using incremental (a and b) and impact (c and d) insertions: (a) dura mater pierced with microneedles after 1100 μm movement of the needle toward the dura mater, and (b) magnified view of pierced dura mater, (c) dura mater pierced using impact force, and (d) magnified view of pierced dura mater.

Figure 10.

Microscopic images ((a), (b), (c), and (d)) and SEM images ((e) and (f)) after biocompatibility test; (a) top view right after the test, (b) top view after rinsing with PBS right after the test, (c) side view of the microneedle after rinsing with PBS, (d) SEM image of platelets adhered on the outlet of the microneedle (→ : single type & – ● : aggregated type and range in size: 2~4 μm).