The Role of NEOVEIL in Hepatectomy and its Future Potential

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OVERVIEW

1. Techniques used in hepatectomy

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<th>Dr. Nagano</th>
<th>Dr. Yoshida</th>
<th>Dr. Oba</th>
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<tr>
<td>1. Transection of liver tissue</td>
<td>CUSA</td>
<td>CUSA</td>
<td>CUSA Ligature (used for mobilization)</td>
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<td>2. Vascular occlusion</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes (Intermittent Pringle maneuver)</td>
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<td>(Intermittent Pringle maneuver)</td>
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<td>3. Fibrin glue</td>
<td>Yes (Painted)</td>
<td>Yes (Sprayed)</td>
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<td>Use in transplant donor</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<td>4. Check biliary tracts and bile</td>
<td>Depending on situation</td>
<td>Depending on situation</td>
<td>No</td>
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<td>Intraoperative cholangiography</td>
<td>Depending on situation</td>
<td>Yes, for all patients</td>
<td>No</td>
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<td>Bile leak test</td>
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2. Covering materials

(i) Cases in which fibrin sheet products are used, reason for use/all liver resection patients in principle or for the purpose of complete hemostasis
(ii) Cases in which NEOVEIL is used, reason for use/use in combination with fibrin glue, all liver resection patients in principle or for the purpose of complete hemostasis, expectation for preventing bile leakage from the peripheral bile ducts
(iii) Comparison of fibrin sheet products versus NEOVEIL

Advantage of fibrin sheet product: Allows pressure hemostasis; Disadvantage of fibrin sheet product: Cannot prevent bile leakage from the peripheral bile ducts
Advantage of NEOVEIL: Can prevent bile leakage from the peripheral bile ducts; Disadvantage of NEOVEIL: Does not allow pressure hemostasis

3. Future potential for NEOVEIL

(i) Future cases, technique development/laparoscopic surgery, living donor liver transplantation, vascular protection (dissection or vascular anastomosis sites)

Future of NEOVEIL/development of compressible forms, dryness, when used in combination with fibrin glue

Dr. Nagano: I’d like to proceed today by seeking your views on the issues raised in the overview. In this forum, let’s focus on hemostasis of the hepatic cut surface, advantages and disadvantages for the prevention of complications, and issues for the future. The participants in today’s forum are all surgeons having extensive experience with hepatectomy in the clinical setting, and I’d like to progress this forum with the aims of ensuring safe and appropriate hepatectomy procedures and improving surgical outcomes.

1. Surgical techniques in hepatectomy

Dr. Nagano: I’d like to ask you about methods you use for transecting hepatic tissue. Dr. Yoshida, I understand that you use CUSA (EXcel). Do you proceed
with one person responsible for handling both the liver transection and blood vessels and hemostasis? For hemostasis of fine blood vessels for example, do you cauterize the vessels yourself using an electrosurgical knife, or is the surgeon’s assistant or first assistant responsible for cautery?

Dr. Yoshida: For transection and hemostasis, both my assistant and I manipulate the electrosurgical knife, and we deal with issues together on a case-by-case basis.

Dr. Nagano: Dr. Oba, I understand that you use CUSA too. How do you proceed?

Dr. Oba: As the surgeon, I expose the blood vessels and other structures with CUSA, these are passed through a Kelly clamp, and my first assistant handles the ligation and cautery.

Dr. Nagano: Dr. Oba, what energy devices (electrosurgical knife etc.) are used at your hospital?

Dr. Oba: We use an electrosurgical knife with high energy output at a fine tip. The electrosurgical knife has a really sharp needle tip, and extremely high power output.

Dr. Nagano: Do you use this knife in a monopolar configuration rather than in the so-called bipolar configuration with infusion?

Dr. Oba: That’s correct. We use the electrosurgical knife in a monopolar configuration.

Dr. Nagano: Dr. Yoshida, do you use the electrosurgical knife in a bipolar or monopolar configuration?

Dr. Yoshida: I use a monopolar configuration. With the power output increased.

Dr. Nagano: As the electrosurgical cautery with a sharp needle tip can be used in a number of modes, which do you use?

Dr. Oba: We use the knife in spray mode.

Dr. Yoshida: I use normal mode rather than spray mode.

Dr. Nagano: What are the differences between those modes?

At Osaka University, we use CUSA and the electrosurgical knife in monopolar configuration, and in this configuration, we use the device in spray mode.

Dr. Oba, do you think there are any differences from the electrosurgical cautery with a sharp needle tip that you use?

Dr. Oba: Well, I feel that spray mode is a little powerful. At our hospital, we have extensive and lengthy experience using the electrosurgical knife. We cauterize the intestine and its afferent vessels and other tissues, and use it with the power output turned up to nearly maximum.

Dr. Yoshida: We expose Glisson’s capsule using CUSA, ligate the remnant liver side, and achieve hemostasis with clips to the opposite side, then transect. For a certain thickness, we tie off with sutures, and cauterize the other side with an electrosurgical knife. Therefore, we make incisions with an electrosurgical knife in coagulation mode that permits normal cutting.

Dr. Nagano: Dr. Oba, for the handling of Glisson’s capsule and intrahepatic hepatic veins, do you use clips for the resected side and the remnant liver side, or ligation?

Dr. Oba: For the remnant liver side, I basically choose ligation. However, I use clipping for the resected side.

Dr. Yoshida: For the remnant liver side, we clip sites where there is a certain thickness of tissue, and where it is relatively thinner, we cauterize using an electrosurgical knife.

Dr. Nagano: It appears that everyone is in agreement here, but if Dr. Sano of Teikyo University, who planned this forum, were here today, the crush and clamp technique with Pean forceps may have been mentioned. Have you actually used that technique? The so-called finger fracture technique, or alternatively, methods like the crush and clamp technique?

Dr. Yoshida: We take a flexible approach and adapt to the individual patient’s circumstances. For example, we may proceed with the crush and clamp technique on the assistant’s side, and with CUSA on the operator side. In any event, saving time is of the essence because the liver is clamped. Hence, there are situations where we use them in combination. When I assist, I may be dissecting with Pean forceps while the junior surgeon is slowly cutting with the CUSA, at another site.

Dr. Oba: Basically, because there were no other alternatives, we have been using CUSA for a long time. However, we have on rare occasions certainly used the finger fracture, or crush and clamp technique, for example, when the CUSA is not working properly, using the process as a teaching scenario.

Dr. Yoshida: Wherever you go around Japan, CUSA is preferred if it’s available, but the finger fracture technique may be required in some situations. You also sometimes have to teach certain young surgeons the crush and clamp technique. The downside of CUSA is easy to break down, for example, aspiration may not be possible, and it may be necessary to proceed with the crush and clamp technique while waiting for the nurse to repair it, in order to save time.

Dr. Nagano: What are your views on other devices?

You all answered on the questionnaire that you use LigaSure for mobilization. Is this when you’re handling the coronary ligament of the liver?

Dr. Oba: Yes, that’s right. For example, mobilization of sites such as the right lobe or the triangular ligament, because there is a considerable number of lymphatic vessels, and when it’s a large tumor etc., there are blood vessels present and sometimes the bleeding won’t stop, even when they’re individually ligated and cauterized. We don’t use it in all cases, but those parts are mobilized using LigaSure.

Dr. Nagano: To prevent lymphatic fistula associated with hepatic cirrhosis or chronic hepatitis, you have to seal the lymph ducts, don’t you?

Dr. Oba: At our center, ligation takes time because the assistants are in their second to fourth years, unlike the situation in university hospitals, and LigaSure is used for that reason from the perspective of saving time too.

Dr. Yoshida: We also use LigaSure. However, given the economic issues, we have also recently considered methods in which LigaSure is not used.

Dr. Nagano: It can be reused, can’t it,
unlike the harmonic scalpel?
Dr. Oba: LigaSure is single-use only.
Dr. Yoshida: But there are LigaSure models that can be reused, aren’t there?
Dr. Nagano: Dr. Oba, have you had occasion to use LigaSure for dissection?
Dr. Oba: Well, since that takes some time, we choose the conventional method and use CUSA.
Dr. Yoshida: When we resect the liver laparoscopically, we choose LigaSure.
Dr. Nagano: We choose the harmonic scalpel for laparoscopic hepatectomy. This mostly involves resection for liver tumors present in the hepatic margin. In any event, what you and I all have in common at our hospitals is that in hepatic transection, it’s essentially a matter of reliably exposing and ligating the vessels after thoroughly considering the anatomy of the intrahepatic vessels and other structures.

Ischemia and Ischemic methods
Dr. Nagano: Next, I’d like to turn to intrahepatic vascular occlusion, or in other words, hepatic ischemia. I understand that you all do it, don’t you? Dr. Oba, can you specifically describe the intermittent method you use?
Dr. Oba: Basically, we adopt the approach of total vascular exclusion. The target clamping time is 12 minutes, and try not to exceed a maximum of 15 minutes. We then declamp for four minutes. In the case of a single lobe, we clamp for about 20 minutes. It’s said that up to 30 minutes is acceptable, but considering the margin of safety, we make it a little shorter.
Dr. Yoshida: In our department, the initial clamping time is 15 minutes, then we clamp for five minutes, and thereafter even 15 minutes is acceptable. When it appears that resection can be completed in this manner, it may be extended to about 30 minutes. In this situation, we employ total vascular exclusion.
Dr. Nagano: Postoperatively, have you encountered any problems with this approach?
Dr. Yoshida: We haven’t seen any postoperative problems. Except, however, that the blood pressure falls after the first declamping only. We decided to occlude the blood supply for a shorter time, for up to 15 minutes, for the first clamping only.
Dr. Nagano: What are the differences and reasons for selection of single lobe and total vascular exclusion?
Dr. Oba: The selection depends on the surgical technique. Situations like those when clamping of one lobe is possible, for example, in cases of anterior segmentectomy and so on. Because Glisson’s capsule is exposed naturally, and by the cut is then made on the anteroposterior boundary with one lobe clamped. We don’t unreasonably enforce an approach of single lobe ischemia in all cases. We decide during the course of the surgery.
Dr. Yoshida: I do the same.
Dr. Nagano: In other words, total vascular exclusion is the base selection, but single lobe ischemia may be chosen to match the resection technique.
Dr. Yoshida: For example, right lobe ischemia may be preferred in posterior segmentectomy, but it might be done with total hepatic ischemia, rather than deliberately exposing the right Glisson’s capsule and performing single lobe ischemia.
When Glisson’s capsule is exposed, we respond flexibly on a case by case basis, such as choosing single lobe ischemia.
Dr. Nagano: In such cases as those when gaps can be definitely seen in the hepatic portal, the previous practice was to tap both the right and left Glisson’s branches in the hepatic portal. However, recurrence was common in cases of hepatoma, and when adhesions are taken into account in repeat hepatectomy, I felt that it’s better not to handle the hepatic portal region. There’s also the problem of lymphatic fistula, and it may be preferable not to touch the hepatic portal wherever possible. By the way, I’d like to present some data from our university concerning the duration of ischemia.

In our university, total vascular exclusion in patients with cirrhotic liver involves clamping for 10 minutes and declamping for five minutes. This doesn’t apply in the case of single lobe occlusion, but the results of much earlier rat studies showed that activation of calpain-μ is a cause of ischemia-reperfusion injury. As evidence for this, it has been shown by western blotting that the previously-mentioned calcium-dependent protease calpain-μ is not activated in ischemia of duration up to 10 minutes, but is activated for a duration of 15 minutes or longer. However, since hepatic failure hardly ever occurs, there is no difference in mortality or morbidity.
When we transfer this result to the clinical setting, AST levels were found to be elevated on postoperative days 3 and 5 after total vascular exclusion in patients for whom the clamping time exceeded 10 minutes. We therefore believe that clamping for 10 minutes and declamping for five minutes may be slightly safer. Given these basic and clinical results, clamping and declamping in total vascular exclusion in the severely cirrhoted liver such that the duration of ischemia is kept to 10 minutes appears to be preferable. We don’t have to worry about it too much for the normal liver, because there were no differences according to duration of ischemia.
Dr. Yoshida: As regards the duration of ischemia, I believe that by contrast, in hepatic cirrhosis, since I am seeking to avoid intestinal congestion, there is no need to be especially rigorous with the timing.
By this I mean that in ischemia-reperfusion injury, I contend that the damage of reperfusion due to intestinal congestion is perhaps greater than the damage of hepatic ischemia. Of course, there is also the damage of ischemia to consider.
Dr. Nagano: As you say Dr. Yoshida, there are two factors to consider in ischemia-reperfusion injury caused by blocking the portal blood flow: hepatic vascular exclusion and intestinal
congestion. It is highly likely that various factors (chemical mediators or cytokines) will be activated because of the latter, intestinal congestion. As well, protease activation will be produced by hepatic ischemia. As regards the Osaka University research, it is an experiment using the duration of ischemia from the perspective of hepatic ischemia only. Therefore, while it may well be inadequate in clinical terms, it does provide one so-called rationale.

**Dr. Yoshida:** At our hospital, we always administer a steroid in the morning on the day of surgery. Doing this, we feel there is less of a problem during reperfusion. There are some other centers where steroids are not used in surgery, but it should be noted that the blood pressure drops after the first reperfusion. We try to limit the duration of ischemia the first time, as a form of preconditioning.

**Dr. Nagano:** In fact, on this issue too, there is research data for preventing the activation of causative factors in ischemia-reperfusion injury such as calpain-μ, with rat studies showing that steroids are effective. Even though this was published in the Journal of Hepatology several years ago, it's yet to gain acceptance in the clinical setting. That you (Dr. Yoshida) recommend the use of steroids suggests that there was no problem with the direction of our research findings.

**Dr. Oba:** We also use steroids at our hospital. Not during surgery, but we feel that the incidence of postoperative fever is low.

**Dr. Nagano:** Routinely?

**Dr. Oba:** Yes, routinely.

**Dr. Nagano:** Dr. Yoshida, when do you administer steroids: before, during, or after surgery?

**Dr. Yoshida:** We try to give steroids immediately before clamping the blood vessels, but since we sometimes forget to do so, we now administer a steroid in the morning of the day of surgery.

**Dr. Oba:** At my hospital, we give steroids once before surgery.

**Dr. Nagano:** What dose do you use?

**Dr. Yoshida:** About 500 mg.

**Dr. Oba:** I use a low dose of 125 mg.

Even so, there's no fever.  
**Dr. Nagano:** What about subsequent infection? Do your anesthetist colleagues have any comments on the preoperative use of steroids?  
**Dr. Oba:** Rather, some suggest that the dose may be a little low, but it is said that concerns are expressed about infection when overly high doses are used.

**Dr. Yoshida:** We get the feeling that problems have decreased since we began administering steroids.

**Dr. Nagano:** At our hospital too, the anesthesiology department doesn’t really favor the use of steroids. They are very hesitant about the use of therapies that might elicit postoperative acute lung injury, such as pulse therapy.

**Dr. Yoshida:** We had a case in our department once, in which we didn’t use steroids, where the patient experienced massive bleeding from the cut surface after declamping.

**Dr. Nagano:** Yes, but isn’t it really difficult to judge whether or not such bleeding might be affected by steroids?

**Dr. Oba:** Is Foy being used by anyone?

**Dr. Yoshida:** We have used Foy intraoperatively, and routinely use it immediately after surgery.

**Dr. Nagano:** Are you saying that you use a protease inhibitor routinely after surgery?

**Dr. Yoshida:** That’s right.

**Dr. Oba:** We also use Foy, but recently, health insurance restrictions surrounding its use have become more stringent in some ways.

**Dr. Yoshida:** There is a possibility of thrombus formation between repeated clamping and declamping. There may also be hesitancy about anticoagulation, and considering this, I think Foy might be a good option.

**Dr. Nagano:** Whatever the case, the discussion has strayed a little from the issue of dissection, but given that most centers seem to perform intraoperative ischemia, I think we can conclude that caution is needed for the prevention of hepatic injury due to postoperative ischemia-reperfusion injury, including the use of steroids or protease inhibitors.

In that sense, today’s DPC generation of surgeons might have a small amount of resistance to preventive administration of something following hepatic resection, but paying adequate attention to hepatic function is absolutely necessary, don’t you agree?

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**Fibrin glue**

**Dr. Nagano:** Next, I’d like to ask whether you use fibrin glue for hemostasis on the hepatic cut surface?

**Dr. Oba:** I use fibrin glue. I use a spray to cover the whole cut surface.

**Dr. Nagano:** What about subsequent infection? Do your anesthetist colleagues have any comments on the preoperative use of steroids?

**Dr. Oba:** Rather, some suggest that the dose may be a little low, but it is said that concerns are expressed about infection when overly high doses are used.

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**Dr. Oba:** I use a low dose of 125 mg.
small holes can be individually sutured with 6-0 prolene, and since filling in the gap would take time, hemostasis with fibrin glue is selected in such situations. However, if bleeding persists postoperatively, once again hemostasis is repeated using NEOVEIL and fibrin glue.

Dr. Nagano: Finally, what do you do after hepatic resection is complete? For example, to stop the bleeding when the resected surface is extensive, and when a small amount of bleeding appears to be a concern, and so on.

Dr. Yoshida: Since we prepare the fibrin glue immediately after starting surgery, we sometimes also spread any fibrin glue remaining after surgery over the whole area, depending on the amount used during the procedure. Of course, fundamentally, using sutures for the liver parenchyma will stop the bleeding, but for the hepatic vein and other vessels, if the sutures are inserted poorly, there is a risk that holes will widen, and fibrin glue is therefore better for halting bleeding.

Dr. Nagano: What do you do for the cut surface of the parenchyma?

Dr. Yoshida: I cauterize the parenchymal surface with an electrosurgical knife, or use ligation if the bleeding is severe. If the bleeding is in the parenchyma, the bleeding stops after cauterization with an electrosurgical knife, even without using fibrin glue. In situations such as those of bleeding from veins located immediately below the parenchyma, I halt the bleeding with fibrin glue.

Dr. Nagano: Have you used any fibrin sheet products?

Dr. Yoshida: I believe they may be promising for their hemostatic ability. Previously however, there was a case involving the use of fibrin sheet products for finishing, in which two or three sheets were used without cutting. However, an abscess formed on the cut surface, and even though a drain was placed immediately adjacent to it, the abscess could not be drained. Ultimately, since there is no sense in applying a fibrin sheet product to an area that is larger than the target bleeding site, I cut the...
sheets into smaller pieces to match the bleeding site and use them for pinpoint bleeding. Naturally, the hemostatic effect is excellent. However, since there are limitations on their use, such as the fact that they can’t be used more than once, and that patients must provide a release after receiving a thorough explanation on the product use before surgery, the opportunities for their use have been scarce.

Dr. Nagano: As a matter of fact, we have been using fibrin glue for some time now.

It’s actually way back in the history of Osaka University, when fibrin glue was originally used in the department of neurosurgery. It was used by spreading manually in the dissolved form on the hepatic cut surface, as described by Dr. Shingo Imaoka of Osaka University, former head of the Osaka Medical Center for Cancer and Cardiovascular Diseases.

At that time, when scientific articles were not routinely written in English, the achievement became the subject of a distinguished lecture for the Japanese Society for Advancement of Surgical Techniques. I believe that this may have probably been the first such report in Japan. Since Dr. Imaoka was a specialist in thrombosis and hemostasis, I think he started to use it on the assumption that it would be acceptable to use fibrin glue on the hepatic cut surface. However, since gaps in the hepatic cut surface cannot be filled with fibrin glue alone, it was thought that combination use with collagen powder would be a better option, hence the use of the old-time powder-type Avitene and fibrin glue together. The modern fibrin sheet product is essentially those two products combined in a set. Until recently, this was the preferred option. However, now it appears that NEOVEIL, plus fibrin glue may be a good choice, and its evaluation is currently underway. In the beginning, fibrin glue alone was found to be inadequate, and sprinkling collagen powder on the irregular hepatic cut surface and allowing cross-linking to occur was seen to produce an excellent hemostatic effect. I believe this is what you might call the previous generation of hemostasis in 1989, about 20 years ago.

Dr. Yoshida: Does this involve using collagen powder after dispersing the fibrin glue?

Dr. Nagano: No, it’s the other way round, with collagen powder sprinkled on the hepatic cut surface, pressed in over the whole surface, then lightly washed. Fibrin glue was then applied. However, the disadvantage of this method is that the coating cannot be cleaned. Using this technique, even after achieving complete hemostasis, vigorous cleaning causes the coating to peel off, with the shape of the hepatic cut surface as it is.

Dr. Yoshida: As explained previously, a film is formed at the time of hemostasis, which becomes a sheet shape. Therefore, problems may occur when the sheet is peeled off, don’t you think?

Dr. Nagano: That’s correct. The use of fibrin sheet products has come about because of that concern in the past. They were used in that situation after being trimmed into eight equal pieces. The advantage of this method is that it allows cleaning, and there are no problems if it comes into contact with water. Before the launch of NEOVEIL, we were using fibrin sheet products with excellent hemostatic effects in most patients.

Dr. Oba: Around 1991, when I came to this hospital, Oxycel, and Avitene were predominantly used, and before long, fibrin glue appeared and we shifted to that. Subsequently, we took up fibrin sheet products after their emergence.

Dr. Nagano: However, there is an impression that it may be difficult to prevent biliary fistula with fibrin sheet products.

Dr. Oba: The possibility of abscess formation even after use of a fibrin sheet product arises when bile flow is not halted.

Dr. Yoshida: The application of a fibrin sheet product to locations at which both blood and bile are halted is not a problem, but the leakage of bile from a location that has been covered is a concern.

Dr. Nagano: If fibrin glue is used, there is also the possibility that it could become the medium for infection, don’t you think?

Dr. Oba: Earlier, we heard about the benefits of rubbing in, but if there’s only a small amount of bleeding, we cut up a fibrin sheet product and say “I think this might do for today”.

Dr. Yoshida: I hear from MRs that immersion in water is a good approach when a fibrin sheet product is used. However, because it is applied to a site with bleeding, we cut up the product, apply it to the tissue surface in the dry state, and rub it in with the fingers, and when it’s used on sites for hemostasis, we try to prevent it from sticking to the hands.

Dr. Oba: Even when gauze is placed on top, the fibrin sheet product may also peel off together with it when the gauze is removed.

Dr. Yoshida: Having had that experience, we rub a great deal while pressing it in. We used that method for fibrin sheet products, and because we now use fibrin glue, the method is simpler.

Dr. Nagano: Do you all use the spray?

Dr. Oba: Yes, I do.

Dr. Yoshida: I do too. Spraying is convenient for a small amount of bleeding during surgery.

Dr. Oba: When you use it a little at a time, doesn’t it harden?

Dr. Yoshida: It’s OK.

Dr. Nagano: In any case, fibrin glue came into use because hemostasis must be achieved for the hepatic cut surface, that’s why. Options for the method of use include spray and collagen sheets.

As a general principle, it’s a matter of using surgical hemostasis for bleeding from the portal vein, or from arteries or other high-pressure sites, and in addition, ensuring complete hemostasis for bleeding from the peripheral veins that is characteristic of the liver.

Dr. Yoshida: Since there is a possibility of stenosis when sutures are inserted for small transverse holes in large-bore veins, I think that spraying fibrin glue will be beneficial. One other thing about using fibrin glue is that painting
to produce a uniform film on the cut surface is the same as using a fibrin sheet product to some extent, and I think it might be preferable to paint glue on the bleeding sites for pinpoint bleeding.

**Dr. Nagano:** For example, bleeding from spots of size one or two centimeters on the edge can be stopped completely using an electrosurgical knife or similar. But, you’d use fibrin glue for risky locations near Glisson’s fissure.

**Dr. Yoshida:** That’s right. As well, fibrin glue is used to prevent leakage of lymphatic fluid from the liver bed region in hepatic cirrhosis patients who have undergone cholecystectomy. However, when fibrin glue is spread in a uniform layer and blood is lost from beneath the layer, you ultimately have to peel off the film and once again check the bleeding, because you don’t know its source. Therefore, it’s a matter of blindly having to use fibrin glue because there’s bleeding present. Basically, only when it can be concluded that you can stop bleeding with an electrosurgical knife or ligation to a certain extent do we decide that it’s time to use fibrin glue for pinpoint bleeding.

**Dr. Nagano:** In other words, achieving complete hemostasis for the hepatic cut surface involves 80% surgical means, and the remaining 20% by approaches such as fibrin glue.

### Checking the biliary tract and bile

**Dr. Nagano:** The next issue I’d like to discuss is that of biliary fistula at the cut surface.

With the products developed to date, problems such as abscess formation have occurred because of infection of the biliary tract or infection due to biliary fistula. Their incidence appears to be about one or two percent of all cases. Prevention of biliary fistula is therefore the next necessary step.

First, I’d like to ask you about intraoperative cholangiography or leak testing. **Dr. Yoshida,** do you use intraoperative cholangiography and other techniques?

**Dr. Yoshida:** I do sometimes when the course of the biliary tract is a concern, but fundamentally, I don’t. We make our judgment on the basis of a preoperative investigation of the biliary tract.

**Dr. Nagano:** Do you do it for the liver donor?

**Dr. Yoshida:** We do for the donor, but not for routine cancer operations. However, we may do it for confirmation purposes, depending on the patient of course.

**Dr. Oba:** We use intraoperative cholangiography for biliary tract surgery, but apart from times such as when we suspect injury to the bile duct, not for routine hepatectomy.

**Dr. Nagano:** At our hospital too, we decide on a case-by-case basis. At any rate, it appears that none of us here do intraoperative cholangiography as a general rule at our hospitals. Next, **Dr. Oba,** do you do bile leak tests?

**Dr. Oba:** No, we don’t.

**Dr. Yoshida:** We do, routinely. First when the gallbladder is removed, the cystic duct stump is left long, and then cut. Next, we insert an articulated catheter after dissecting the liver, and clamp the lower biliary tract by hand, and when air enters, it is possible to check whether or not a leak is present. One paper claimed that the results were no different, whether or not leak testing is performed, but I believe that it is useful from the standpoint of preventing biliary fistula in patients in whom leaks are detected via leak testing.

**Dr. Oba:** (Leakages of bile that can be detected by leak testing) It is connected if contrast enhanced from below. Hence, if bile does flow downwards, it probably won’t leak very much.

**Dr. Yoshida:** That’s right. When it’s first inserted, we check for leaks in the natural state without clamping the common bile duct. Next, the common bile duct is clamped with the fingers, and since it may burst from somewhere if it is clamped too tightly of course, I adjust the pressure myself. When the common bile duct is in tension to a certain extent, the grip is released and I confirm that bile quickly flows down. If there is no leak with this level of pressure, we judge that everything’s ok.

**Dr. Nagano:** Since we do intraoperative cholangiography for all liver donors, we ultimately also do leak testing of the biliary tract. The purpose is not to check for biliary fistula from the hepatic cut surface, but rather, a major biliary fistula may be formed if gaps are created, because the bile duct stump is ligated and sutured with 6-0 PDS. That’s what our leak testing is intended to check. Meanwhile, does air ever leak from the hepatic cut surface?

**Dr. Yoshida:** Yes, of course it does. We ligate the hepatic cut surface with needle sutures. Occasionally, there may be a leak from the bile duct near the hepatic portal. If the leak is from the bile duct stump and that it is ligated, it is sufficient, but since there is a risk of stricture when the side of the bile duct is repaired, we use fibrin glue plus NEOVEIL.

**Dr. Nagano:** It seems to be the case that fibrin glue plus NEOVEIL is effective for biliary fistula, because the adhesive strength is greater. Isn’t that so?

For peripheral-type biliary fistula, a hemostatic agent that could seal the biliary duct a little better would help avoid postoperative biliary fistula, and prevent repeat laparotomy. In the first instance, I think “we must pay attention to peripheral-type biliary fistula”.

**Dr. Oba:** A long time ago, we would use a magnifier, and when the junior surgeons tied off their sutures, they would loosen afterwards. Later, we made it a rule to always ligate twice, using 4-0 silk sutures for Glisson’s sheath of thickness about 2 mm. In any event, you can prevent biliary fistula if ligation is performed carefully. However, there are cases where leakage occurs from the surroundings of the stay sutures applied to the liver.

**Dr. Nagano:** What do you mean by stay sutures?
Dr. Oba: They are sutures that hold the liver during the dissection process. At our hospital, we resect the liver with sutures applied in tension to the liver on both the resected side and the remnant side. Bile can leak from these needle holes, and to prevent this, our longstanding practice has been to leave the sutures in place.

Dr. Nagano: Are both ligated sutures and stay sutures left in place?

Dr. Oba: That’s what we did. However, when stay sutures were left behind, there were some cases where bile would leak from the needle holes, and we paid close attention when it did. From that point on, we always removed the stay sutures after dissection, cauterized the needle holes to stop bleeding, and applied a hemostatic agent (fibrin glue) to the site. This way, we felt that we could reduce the occurrence of biliary fistula somewhat. In 2007 and 2008, the incidence of biliary fistula decreased to about 1.3%, or two in 150 cases. Therefore, just by ligating securely, we feel it is possible to prevent biliary fistula without using a contrast agent.

Dr. Nagano: Since the figure of 1.3% for biliary fistula is very low, that is a good approach, don’t you agree?

Dr. Oba: Tying off sutures twice and releasing them is time-consuming, but I think this method is useful.

Dr. Nagano: When cutting Glisson’s branch, we have made it a practice to use a perforating ligature in situations where it used to be adequate with a single ligature. Using ligation strategies, we try to prevent biliary fistula by surgical means.

Dr. Yoshida: You use stay sutures on the resected side, but you tend not to use sutures to any great extent on the remnant side.

Dr. Nagano: The Osaka University approach is not to use stay sutures very much during hepatectomy. At which center was this practice initially started?

Dr. Oba: This has been used since I arrived at Shizuoka General Hospital. The method whereby sutures are placed and tensioned was first described by Dr. Hiroshi Hasegawa at the National Cancer Center.

Dr. Nagano: That’s a method with a long history, isn’t it. Whatever the case, whether leak testing is done depends on the patient, and as far as possible, the main issue is somehow trying to prevent biliary fistula.

Decompression tubes

Dr. Nagano: Do you use biliary decompression tubes?

Dr. Yoshida: We have almost no experience with the placement of biliary decompression tubes. They may be used in cases with unusually large transverse holes.

Dr. Nagano: Depending on the patient, it’s better to use a decompression tube only when there’s leakage of bile with unexplained cause.

Dr. Yoshida: In patients with a large transverse hole in the bile duct in the vicinity of the hepatic portal, it’s a case by case decision. However, I think there are times when it’s necessary to insert a decompression tube.

Dr. Nagano: In your situation Dr. Yoshida, you do both bile duct and bile tests intraoperatively don’t you? After the completion of surgery, the tube is removed and ligated to finish, that’s right isn’t it?

Dr. Nagano: Dr. Oba, you don’t use biliary decompression tubes at your center either, do you?

Dr. Oba: There are situations for example, where a biliary decompression tube is inserted when intervention is needed because of bile duct injury, but we don’t use them for decompression.

Dr. Nagano: There are cases in which biliary decompression tubes are used, right?

In patients with a tumor embolism in the biliary tract, we close the bile duct with sutures when a large defect has been produced by cutting into the bile duct.

In cases of hepatocellular carcinoma, since TAE cannot be done later in an choledocojejunostomy, we like to leave the bile duct alone as far as possible. It’s only in those situations that we use a biliary decompression tube. Thanks to advancements in technology, ERCP can now be performed when problems such as bile duct stricture arise, but deformation caused by gastrointestinal tract adhesions following liver resection may prevent ERCP, and PTBD may instead be necessary. In this context, there were cases in the past in which the bile ducts could not expand in the regenerating or cirrhosted liver, and it was not possible to release surgical jaundice, to which we need to pay attention. In other words, even when jaundice has developed, there are cases where the bile duct will not dilate.

2. Covering materials

Cases in which fibrin sheet products are used, and reasons for use

Dr. Nagano: Next, I’d like to turn to materials for covering, and sealing of the hepatic cut surface.

I think expectations are high for stopping bleeding at the hepatic cut surface, or peripheral-type biliary fistula.

Dr. Noriyuki Oba
First, can you tell me about cases in which fibrin sheet products are used, and the reasons for their use.

Dr. Oba, what do you think?

Dr. Oba: We use fibrin sheet products as a final finishing step for situations such as small amounts of bleeding from small holes in veins. We also use them for reinforcing sites where the tissue is thinner after CUSA application on the bile ducts and so on. The final objective of using NEOVEIL is also the same.

Dr. Nagano: Dr. Yoshida, do you use fibrin sheet products?

Dr. Yoshida: Now, I kind of feel that it might be a bit worrying to use such products on a thin part of the bile duct the way Dr. Oba described. We cut up small pieces to use only at sites where the bleeding won't stop. Because it would be a waste, we avoid applying them here and there in unnecessary places.

Dr. Nagano: Fibrin sheet products are effective for bleeding, but since they don't prevent biliary fistula, they are used for completing hemostasis in hepatectomy patients, aren't they?

Cases in which NEOVEIL is used, and reasons for use

Dr. Nagano: Next, I'd like to ask about the reasons for using NEOVEIL. Have you ever used NEOVEIL by itself? Dr. Oba and Dr. Yoshida: No, not by itself.

Dr. Nagano: Everyone is the same then, proficiently using NEOVEIL and fibrin glue in combination. What are your expectations, and how have you made the decision to date on whether to use fibrin glue alone or fibrin glue plus NEOVEIL in combination?

Dr. Oba: During the procedure, I apply a small piece of fibrin sheet product to sites with a little bleeding. Separately, I may also finally apply it for the hepatic vein or Glisson's capsule. As opposed to this, I use NEOVEIL as the final finishing step in the caudate lobe and in patients with extended left lobectomy, where there is no bleeding of any concern. I use it for veins over an extended area, or for Glisson's. I don't place any particular restrictions on use for different patients, but adapt to the flow of the surgery.

Dr. Nagano: How about you Dr. Yoshida?

Dr. Yoshida: When we first started using NEOVEIL, for bleeding from a vein, and for sites where we previously rubbed in fibrin glue alone, we would first paint on fibrin glue, then place NEOVEIL on top, and then finally paint fibrin glue over the top of that. We started using the combination with NEOVEIL because we liked the fact that bleeding could be stopped without having to press very much.

Once, we were wondering what we should do in a patient with bile duct injury and a hole near the hepatic portal, perhaps insert a decompression tube or something else, and then we tried NEOVEIL. The patient's postoperative course was smooth and trouble-free, without requiring a decompression tube. And, liking the combination of NEOVEIL plus fibrin glue, we are now using NEOVEIL plus fibrin glue for bile leakage from the cut surface, even when the cut surface is near Glisson's, and even if bile is leaking and repair proves difficult.

We've always used NEOVEIL plus fibrin glue in combination since then, but recently, there was a case in which biliary fistula developed for the first time after we started using NEOVEIL. This was a case of surgery involving isolated lobectomy of the caudate lobe and complete preservation of the hepatic veins and Glisson's capsule, but there were considerable adhesions of Glisson's capsule, and we checked for leaks from the left bile duct on the side of Glisson's capsule.

A transverse hole was present in the bile duct branches of the caudate lobe toward the rear, and bile was leaking from a valley in the cut surface. We used NEOVEIL, but it didn't fit snugly because of the valley, unlike our previous experience. We therefore spread fibrin glue on the surface, filled it again with NEOVEIL and sprayed fibrin glue on top of that. This was our first case of biliary fistula in a patient in whom NEOVEIL was used.

Dr. Nagano: What you're saying, Dr. Yoshida, is that in this case, a hole from which bile was leaking from a central-type biliary fistula was invisible?

Dr. Yoshida: No, since the hole was visible, we thought we would be able to repair it if we tried, but there was particular concern about secondary problems such as biliary fistula from needle holes or repair-induced stricture. Therefore, we use NEOVEIL plus fibrin glue for rather small holes.

Dr. Nagano: In other words, because NEOVEIL was packed in to fill irregularities, the problem was perhaps that the NEOVEIL sheet didn't fit snugly.

Dr. Yoshida: Yes, that's right. Basically, in the case of a flat surface with open holes, it would probably be better to coat the site with fibrin glue and then cover with NEOVEIL. For parts that are difficult to fit snugly such as valleys on the hepatic cut surface, the holes may not have been completely blocked. However, we anticipated that as the liver regenerated, any gaps would have been filled in.

Dr. Nagano: In that context, when things go well, NEOVEIL is even easier to use.

Dr. Yoshida: In this case in which the leak was confirmed, the problems occurred because the visual field was extremely narrow and it was not possible to plug the hole. In other patients, everything has gone well.

Dr. Nagano: In my case, it's been quite a while since I started using NEOVEIL. We first used it for the lungs, where we would apply NEOVEIL to the resected stump and then spray over the top with fibrin glue, and we were surprised to find that we were able to completely eliminate pulmonary fistula.

When we examined electron micrographs of the cut surface of the lung on which NEOVEIL plus fibrin glue was used, we were surprised to see that NEOVEIL plus fibrin glue had neatly filled the holes. Essentially, we felt that it would be difficult to completely fill the uneven cut surface because the material of the fibrin sheet is hard. By contrast, NEOVEIL is extremely soft, and when I first touched NEOVEIL, I thought “With this softness, it should be able to cover and reinforce uneven cut surfaces too”, which was
The Role of NEOVEIL in Hepatectomy and its Future Potential

my motivation for trying it. However, the concern for NEOVEIL, as for fibrin sheet products, is whether or not it can be cleaned. Since cleaning was not possible in the age of collagen powder and fibrin glue, I was somewhat concerned.
I believe that cleaning for prevention of postoperative infection is vital. With NEOVEIL plus fibrin glue, there were no problems, even when the hepatic cut surface was cleaned at high pressure. Because it is possible to clean the surface with a sufficient volume, one can rest easy.
Therefore, we first conducted a pilot study of NEOVEIL plus fibrin glue. Since the doctors at this hospital were very enthusiastic about NEOVEIL, they used it in the first ten cases. Most involved liver cancer. Of all ten cases in which NEOVEIL plus fibrin glue were used in combination, not one instance of biliary fistula was seen. The mean incidence of biliary fistula at our hospital is about 3%, but no instances have been recorded with the use of NEOVEIL plus fibrin glue. The efficacy for hemostasis was similar to that achieved for fibrin sheet products.
Next, we conducted a retrospective study at our hospital in 43 patients of fibrin sealing of the hepatic cut surface in combination with PGA felt (NEOVEIL) (Slide 1).
In the retrospective analysis, 39 patients in the CF group received a fibrin sheet product and 34 patients in the FS group received fibrin glue plus NEOVEIL. Since there was no postoperative bleeding in either group, changes in postoperative hemoglobin levels were used as a substitute indicator. However, no differences were seen here either (Slide 2). Second, four events of biliary fistula occurred in the CF group, as against none at this stage in the FS group (Slide 3). This could either be regarded as purely beginner’s luck, or because it was initially a matter of using NEOVEIL very carefully in the first 30 or so patient.
Finally, what are some of your key tips for using NEOVEIL appropriately? As Dr. Yoshida said earlier, the drawback is that it might prove a little difficult to use in patients in whom it can’t be fitted snugly and the surface is not well defined.

Dr. Yoshida: Yes, that’s right. In the end, firmly and securely fixing NEOVEIL to the tissue so that gaps are filled is the key point, I think. Even in locations that are deep and where it is

### Fibrin sealing of the hepatic cut surface using PGA felt in combination

**RETROSPECTIVE STUDY (43 patients)**

<table>
<thead>
<tr>
<th>FS</th>
<th>CF</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>34</td>
</tr>
<tr>
<td>Age (years)</td>
<td>67.3 ± 2.2</td>
</tr>
<tr>
<td>Years</td>
<td>24</td>
</tr>
<tr>
<td>F</td>
<td>10</td>
</tr>
<tr>
<td>Child Pugh score</td>
<td>6.0 ± 0.1</td>
</tr>
<tr>
<td>HCV or HBV</td>
<td>22</td>
</tr>
<tr>
<td>Tumor size (mm)</td>
<td>46.5 ± 4.9</td>
</tr>
<tr>
<td>Percentage of liver resected, for lobectomy or greater</td>
<td>11 (32%)</td>
</tr>
<tr>
<td>Operative time (min)</td>
<td>283 ± 24</td>
</tr>
<tr>
<td>Blood loss (g)</td>
<td>608 ± 98</td>
</tr>
<tr>
<td>Resected liver weight (g)</td>
<td>201 ± 33</td>
</tr>
</tbody>
</table>

Data are mean±SEM.

### Slide 1. Patient Demographic and Clinical Characteristics

[Provided by Dr. Nagano]

### Slide 2. Postoperative hemoglobin level

[Provided by Dr. Nagano]

### Slide 3. Number of Complications

[Provided by Dr. Nagano]
difficult to secure an adequate field of vision, I think it will be fine if NEOVEIL can be securely adhered to the tissue, but that is not to deny other difficulties in the area.

**Dr. Nagano:** All of you choose the spray approach, don’t you. How do you use it? Do you first spray a thin layer of a mixture of Solutions A and B on the cut surface, apply NEOVEIL, then spray once again over the top?

**Dr. Oba:** Firstly, we paint an appropriate amount of Solution A alone directly onto the cut surface by hand. Next, NEOVEIL is applied, then the solution is sprayed over the top. Because the NEOVEIL peels off with the spray when only a small amount is applied initially, it is important to paint a sufficient amount of Solution A on the surface first of all.

**Dr. Nagano:** The key to using NEOVEIL better is to only apply the NEOVEIL after providing a firm anchoring surface with Solution A.

**Dr. Oba:** However, because Solutions A and B come in approximately equal volumes, if too much of Solution A alone is painted onto the cut surface before application of NEOVEIL, the volumes will be unbalanced when spraying for the final time. The method described by Dr. Nagano is firstly to spread Solution A alone over the entire cut surface, and then apply NEOVEIL, and with the remaining Solution B, spray over the entire surface, isn’t that right?

**Dr. Nagano:** Like Dr. Oba, I first manually paint about 1 cc to 1.5 cc of Solution A on the cut surface, and after attaching NEOVEIL, I spread the remaining Solutions A and B by hand alternately on the entire surface. I don’t spray a second time because it is troublesome.

**Dr. Yoshida:** I concur with Dr. Nagano that preparing the spray takes care, but making a spray by mixing Solution A and Solution B is something that nurses can handle by themselves. I don’t feel it’s that great a burden.

**Dr. Oba:** It’s certainly preferable to have prepared at the beginning, don’t you think?

**Dr. Yoshida:** Because I have the fibrin glue dissolved soon after the surgery begins, the fibrin glue is just about ready before I start the hepatic resection. Basically, it’s the technique that involves painting Solution A first, but in my situation, because it’s prepared in a spray form, we spray the mixture of Solution A and Solution B on the cut surface, lay down the NEOVEIL, then spray the remaining mixture on top. You could probably call it a sandwich style technique. Since there are no problems in particular with this technique, I think this is a satisfactory approach at present. As our previous practice involved rubbing the sprayed locations with fibrin glue alone, supplementing that with NEOVEIL and spraying fibrin glue on top will make this technique more robust than previous approaches.

**Dr. Nagano:** It really is one key tip for effective use, ensuring the fibrin glue is dissolved before starting the procedure.

**Dr. Yoshida:** That’s because we can’t wait for the transection to be finished and the moment the abdomen is finished to be closed to begin dissolving the fibrin glue.

**Dr. Nagano:** With a fibrin sheet product, it may be possible to immediately use the product after opening the packaging, isn’t that right?

**Dr. Yoshida:** I think that products that must be used during surgery should be prepared at the outset.

**Dr. Nagano:** If we talk about increasing efficiency of time and human resources, that may be a major hint.

**Dr. Yoshida:** In my situation, it’s not only the prior preparation of fibrin glue, but also, I instruct my staff to prepare other consumables used during surgery beforehand, and thereby aim to make the most effective use of the operative time.

**Dr. Nagano:** Dr. Yoshida, I’m well aware of your high regard for time and human resources (Laughter).

### Table: Comparison of fibrin sheet product versus NEOVEIL

<table>
<thead>
<tr>
<th><strong>fibrin sheet product</strong></th>
<th><strong>NEOVEIL</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Objectives of use</strong></td>
<td>Control of mild bleeding or prevention of relapsing bleeding from the cut surface, hepatic veins, and Glisson’s capsule (use during or after liver transection)**</td>
</tr>
<tr>
<td><strong>Ease of use</strong></td>
<td>Can be used immediately. Can be cut into various shapes.</td>
</tr>
<tr>
<td><strong>Hemostatic performance/Adhesive strength</strong></td>
<td>When bleeding is copious, it sticks well even when the cut surface is rounded or if bleeding is somewhat copious.</td>
</tr>
</tbody>
</table>

*When fluids are increased after completion of heptectomy, bleeding may occur.*

**Comparison of fibrin sheet products with NEOVEIL**

**Dr. Nagano:** Next, I’d like us to consider the advantages and disadvantages of fibrin sheet products and NEOVEIL, which were earlier summarized for us by Dr. Oba. (Slide 4)

**Dr. Oba:** From the point of view of convenience, fibrin sheet products can be used straight after opening the packaging. By contrast, NEOVEIL is quite difficult to trim to size because it’s a nonwoven fabric, and it is possible for it to peel off when a small amount of fibrin glue is used. From the hemostatic strength aspect, I have the impression that NEOVEIL can be used reliably with assurance if used proficiently. When bleeding is profuse, a fibrin sheet product adheres poorly to tissue, and blood may leak from around the edges. In that sense, if completed proficiently, using NEOVEIL and fibrin glue in combination may also be possible to have greater ability to halt bleeding.

**Dr. Nagano:** Dr. Yoshida, do you have any comments on this issue?

**Dr. Yoshida:** The method involving
the use of NEOVEIL plus fibrin glue in combination is similar to that for fibrin sheet products, but as you might expect, there is resistance to the use of fibrin sheets for bile ducts.

**Dr. Nagano:** I agree. All in all, I feel they may have a weakness in the management of biliary fistula.

**Dr. Yoshida:** NEOVEIL can be used for that.

**Dr. Oba:** Since fibrin sheet products are hard, NEOVEIL gives the impression of being the appropriate choice for tissues with curved surfaces.

**Dr. Nagano:** The combination of NEOVEIL plus fibrin glue for uneven surfaces after hepatic resection appears to have good adhesion to tissues.

To more easily trim NEOVEIL, the method conceived by our nurses in the surgical unit at our hospital involves cutting the sheet in its plastic bag without taking it out first. NEOVEIL sheets are enclosed in plastic bags, and it is better when the product is cut in each plastic bag, then taken out individually and used. This too, might be a useful tip.

**Dr. Yoshida:** We used NEOVEIL for hepatectomy today too, and the nurses cut NEOVEIL without removing it from the plastic packaging. Our junior surgeons cautioned the nurses “Shouldn’t you open the packaging before you cut it?”, but after seeing it done, acknowledged that cutting NEOVEIL in its unopened plastic packaging may in fact be a good approach.

**Dr. Nagano:** There is one characteristic of NEOVEIL plus fibrin glue that I’d like to see improved. As fibrin sheet products are dry and the product is hard, they have the advantage that they can be compressed, although it does depend on the extent and degree of hemostasis. Since the fundamental principle of hemostasis involves compression, there may be a difference between using a product that allows pressure hemostasis and one that does not. Via product improvement etc., a method that allows NEOVEIL to be successfully compressed would be even more useful.

**Dr. Yoshida:** I compress NEOVEIL when I use it. I spray fibrin glue, apply NEOVEIL, then use more fibrin glue. Then I rub slowly with the fingers. If it doesn’t stick to the gloves completely even when it moves a little, I compress with the fingers in this state.

**Dr. Nagano:** When it’s in the dried form and it can be cleaned, can it be compressed?

**Dr. Yoshida:** I spray fibrin glue, then apply NEOVEIL, and once again use fibrin glue, and immediately thereafter, I rub with my fingers. If it doesn’t stick to the gloves being used for rubbing, I stop moving my the fingers for a little while, and compress for 10 to 20 seconds.

As well, you noted before that fibrin sheet products cannot be used on uneven surfaces. However, if you cut them into smaller pieces, and as with NEOVEIL plus fibrin glue, rub the fibrin sheet product with the fingers, they too, can be comfortably fitted to uneven surfaces.

**Dr. Nagano:** If you correctly select the method of use and location, compression is actually possible with NEOVEIL plus fibrin glue, isn’t it?

**Dr. Oba:** After applying NEOVEIL plus fibrin glue, we spread out a plastic glove over the site, then add a layer of gauze on top and compress.

**Dr. Yoshida:** It’s probably all right to compress with rubber gloves or gauze, but if you’re trying to press rubber gloves or gauze over pinpoint bleeding, you just can’t apply pinpoint compression.

All the same, I think that the fingertips would be convenient for compression in pinpoint bleeds. However, as mentioned earlier, since the fibrin glue has a tendency to stick to your fingertips, you should keep them moving. Because moving the fingertips for about five seconds will avoid sticking, it is possible to halt the bleeding afterwards if compression is applied for a little while.

**Dr. Nagano:** In addition to the list of advantages and disadvantages prepared by Dr. Oba, a number of other pitfalls and hints for proficient usage and handling the product have emerged today. I think these will also be beneficial for others in the future.

### 3. Future possibilities for NEOVEIL

#### Future indications, surgical technique development

**Dr. Nagano:** Finally, let’s discuss the future possibilities for NEOVEIL.

What are your thoughts on issues such as future methods of use and the development of surgical techniques?

**Dr. Oba:** I’m trying it out in situations like laparoscopically-assisted surgery, and as you might expect, because the visual field is poor in this modality, I’d like to achieve complete hemostasis using NEOVEIL.

Another consideration is the present method of NEOVEIL plus fibrin glue uses blood products, and I think it would be an improvement if similar efficacy to current methods could be obtained without the use of blood products. We have recently seen the emergence of starch-based hemostatic agents, and I feel it’s a positive sign to see such developments.

**Dr. Nagano:** If that were to occur, several problems with blood products could be avoided couldn’t they. As a characteristic, don’t you believe that a paste-like consistency would be better?

**Dr. Oba:** Yes, that’s right.

**Dr. Nagano:** What do you think Dr. Yoshida?

**Dr. Yoshida:** I think vascular suturing. For complications that arise in locations where blood vessels are sutured in liver transplantation, or when blood vessels are exposed to leaking pancreatic fluid
in pancreateoduodenectomy, I get the impression that using NEOVEIL will relieve the situation a little. There is no evidence for this, but it seems that it may in fact be effective because it provides a covering.

Dr. Nagano: I am in complete agreement on this point. I think it would be advantageous if NEOVEIL could be used for covering blood vessels, or for preventing lymphatic fistula. In cases of lymph node dissection or when cancer is near an artery, and they are to be detached, or cases in which an outer membrane must be detached, long ago we used a product known as Biobond. However, Biobond fell out of use because of problems arising with artificial heart-lung machines. Now, given that there are no longer any reinforcement materials for blood vessels, being able to use NEOVEIL as a reinforcement for blood vessels would be extremely beneficial.

In one case, a patient with retroperitoneal tumor, a retroperitoneal tumor was removed from between the celiac artery trunk and the superior mesenteric artery. A small opening that had formed at the stripping line of the superior mesenteric artery had been reinforced with an external membrane and 8-0 prolene sutures, but because of concern about a false aneurysm, we used NEOVEIL and fibrin glue. We will be very grateful when the indications for NEOVEIL are expanded even a little, for example, as an outer membrane reinforcing material, as a filler for lymphatic fistula, or as a material to reinforce blood vessels to replace Biobond in cancer of the pancreas or stomach, or retroperitoneal tumor. Dr. Yoshida mentioned the use of NEOVEIL for the pancreas, and the upper gastrointestinal tract group at our institution is trialling the use of NEOVEIL in a pilot study for preventing pancreatic fistula in surgery for advanced stomach cancer, in cases in which the pancreatic fascia must be detached. As a trial, they are using NEOVEIL in procedures where a pancreateojejunostomy is performed after pancreateoduodenectomy. A conclusion is yet to be reached as to whether or not NEOVEIL offers any benefit, but we already know at least that no infection of any form has occurred to date.

Previously, you have discussed the use of NEOVEIL as a vascular covering or in vascular anastomosis. In that context too, since NEOVEIL is a nonwoven fabric and is made of extremely soft material, it will help a great deal when the contraindications for cardiac vessels can be removed. I believe that hepatobiliary-pancreatic surgeons handle blood vessels more frequently than other gastrointestinal surgeons, and in that sense, I would be grateful for developments in that area. Otherwise, are there any other easy to use shapes or methods or devices?

Dr. Yoshida: In relation to its ease of use, I believe it is quite easy to use in this shape. Also, to add to the previous discussion on blood vessels, I think it may be preferable when cladding blood vessels to wrap NEOVEIL only partway around the vessel, rather than all the way round, like a muffler.

Dr. Nagano: Yes, that’s right. Since there is the potential for stenosis and other concerns, wrapping NEOVEIL all the way round the vessel and securing it, by contrast, may not be a good approach.

Dr. Yoshida: Additionally, if we’re talking about vascular anastomosis, I think it would preferable to leave a gap in one location only. I also wonder whether you could say this about the hepatic cut surface too. On the whole, I believe it may be better to apply NEOVEIL with a gap left open, rather than covering the entire surface with NEOVEIL.

Dr. Oba: Is it OK to wrap NEOVEIL around the pancreatic and jejunal surfaces?

Dr. Yoshida: I feel that I’d like to wrap NEOVEIL all around, but I also wonder whether problems might occur when it’s completely sealed.

Dr. Nagano: There may not be much in the way of problems if the pancreas is fully sealed, but I suspect that stenosis of the portal vein or other venous vessels may be a possibility. For arteries on the other hand, it would probably be fine, since stenosis of the arterial wall can hardly be expected.
The Role of NEOVEIL in Hepatectomy and its Future Potential

with NEOVEIL. However, I feel it would be beneficial to pay attention with regard to the types of blood vessel.

2 The future for NEOVEIL

Dr. Nagano: Dr. Oba, what are your views on new devices?
Dr. Oba: It would be a good outcome if they could be as easy to use as a Band-Aid.
Dr. Nagano: Something with the ease of use of sheet-type fibrin glue, perhaps for NEOVEIL?
Dr. Yoshida: Certainly a glue would stick to NEOVEIL, and one that can immediately be applied when a paste-like product is peeled off would be good.
Dr. Nagano: In actual fact, sheet-type fibrin glues are a single product made of collagen powder and fibrin glue combined into a sheet. Like fibrin sheet products, I think that the softness of NEOVEIL would somehow disappear if it had high fixing strength, but a product composed of NEOVEIL and a base fixative that could be used in one sheet it would be a good option for the future. That’s fairly much the situation isn’t it. For transection of the liver, the approach is fairly much the same at all hospitals, and as you might expect, hepatectomy fundamentally involves 80% surgical techniques and the remaining 20% using covering materials such as NEOVEIL for more completeness. There are subtle differences among various products to date, but the overall approach is the same. At any rate, for bleeding that is difficult to stop with surgical means only, or bleeding from locations that cannot be reached with the surgeon’s hands, NEOVEIL is used with the objectives of preventing complications, bleeding, and infection. Even among the recent concerns that have arisen, we are not now in an era in which bleeding is feared because the liver is to be cut. At all three hospitals, the likelihood is that intraoperative blood transfusions are not required, and probably none postoperatively too.

The next issue raised was that of the problem of biliary fistula. NEOVEIL plus fibrin glue is a covering material with great potential for this application, and probably the same as Dr. Sano was saying, expectations for this seem to be extremely high among the surgeons from the three hospitals represented here.

There are several proposals for improving NEOVEIL, and I believe that the manufacturer is wanting to develop the product in various forms. As “must-haves” for we surgeons, I feel it’s a matter of compiling evidence. I think we can all agree that today’s conclusion is that NEOVEIL is a promising product and covering method.

Commentary

Telkyo University Hospital
Dr. Keiji Sano

My first priority when planning this round-table discussion was to elicit information that was immediately useful to readers, and to draw out the participants’ “tips” that cannot be expressed in the form of data. To that end, we invited three surgeons who are active on the front line of their craft in different traditions. Unfortunately, I was unable to participate on the day itself due to other urgent business, but when I look at how this forum developed, thanks to Dr. Nagano’s skills as moderator (despite being called on very short notice), I see it was full of information that just can’t be found in any textbook – the skills in routine surgery and careful consideration that belle Dr. Yoshida’s physical characteristics, and Dr. Oba’s soft and gentle manner of speech, and precise surgical management. That I was unable to participate is a great regret. As well, I was extremely impressed with Dr. Nagano’s scientific approach to the evaluation of surgical procedures. The conclusion reached by these hepatectomy professionals is that NEOVEIL shows its advantages for biliary fistula in a way that is unrivaled by other products, and I too, am in complete agreement. Otherwise, I think it is necessary to wait for further evidence regarding efficacy in reinforcing vascular anastomoses or treatment of the pancreatic stump.

I hope that the readers of this piece are able to gain even more useful information for your next hepatectomy, and that the possibilities for NEOVEIL are further enhanced, and the safety of hepatectomy improved.
[Warning]
(1) Do not apply nor use in conditions where excessive tension and load act upon NEOVEIL; nor should it be used in cases where NEOVEIL is torn or damaged.
(2) Do not apply to infected regions.

[Contraindication]
(1) Do not use NEOVEIL in patients with systemic complications.

[Prohibited]
(1) Do not use.
(2) Do not use in regions which take a long time to heal. Moreover, do not use NEOVEIL for the eternal purpose. (It might be unable to keep adequate fixation because of the characteristic of this product)
(3) Do not use on nerve system and cardiac vessels, since the safety and efficiency for these applications are not confirmed yet.
(4) Do not use to make up an epidural deficiency area.

[Care for usage]
Read contraindication, warning and the following lines before usage.

1. Usage note
   (1) The use of NEOVEIL for the patients who have allergic should be considered from the characteristic of this product.
   (2) Consider the possibility of using this product to weak patients and those wounds take a long time to heal.

2. Important basic cares
   In case of postoperative infection, treat with debridemet after removing this product.

3. Disadvantages and adverse reaction
   No NEOVEIL related disadvantages or adverse reaction were reported. However, the following disadvantages may occur with the characteristic of this product.
   As with any foreign body, prolonged contact of this product with the ureter or the biliary might result in calculus formation. Failure to support the region due to excessive tension Failure to support the region of elderly patients, weak patients or those whose wounds take a long period to heal.
   Minimum acute tissue inflammation
   In case of use in little blood stream regions or regions near the skin
   *Inflammation or partial extrusion of material with late absorption or mechanical irritation
   *Local pH decrease by accumulation of this dissolved unmetabolized material, and inflammation caused from pH decrease

4. Application of the elderly patients
   The use of NEOVEIL for the elderly patients should be considered from the characteristic of this product.

5. Application of the pregnancy or the lactation
   The use of NEOVEIL for pregnant women, lactated women or women suspected of being pregnant should be considered from the characteristic of this product.

6. Application of the child patients
   Sufficient knowledge about using this product for child patients has been not obtained. Therefore the use of NEOVEIL for the child should be considered from the characteristic of this product.

[Result of clinical trial]
134 cases of clinical trials for reinforcing and preventing air leakage of the suturing part and hemostasis were conducted surgical procedure of respiratory organ and digestive organ from October 1989 to September1990. Fibrin glue was used for hemostasis at the same time.
In general evaluation which based on the working easiness, the clinical efficacy and the side effect was that 68 cases were "very useful", 62cases were "useful" and 4 cases were "not deemed useful".
602 case of PMS studied from March 1992 to April 2000. In any case, side effect, disadvantage and adverse reaction which caused by this product were not existent.

[Storage]
1. The available period is 3years from a manufacture day. The expiration time is defined on each package. Do not use the product past the term.
2. Handle and store carefully to avoid damaging the package.
3. Store this product in a clean place, and avoid high temperatures (over 40°C), direct rays of the sun and moisture.
4. Please use the product immediately after opened an aluminum bag. If the product exposed to the air, it may degrade due to moisture contained in the air.
5. When this product store, use in order of production days.

[Product Variation (sterilized by EOG)]

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Manufacturer
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