Comparison of non-porous versus porous polyurethane tubes for the replacement of cervical esophagus in rabbits

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I dedicate this thesis to my teachers and mentors who were so influential in the development of my career and completion of present study. Specially, I would like to express my gratitude to Professor Kyung Young Chung and Professor Hwal Suh. With their advices and guides, I could accomplish this experiment. I dedicate this thesis to my family for their understanding, tolerance and loving support. I finally would like to dedicate this thesis to all my colleagues who, through their daily commitment to and care for their patients, are caring forward the legacy of great pioneers of thoracic surgery.

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<ABSTRACT>

Comparison of non-porous versus porous polyurethane tubes for the replacement of cervical esophagus in rabbits

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(Directed by Professor Kyung Young Chung)

This study is intended to reveal the biocompatibility of polyurethane (PU) tubes for esophageal replacement and to determine which type of PU is ideal for artificial esophagus in combination with various materials using a rabbit model. Porous and non-porous PU tubes were investigated alone and in combination with small intestinal submucosa acellular matrix or polyethylene glycol. Two-centimeter long cervical esophagi were replaced by each type of artificial esophagus in 28 rabbits. Status of stenosis, infection, and survival were scored after 2 weeks. Stenosis scores of porous PU groups (mean=6.3) were higher than non-porous PU groups (mean=4.6). Infection was more prevalent in porous PU groups than non-porous PU groups. If the polyethylene glycol grafted group is excluded, the score of the porous PU group (mean=2) was higher than the non-porous PU groups (mean=0.5). The survival score was lower in

porous PU groups (mean=2.6) than in non-porous PU groups (mean=3.6). Outcomes of porous PU with polyethylene glycol grafted groups were similar to non-porous PU based groups. In conclusion, the non-porous PU tube was superior to porous PU tubes for the prevention of stenosis and infection in esophageal replacement. Polyethylene glycol grafted porous PU tube also showed good outcomes similar to those of non-porous PU tubes.

Key words: artificial esophagus, polyurethane

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I. INTRODUCTION

Esophageal reconstruction after esophagectomy is one of the most complicated surgical procedures. Patient's normal gastrointestinal organs, such as stomach, colon or jejunum, are used as a substitutes.[1] Thus, a supplementary abdominal procedure is inevitable and the preparation procedure demands considerable time, cost, and effort. Reconstruction procedures also inevitably induce short and long-term adverse events.[1] Thus, the ultimate goal to improve esophageal resection surgery outcomes is to develop a functionally ideal and practically simple artificial esophagus (AE). Although the function and structure of esophagus is relatively simple, immature AEs are still being investigated in animal models. Various synthetic materials were investigated for AE during the early period of development and the results were not promising.[2,3,4,5] Recently, tissue-engineered AE were investigated and showed better outcomes than synthetic materials in animal models.[6,7,8,9,10] Tissue-engineered AE is more

physiologic, functional, and has remodeling capacity. However, disadvantages exist because tissue engineering science is not mature at present. Tissue-engineered AE are costly and time consuming to produce. Also, installing tissue-engineered AE requires a complicated and staged surgical procedure and the success rate of implantation had not reached an acceptable range. Another problem is that synthetic scaffold or stent is necessary during the early period of implantation to maintain 3-D contours and induce tissue growth.[8] In spite of failures in earlier studies, synthetic AE still presents numerous benefits. Synthetic AE are easy to make and readily available for use. There are no length limitations and reliable blood supply is not necessary. If stenosis and infection can be overcome, synthetic AE would be an ideal AE model. Therefore, new materials should be investigated to discover potential AE candidates. Polyurethane (PU) has been applied in several fields of biomaterial research.[11,12,13,14] Qin et al. reported that esophageal high order structures can be regenerated and PU provided a temporary support for the development of three-dimensional structures.[15] PU can be fabricated as porous and non-porous types. Porous PU has numerous pores in the wall of the PU and these pores can act as communicating channels for cells and humoral factors. Also, the pores form a scaffold for implantaton and growth of autologous cells. In vascular prosthesis models, PU acted as prosthesis and scaffolds for tissue growth.[12] Non-porous PU have no pores. A complete barrier between the lumen and body space is important for AE because the esophageal lumen is a contaminated space. This

study intends to reveal biocompatibility of PU tube for esophageal replacement and to determine which type of PU is ideal for AE in combination with various materials using small animal model. Consequently, an ideal PU tube based AE will hopefully be developed for subsequent study with large animal models.

II. MATERIALS AND METHODS

1. Overview of experimental design

Seven types of AE were investigated, which were divided into seven groups, as follows: the small intestinal submucosa acellular matrix only (SIS) group, pPU group, pPU+SIS group, pPU+PEG group, nPU group, nPU+SIS group, and nPU+PEG. Both porous PU tubes (pPU) and non-porous PU tubes (nPU) were made. Each type of PU tube was investigated alone or in combination with SIS or polyethylene glycol (PEG). Four New Zealand White rabbit were allocated to each group. Two centimeters of cervical esophagus was replaced by an AE in each of the 28 adult New Zealand White rabbits, which weighed 3 kg each. AE status was evaluated by gross and histologic examinations after 2 weeks. This experiment was approved by the Institutional Animal Care and Use Committees of the Yonsei University College of Medicine.

2. Small intestinal submucosa acellular matrix.

A four cm-long section of harvested small intestine was stripped to turn out the mucosa. Small intestine sections were washed 3 to 5 times using phosphate-

buffered saline (PBS) containing penicillin (100 IU/mL) and streptomycin (100 mg/mL). Washed small intestines were soaked in 0.25% trypsin-EDTA for 5 minutes and 10 minutes, respectively, to remove cellular components. Absence of cellular components was confirmed by light microscopy after hematoxylin-eosin stains.

3. Polyurethane tube

A. Fabrication of the PU tube

(A) Non-porous PU tube

Non-porous PU were fabricated with PU (Tecoflex®, Thermedics Inc., Woburn, MA, USA) using a modified dipping method.[16,17,18] PU was dissolved in chloroform to a final concentration of 12 % (w/v). Glass rods, with diameters of 0.7 cm, was worn with 12 % PU solution and then air-dried for 6 hours. Next, glass rods were worn 4 times using the same process in order to be worn uniformly, and then dried under a vacuum for 12 hours. After the wearing process, the PU tubes were separated from the glass rods. The resulting PU tubes were dried under a vacuum.

(B) Porous PU tube

Porous PU tubes were fabricated with PU (Tecoflex®, Thermedics Inc., Woburn, MA, USA) using a modified

dipping method. PU was dissolved in chloroform to a final concentration of 12 % (w/v). Sodium chloride particles (100-200 μm) were added to the PU solution at a 1:9 (w/w) ratio of PU to NaCl and stirred thoroughly. Glass rods, with diameters of 0.7 cm, were worn with 12 % PU solution and then air-dried for 6 hours. After that, the glass rods were worn again in the reverse direction, using the same process in order to uniformly worn them, and then dried under a vacuum for 12 hours. Completely dried samples were swollen with methyl alcohol (Duksan Pure Chemical Co., Ansan, Korea) for 40 minutes. After the swelling and wearing process, PU tubes were separated from the glass rods. The resulting PU/salt complex was immersed in distilled water on a shaker at room temperature for 48 hours to leach out the remaining salt, and then they were dried under a vacuum.

B. Ozonation and PEG Grafting

Methoxy Polyethylene Glycol (P1AM2®, Sunbio, Anyang, Korea) was dissolved in distilled water at the concentration of 10% by weight ratio, and the ozonated scaffold was placed in the PEG solution and left for 24 hours at 50 °C.

C. Sterilization

The prepared scaffolds were soaked in 70% ethanol for 1 hour. After 5-6 washings with sterilized PBS, the scaffold was sterilized in an ultraviolet chamber at 4°C for 2 hours.

4. Replacement of AE and postoperative care

Rabbits were fasted overnight. Operations were conducted under general anesthesia with endotracheal intubation. After shaving and cleansing the cervical area in the supine position, a 5 cm-long left oblique skin incision was made. Cervical esophagus was isolated and then 2 cm of esophagus was resected. The artificial esophagus was connected to both ends of the native esophagus with continuous absorbable monofilament sutures in single layer. A naso-gastric tube was inserted. A rubber drain was placed and the wound was repaired. Parenteral nutritional support was administered for three days. Naso-gastric tube feeding started from the 4th postoperative day. On the 7^{th} day, oral feeding was started.

5. Assessment

The status of replaced AE and the native esophagus was evaluated by gross and histologic examination. The status of infection of periesophageal tissue was scored (Inf) as 0 (no infection) or 1 (clinical infection). The degree of stenosis was graded in 4 degrees and scored (St) 0 to 3: 0, no stenosis; 1, < 30%; 2, <

60%; and 3, > 60%. Survival score (Sv) was designated 1 to survival and 0 to death. Overall result score (Or) was calculated using the equation: Or = Inf + St -Sv.

III. RESULTS

1. PU tubes

The thickness of non-porous PU tube was 0.4 mm. Inner and outer surfaces were even and there no communicating channel was found on scanning electron microscope in the wall. (Figure 1)

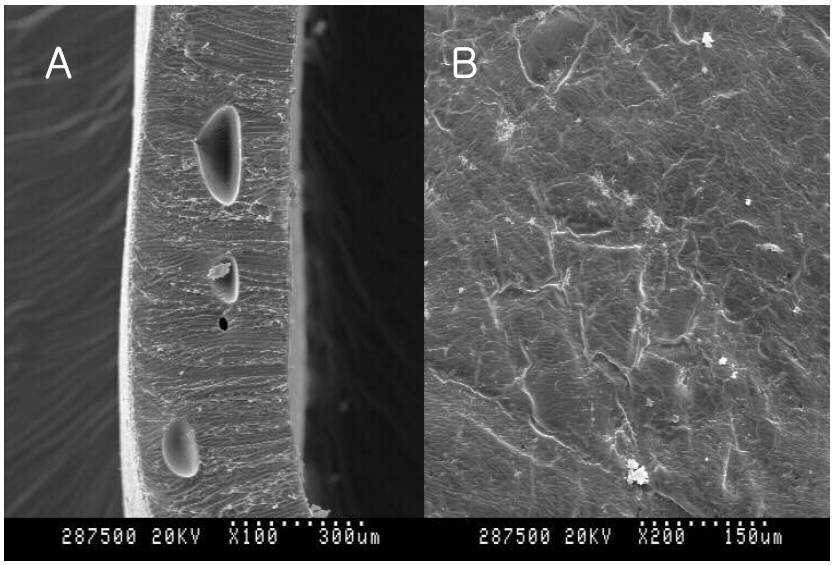

Figure 1. Cross sectional and surface images of non-porous poly-urethane tube using a scanning electron microscope. No communication channels exists in the wall on the cross sectional image. Vacuoles in the wall increase compliance of

the tube. (A, x 100) Surface is even and no pores exists. (B, x200)

The thickness of porous PU tubes was 0.6 mm. Numerous, various-sized pores were noted on scanning electron microscope in cross sectional image and surface image. (Figure 2)

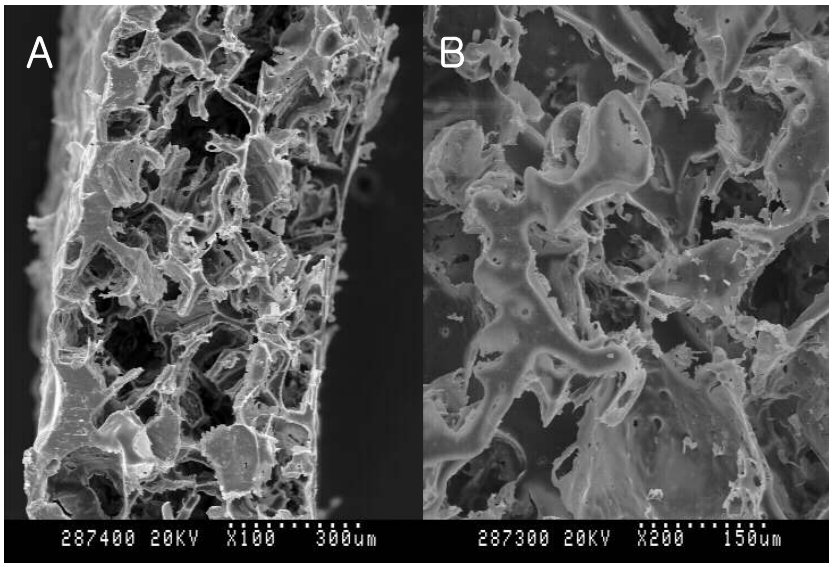

Figure 2. Cross sectional and surface images of a porous poly-urethane tube using a scanning electron microscope. Numerous communication channels exist in the wall. (A, x100) Various sized holes exist on the surface of the tube. (B, x200)

2. Clinical outcomes

Three out of four subjects in the SIS group showed grade 3 stenosis of SIS itself.

Infection developed in the periesophageal tissue in one case and grade 3 stenosis was observed in this case. (Figure 3) Two out of four died on the 7th day because of infection and aspiration pneumonia due to stenosis. Only one maintained lumen for diet until the 14th day.

Figure 3. Stenosis of the small intestine submucosal acellular matrix. Stenosis of the small intestine submucosal acellular matrix which occurred due to shrinkage and fibrosis at 2 weeks after implantation.

In the pPU group, grade 2 and grade 3 stenosis developed in two cases at the anastomosis site without luminal marrowing. (Figure 4) Infection in periesophageal tissue was noted in two cases. Both died at the 5th and 7th day.

Dark-brownish plaque was deposited on the inner surface in all cases. (Figure 5)

Figure 4. Anastomotic stenosis in a porous polyurethane tube.

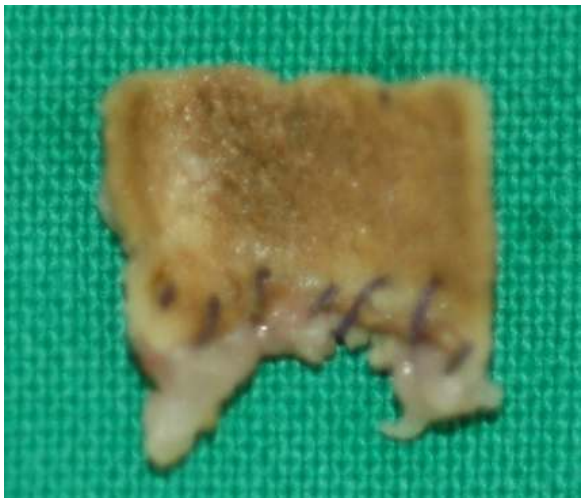

Figure 5. Dark-brownish deposit on the inner surface of a porous polyurethane tube.

pPU+SIS group showed similar results. There were two cases with grade 2 stenosis and two cases with grade 1 stenosis. Two cases of periesophageal infection was noted. Necrosis of SIS was observed in all cases. pPU+PEG group showed grade 2 anastomotic stenosis in two cases. However, no periesopahgeal infection was noted. The inner surface was clear in all cases. In the nPU group, one grade 2 anastomotic stenosis and one infection developed. There was no deposited material on the inner surface of nPU tube. (Figure 6)

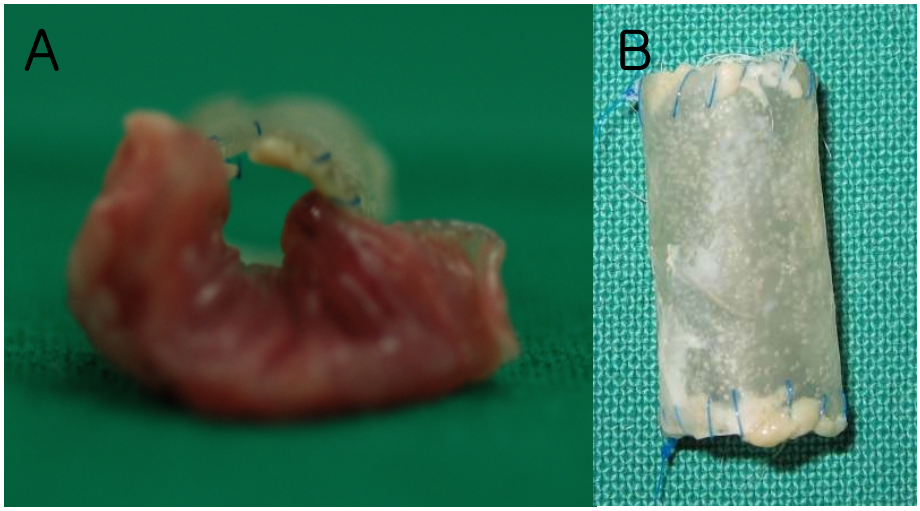

Figure 6. Two weeks after non-porous polyurethane tube implantation. Grade 2 anastomotic stenosis was observed. (A) There was no deposit on the inner surface of the tube. (B)

The nPU+SIS group showed one stenosis and no infection. Similarly to the pPU+SIS group, none of the SIS subjects survived. The nPU+PEG group

showed no stenosis. One case of grade 2 infection developed due to anastomotic leakage and the animal died on the 7th day. The stenosis score of the pPU-based groups (mean=6.3) were higher than the nPU-based groups (mean=4.6). Infection was more prevalent in the pPU-based groups than the nPU-based groups. If the PEG graft group is excluded, the score of the pPU-based group (mean=2) was higher than the nPU-based groups (mean=0.5). The survival score was lower in the pPU-based groups (mean=2.6) than in the nPU-based groups (mean=3.6). Overall score was better in the nPU-based groups than in the pPU-based groups. Outcomes in the pPU+PEG group were similar to the nPU-based groups. (Table 1)

Table 1. Clinical outcomes after artificial esophagus implantation

Group	Stenosis	Infection	Survival	Overall
SIS	11	1	2	10
pPU	7	2	2	7
pPU+ SIS	6	2	3	5
pPU+ PEG	6	0	3	3
nPU	5	1	4	2
nPU+ SIS	5	0	4	2
nPU+ PEG	4	1	3	2

IV DISCUSSION

PU is widely used for medical purposes. This study revealed the new possibility of PU tube as a synthetic AE. PU tubes showed good patency in the early period after implantation. Of the two types of PU tubes, nPU tubes showed less stenosis, fewer infections, and better survival than pPU tubes. Stenoses of anastomosis and graft impair the function of AE and worsen long term outcome. Stenosis of AE itself is the main problem of tissue-engineered esophagus. Regeneration of normal esophageal structures (mucosa, submucosa, and proper muscle layers) is essential to prevent stenosis in tissue-engineered AE.[7,8] Tissue regeneration is related with blood supply and length of graft. However, the blood supply to the AE relies on simple diffusion. Therefore, sufficient nutritional and oxygen support is not possible. Simple diffusion is less effective due to negative pressure, pleural epithelial lining and continuous flow of pleura fluid, especially in thoracic cavity. Generally, the length of AE is relatively long, which causes longer periods to get sufficient tissue regeneration, and fibrosis with stenosis is inevitable in tissue-engineered AE. To solve this problem, various synthetic stents have been applied over a long period of time.[8,19] Contrarily, synthetic AE is relatively free from this problem. PU tubes showed good capability of maintaining three-dimensional contours and resistance to stenosis with relatively thinner wall thickness. Although pPU tubes showed luminal narrowing due to foreign material deposit at the inner surface, nPU tubes and pPU with PEG grafting were resistant to foreign material deposit.

No luminal narrowing was observed in these two groups. Anastomotic stricture is a problem of synthetic AE because foreign body reactions and infection induce fibrosis at anastomosis sites. Anastomotic stenosis was lower in nPU tubes than pPU tubes. This may be related to the fact that there were fewer infections in nPU tubes, because inflammation attracts fibroblast and induce fibrosis in the native esophageal wall. Infection is also important problem of AE. Esophageal lumen communicates with the extracorporeal environment and AE is vulnerable to infection. Infection and subsequent complication are the main causes of failure in previous studies that applied synthetic AE.[4,5] Tissue-engineered AE is more resistant to infection than synthetic AE. Infection can be prevented in synthetic AE by inhibiting bacterial colonization in the wall and permeability to the adjacent tissues. Non-porous PU is intended to completely block sources of infection. It is known that fluid could leak from the lumen in highly porous PU vascular grafts.[20] Non-porous PU tubes showed lower risk of infection than porous PU because bacteria can not colonize on the wall and septic materials could not proliferate to the adjacent tissues. The risk of infection of pPU tubes can also be reduced by surface sealing with PEG grafting. PEG creates a non-ionic surface and reduces protein absorption and cell adhesion.[21] Although, pPU can not be used as an AE by itself, PEG grafted pPU may be a good candidates for synthetic AE because it has similar characteristic to nPU for blocking foreign materials and can also act as a scaffold for native cell growth. Furthermore, pPU is superior in compliance than nPU. Survival

and overall outcomes were better in the nPU-based groups because stenosis and infection were lesser in nPU-based groups. SIS was unreliable AE by itself in this study. The stricture of SIS was the most important limitation. However, SIS was resistant to infectious complications. Adding SIS to non-porous PU revealed no benefit, because internal SIS could not get a blood supply. Although the structure and function of esophagus is simpler than other organs, AE is still in its infancy due to numerous reasons other than stenosis and infection. AE must be long enough to replace resected esophagi. This requirement is very important in esophageal cancer surgery. Synthetic AE are superior at this point to tissue-engineered AE. PU tubes can be made long enough to suit patients' needs. To overcome insufficient blood supply, tissue-engineered AE requires an additional procedure to develop sufficient vascular structures or to be prepared with innate blood supply at other site of the body before implantation.[8] This technique is more complicated than the current practice and adds no benefit. Peristaltic movement is beneficial for smooth swallowing. Coordinated contracture of neo-smooth muscle fibers is impossible at this stage of tissue-engineered AE. A mechanical continuous contracture system using an electromagnetic system has been examined but is still not practical.[22] Limitation of this study is its small population. To overcome this problem, experimental conditions were stricktly controlled and the qualified surgery was done by an experienced surgeon. Thus, the result of this experiment can be a reliable baseline for following studies. From this study, a new model of AE constructed

with inner non-porous PU tube and outer scaffold can be suggested. The scaffold may be consists of an acellular matrix, elastin patch, collagen sponge, AlloDerm, porous PU or bio-degradable polyesters.[23,24,25,26,27] PEG grafting instead of inner non-porous PU is also a good solution for inner surface sealing. In the future, larger animal study with this new AE model will help foster the clinical availability of an artificial esophagus.

V. CONCLUSION

The non-porous PU tube was superior to porous PU scaffolds for the prevention of stenosis and infection as esophageal replacements. PEG grafted porous PU tubes also showed good outcomes that were similar to non-porous PU tubes. Subsequent experiments with large animal models with these new AE models are necessary in order to propose simple, convenient, and reliable AE.

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< ABSTRACT(IN KOREAN)>

토끼 경부식도에 이식한 무공성 폴리우레탄 튜브와 다공성 폴리우레탄 튜브의 효과 비교

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박 인 규

식도 절제술의 결과를 향상 시키기 위해서는 기능적으로 이상적이고 실제 이용하기 간편한 인공식도를 개발하는 것이 궁극적인 과제이다. 합성물질을 이용한 과거의 인공식도 연구는 성공적이지 않았으나, 합성물질이 가진 장점이 많으므로 새로운 물질에 대한 연구가 필요하다. 보 연구는 폴리우레탄 튜브가 인공식도에 적용 가능한지와 다공성 및 무공성의 폴리우레탄튜브 중 어느 것이 더 이상적인 인공식도의 조건을 갖추었는지를 규명하기 위해 시행되었다. 무공성 및 다공성의 폴리우레탄 튜브를 단독으로 사용하거나 소장무세포기질 또는 폴리에틸렌글라이콜과 결합하여 인공식도를 제작하였다. 뉴질랜드 흰토끼 28마리를 대상으로 경부식도를 2cm 절제한 후 각각의 인공식도를 이식하였다. 이식 2주 후에 협착정도, 감염여부 및 생존여부 등을 평가하여 비교하였다. 무공성 폴리우레탄 튜브는 세공 및 연결통로가 없었고 표면이 균일하였다. 다공성 폴리우레탄 튜브의 벽과 표면에는 다양한 크기의 세공과 연결통로가 존재하였다. 다공성 폴리우레탄 튜브의 협착수치 (평균=6.3)는 무공성 폴리우레탄 튜브 (평균=4.6) 보다 높았다. 다공성 폴리우레탄 튜브는 무공성

폴리우레탄 튜브에 비해 감염의 빈도가 높게 나타났다. 폴리에틸렌 글라이콜 군을 제외하였을 때 다공성 폴리우레탄 튜브의 감염수치의 평균은 2로 무공성 폴리우레탄 튜브의 감염수치의 평균 0.5보다 높았다. 생존수치는 각각 2.6 대 3.6으로 다공성 폴리우레탄 튜브군에서 낮게 나타났다. 전체 성적에서도 무공성 폴리우레탄 튜브가 다공성 폴리우레탄 튜브에 비해 우수한 수치를 보여 주었다. 무공성 폴리우레탄 튜브 군중에 폴리에틸렌글라이콜을 도포한 군은 무공성 폴리우레탄 튜브 군과 유사한 결과를 나타냈다. 결론적으로 무공성 폴리우레탄 튜브 인공식도는 다공성 폴리우레탄 튜브 인공식도에 비해 우수한 협착방지 및 감염방지 효과를 보여 주었고 이는 생존율의 향상으로 이어졌다. 폴리에틸렌글라이콜의 도포는 다공성 폴리우레탄 튜브가 무공성 폴리우레탄 튜브와 같은 효과를 나타낼 수 있게 하였다.

핵심되는 말 : 인공식도, 폴리우레탄