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Clinical Safety and Performance of GATT-Patch for Hemostasis in Minimal to Moderate Bleeding During Open Liver Surgery

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ABSTRACT

Introduction: Intraoperative blood loss and postoperative hemorrhage affect outcomes after liver resection. GATT-Patch is a new flexible, pliable hemostatic sealant patch comprising fibrous gelatin carrier impregnated with N-hydroxy-succinimide polyoxazoline. We evaluated safety and performance of the GATT-Patch for hemostasis at the liver resection plane.

Methods: Adult patients undergoing elective open liver surgery were recruited in three centers. GATT-Patch was used for minimal to moderate bleeding at the liver resection plane. The primary endpoint was hemostasis of the first-treated bleeding site at 3 min *versus* a prespecified performance goal of 65.4%.

Results: Two trial stages were performed: I ($n = 8$) for initial safety and II ($n = 39$) as the primary outcome cohort. GATT-Patch was applied in 47 patients on 63 bleeding sites. Median age was 60.0 (range 25-80) years and 70% were male. Most (66%) surgeries were for colorectal cancer metastases. The primary endpoint was met in 38 out of 39 patients (97.4%; 95% confidence interval: 84.6%-99.9%) *versus* 65.4% ($P < 0.001$). Of all the 63 bleeding sites, hemostasis was 82.7% at 30, 93.7% at 60, and 96.8% at 180 s. No reoperations for rebleeding or device-related issues occurred.

Conclusions: When compared to a performance goal derived from state-of-the-art hemostatic agents, GATT-Patch for the treatment of minimal to moderate bleeding during liver

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surgery successfully and quickly achieved hemostasis with acceptable safety outcomes. (ClinicalTrials.gov Identifier: NCT04819945).

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Introduction

Liver surgery has been associated with considerable morbidity and mortality, and the short-term and long-term outcomes may be influenced by intraoperative blood loss and a need for blood transfusion, as well as postoperative hemorrhage.[1,2] A retrospective analysis of approximately 1.6 million surgical procedures, including cardiac, vascular, solid organ, and spinal surgeries, indicated that the rate of bleeding-related complications was approximately 30%, with blood transfusions required in more than 20% of all patients.[3] There are significant benefits to patients when hemostasis is addressed efficiently, and effective treatment of intraoperative bleeding may reduce blood loss and postoperative complications.[3]

During liver surgery, commonly used techniques to limit and control bleeding include temporary occlusion of inflow vessels and control of bleeding from outflow vessels,[4,5] and the use of specific transection devices such as Cavitron Ultrasonic Surgical Aspirator or vessel sealants. Nevertheless, during and after transection, bleeding may still occur from the cut surface and can be problematic to control with standard surgical techniques of ligation, suturing, or electrocautery. In those situations, several topical hemostatic agents are available to aid in achieving hemostasis to limit blood loss, reduce operating times, and reduce postoperative complications.

There is a wide variety of topical hemostatic agents indicated for use during liver resection surgery, ranging from nonactive products typically used for minimal to mild bleeding, to more advanced products with active components (e.g., fibrinogen and thrombin) or a polymer-based technology (e.g., N-hydroxy-succinimide functionalized polyethylene glycol) that are typically used for problematic bleeding. However, many of the currently available topical hemostatic agents have clinical limitations related to their (i) success rate, particularly in difficult-to-control bleeding, (ii) ease of use, being rigid or friable, and (iii) applicability in a wide variety of bleeding, including difficult-to-access bleeding or deep cavities, as well as economical limitations related to costs.[6-10]

GATT-Patch (GATT Technologies BV, Nijmegen, The Netherlands) is a new hemostatic sealant patch that consists of a fibrous gelatin carrier impregnated with poly(2-oxazoline) (N-hydroxy-succinimide polyoxazoline) to provide fast and robust hemostatic performance and with flexibility and pliability to allow ease of use.[11,12] In previous animal studies, use of GATT-Patch has demonstrated safety and efficacy during open and minimally invasive procedures on solid organs.[12,13] The aim of this first-in-human study was to evaluate the safety and the performance of GATT-Patch in elective open liver surgery.

Methods

Study design

A prospective, single arm, multicenter, first-in-human clinical investigation was performed to determine the clinical safety and performance of GATT-Patch for management of bleeding during elective open liver surgery. The study was performed at three investigational sites in the Netherlands in two stages. Stage I planned to enroll a maximum of 12 patients, with at least two from each site, who were followed for 2 wk and then reviewed by the Data Monitoring Committee (DMC). After the DMC recommended the study to proceed as designed, stage II was performed in which an additional 39 patients were treated with GATT-Patch (Supplemental Fig. S1).

This study was performed in accordance with ISO 14155, the Code of Ethics of the World Medical Association (Declaration of Helsinki), and all relevant national guidelines. The study was approved by the Central Committee on Research Involving Human Subjects (The Netherlands) and each investigational site approved the study. All patients provided written informed consent. All authors have reviewed and approved the final version of this manuscript.

Patients and procedures

Adult patients (>18 y) undergoing elective open liver surgery were asked to participate in the trial. Key exclusion criteria were as follows: surgery on additional organs other than the liver, an active or suspected infection at the surgical site, the device would be used at the site of a synthetic graft or patch implant, previous or planned organ transplantation, multiple antithrombotic therapies (allowing only single use of acetylsalicylic acid), platelet count $<100 \times 109$/L, and activated partial thrombin time of >100 s, an international normalized ratio >2.5 or total bilirubin level of ≥2.5 mg/dL (International System of Units conversion factor = 17.104 reported as μmol/L), American Society of Anesthesiology classification of 4/5,[14] severe congenital or acquired immunodeficiency, pregnancy or actively breast-feeding, hypersensitivity to brilliant blue, or a life expectancy of less than 3 mo.

Intraoperatively, patients had to have minimal, mild, or moderate bleeding (Severity Bleeding Surface Scale [SBSS] of 1, 2, or 3)[15] at a target bleeding site at the liver resection plane for which any standard surgical techniques (e.g., suture, ligature, or cautery) for hemostasis were ineffective or impractical and the surgeon had made the decision to apply a topical hemostatic product. The first target bleeding site for which a GATT-Patch was required and applied was analyzed for the primary endpoint. Data on additional target bleeding sites where GATT-Patch was used were also collected for secondary analyses.

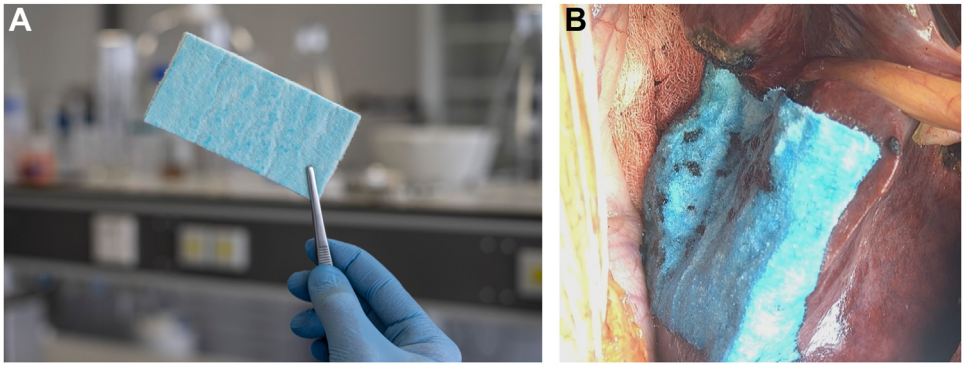

Fig. 1 – GATT-Patch. (A) GATT-Patch pliable hemostatic sealant patch before placement and (B) after placement on a bleeding site. Images courtesy of GATT Technologies ©2023.

The surgical procedure was performed according to local hospital and surgeon standards. Besides the use of GATT-Patch, no protocols for the surgical procedure were dictated.

Product

GATT-Patch is a blue (FD&C No. 1 colorant) hemostatic 10 × 5 cm sealant patch that can be cut to size if needed (Fig. 1). The patch is 3-dimensionally impregnated with polymer and can therefore with either side be applied to the tissue. Surgeons were instructed to overlap the target bleeding site by a margin of 1 cm of nonbleeding tissue on all sides. GATT-Patch was placed dry on the target bleeding site and applied for 30 s with a saline-wetted gauze, after which hemostasis was checked. If no hemostasis was achieved, an additional 30 s of pressure was required. If hemostasis was still not achieved, an additional piece of GATT-Patch could be placed to achieve hemostasis. This (partly) patch-on-patch application was also allowed for large bleeding areas that could not be covered by a single patch. Use of up to three *in situ* GATT-Patches per procedure was allowed.

Outcomes

The primary performance endpoint was noninferiority of GATT-Patch compared the proportion of patients that achieved hemostasis (defined as SBSS of 0) within 3 min as compared to a literature-based performance goal of 65.4% derived from state-of-the-art hemostatic agents. This performance goal was the lower 95% confidence interval (CI) of the weighted average of hemostasis at 3 min in six randomized controlled trials performed with benchmark hemostatic agents.[16-21] The agents used in these trials consisted of TachoSil ($n = 3$ trials), Fibrocaps ($n = 2$ trials), Surgicel ($n = 2$ trials), gelatin sponge ($n = 2$ trials), Vistaseal/Veraseal ($n = 1$ trial), Sangustop ($n = 1$ trial), and Veriset ($n = 1$ trial).

The secondary performance endpoints were mean time to hemostasis (TTH) in seconds, and the percentage of patients with hemostasis achieved at 30, 60, 90, 120, and 150 s.

The safety of GATT-Patch was assessed by the nature, severity, and incidence of device-related events. Device-relatedness was determined to be possibly related, probably related, or causal relationship, according to ISO 14155 standards. Serious adverse events (SAEs) were defined according to ISO 14155 as events resulting in (a) death ; (b) serious deterioration in the health of the subject defined as one of the following: (i) life-threatening illness or injury, (ii) permanent impairment of a body structure or a body function including chronic disease, (iii) in-patient or prolonged hospitalization, or (iv) medical or surgical intervention or prevent life-threatening illness or injury, or permanent impairment of a

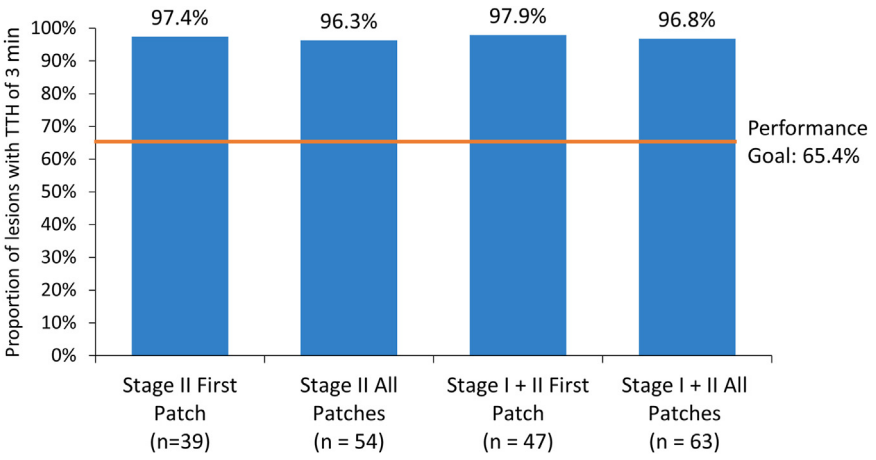

Fig. 2 – Primary endpoint of 3-min hemostasis. The proportion of bleeding sites with a time to hemostasis by 3 min for Stage I and Stage II. TTH = time to hemostasis.

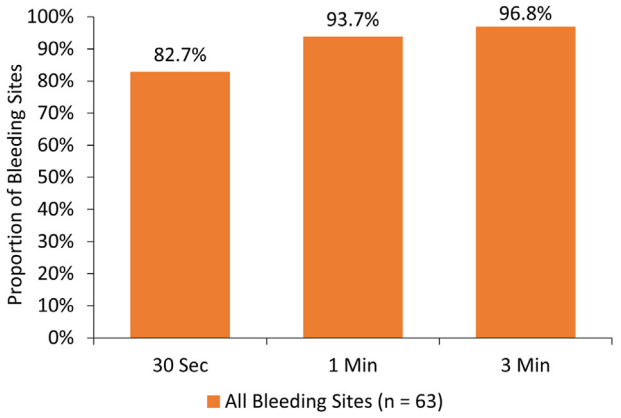

Fig. 3 – Time to hemostasis. The proportion of bleeding sites (stage I and stage II) in which hemostasis was achieved at 30 s and at 1 and 3 min.

body structure or a body function; or (c) fetal distress, fetal death, a congenital abnormality, or birth defect including physical or mental impairment. All SAEs were monitored during surgical hospitalization and through a 6-wk follow-up period that was concluded by an in-hospital visit. This 6-wk visit included an ultrasound of the liver to check any (i) device encapsulation, (ii) rolling up of the device on the cut surface, (iii) pseudoaneurysm forming under the patch, and (iv) evidence of biloma. If a computed tomography (CT) scan or other imaging was performed for clinical reasons in the window of the ultrasound imaging, there was no need for an additional ultrasound. The events on routine ultrasound were categorized according to the worst-case event that was mentioned in the imaging report.

To evaluate device usability, the surgeons completed a questionnaire that consisted of a standard System Usability Scale (SUS)[22] and a device-specific questionnaire. The SUS is a 10-item scale that provides a global view of subjective assessments of usability, with cumulative scores ranging from 0 to 100 and higher scores representing better usability. The device-specific questionnaire comprised 27 questions using the 5-point Likert scale: “strongly disagree”, “disagree”, “neutral”, “agree”, and “strongly agree”.

Statistical analysis

The main analysis cohort for the primary endpoint comprised patients treated in stage II and is reported using the Full Analysis Set. The sample size was determined to be 39 evaluable patients (or 36 assuming a dropout rate of 7.5%) and was powered with 90% on the primary noninferiority endpoint, assuming that GATT-Patch would reach hemostasis at 3 min in 89% of treated patients with the lower bound of the 95% CI being higher than the predefined performance goal of 65.4%. An interim analysis at 25 evaluable stage II patients allowed for possible early stopping for overwhelming performance success or sample size re-estimation according to the Mehta-Pocock Promising Zone approach to increase the sample size to 61 patients if required to maintain statistical power.[23] The Lan-DeMets[24] approach with an O’Brien-Fleming alpha-spending function was used to control the overall Type I error rate of the study at a one-sided 0.025 level. The proportion of patients achieving hemostasis at 3 min using GATT-Patch was compared to the performance goal of 65.4% using the continuity corrected z-test of proportion at the one-sided 0.0229 significant level. The analysis cohort for the safety endpoints comprised all patients in stage I and stage II. Post

Table 1 – Patient characteristics.

Characteristic	Stage I $n = 8$	Stage II $n = 39$	All patients $n = 47$
Median (range) age, y	64.5 (53.0, 74.0)	59.0 (25.0, 80.0)	60.0 (25.0, 80.0)
Male sex	7 (87.5)	26 (66.7)	33 (70.2)
Body mass index, kg/m^2	29.1 ± 6.5	25.9 ± 4.2	26.4 ± 4.8
Cardiac disorder	1 (12.5)	7 (17.9)	8 (17.0)
Renal dysfunction	1 (12.5)	0 (0.0)	1 (2.1)
Diabetes mellitus	3 (37.5)	6 (15.4)	9 (19.1)
Previous abdominal surgery	6 (75.0)	23 (59.0)	29 (61.7)
Hereditary blood disorders	0 (0.0)	1 (2.6)	1 (2.1)
Hemoglobin, g/dL*	8.7 ± 1.0	8.2 ± 0.8	8.3 ± 0.8
Platelets, 109/L*	255.0 ± 131.1	212.2 ± 64.0	219.4 ± 79.1
Total bilirubin, mg/dL*	10.9 ± 3.1	8.9 ± 5.2	9.3 ± 4.9
ASA classification			
2	5 (62.5)	22 (56.4)	27 (57.4)
3	3 (37.5)	15 (38.5)	18 (38.3)

Data presented as median (range), number of patients (percentage) or mean ± standard deviation.
ASA = American Society of Anesthesiologists.
* Preoperative. For International System of Units, the conversion factor for hemoglobin is 10 with units of g/L, and for bilirubin, the conversion factor is 17.104 with units of μmol/L.

hoc analyses of the performance outcomes were also performed for the stage I cohort. For the per-bleeding site hemostasis results, estimated percent and CI based on a repeated measures logistic regression using an unstructured covariance matrix. Continuous variables are reported as mean ± standard deviation, median (interquartile range [IQR]) or median (range) and categorical variables are reported using frequencies as percentages of patients in each group.

Results

Patients and treatment

Between April and November 2021, 56 patients were enrolled at three investigational centers in the Netherlands. Stage I comprised eight patients, with a minimum of two patients treated at each site. Stage II comprised 39 patients; the interim analysis results were reviewed by the DMC and although there was an option to stop the trial early, the Sponsor decided to continue the trial to the full sample size to maintain statistical power on a broader, potentially increasing heterogenous patient population. Of the 56 patients, subsequent exclusions were due to screening failure ($n = 1$), no bleeding during surgery ($n = 5$), or withdrawal for other reasons ($n = 3$), leaving 47 patients with 63 bleeding sites treated with GATT-Patch.

Baseline clinical characteristics are shown in Table 1. Overall, mean age was 60 y and 33 (70.2%) were male. The most common diagnosis for surgery was colorectal cancer metastases in 66% of the cases. The type of surgery was nonanatomical wedge resection in 15 patients (32%), left or (extended) right hepatectomy in 11 (23%), and other anatomical resections in 15 (36%). The most common transection method was Cavitron Ultrasonic Surgical Aspirator alone (75%) or in combination with other techniques (89%) (Table 2). The hepatic parenchyma as scored by the surgeon during surgery was deemed normal in 79%, steatotic in 13%, and cirrhotic in 6% of patients.

Patient bleeding characteristics are shown in Table 3. Of the 63 total bleeding sites (stage I and stage II patients), one had an SBSS of 4, which was a protocol violation. Types of bleeding were venous (60%), arterial (2%), or mixed (38%). Primary hemostatic techniques used before GATT-Patch application consisted mainly of electrocautery (38%) and clips (21%). There were two patients (4.3%) that required blood transfusion during surgery or the postsurgical hospitalization period.

Table 2 – Surgical characteristics.

Characteristic	All patients $n = 47$
Indication for surgery	
Colorectal cancer metastases	31 (66.0)
Hepatocellular carcinoma	5 (10.6)
Cholangiocarcinoma	4 (8.5)
Noncolorectal cancer metastases	4 (8.5)
Other	3 (6.4)
Type of procedure	
Nonanatomical wedge resection	15 (31.9)
Right hepatectomy*	10 (21.3)
Left hepatectomy	1 (2.1)
Other nonhepatectomy anatomical resection	17 (36.2)
Other	4 (8.5)
Surgical time, min	221 ± 147
Blood loss, mL	793 ± 737
Blood transfusion during hospitalization	2 (4.3)
Transection method†	
CUSA alone	35 (74.5)
CUSA in combination with bipolar, harmonic, LigaSure	12 (25.5)
Blood inflow reduction method	
None	27 (57.4)
Pringle	18 (38.3)
Other	2 (4.3)
Liver parenchyma type	
Normal	37 (78.7)
Staetotic	6 (12.8)
Cirrhotic	3 (6.4)
Other	1 (2.1)

Data presented as number of patients (percentage) or mean ± standard deviation.
SBSS = severity bleeding surface scale, CUSA = cavitron ultrasonic surgical aspirator.
* Includes extended hepatectomy.
† No transection was performed in two patients, but bleeding of the liver occurred during manipulation or radiofrequency ablation.

Primary outcomes

The primary performance endpoint in the stage II cohort was met with hemostasis achieved within 3 min in 38 patients (97.4%; [95% CI: 84.6%-99.9%]) as compared to the performance goal of 65.4% ($P < 0.001$) (Fig. 2). Hemostasis was achieved at 30 s in 32 patients (82.1%; [95% CI: 65.9%-91.9%]), at 1 min in 37 patients (94.9%; 95% CI [81.4%-99.1%]), and at 3 min in 38 patients (97.4%; 95% CI [84.6%-99.9%]) (Fig. 3). The mean TTH was 54.6 ± 107.48 s (median 30 s [IQR 30 s-30 s]).

In the single case where hemostasis at the first target bleeding site was not achieved within 3 min, a hematoma was observed at 5 min. Per Instructions for Use, that part of the patch was removed, and an additional piece of patch added, after which hemostasis was achieved.

For the 63 total (primary and additional) bleeding sites, hemostasis was achieved at 30 s in 52 (82.7% [95% CI, 71.0%-90.3%]); at 1 min in 59 (93.7% [95% CI, 84.5%-997.6%]), and at 3 min in 61 (96.8% [95% CI, 88.2%-99.2%]). Hemostasis was not achieved within 5 min in two bleeding sites, but hemostasis was achieved with GATT-Patch after 5 min: one time with additional electrocoagulation and one time with an additional piece of GATT-Patch.

In nearly all (98%) bleeding sites, only one (or a portion of one cut to a smaller size) GATT-Patch was used, and only once there was a requirement to use more than one (but less than two) full-sized GATT-Patch(es).

Table 3 – Patient bleeding characteristics.

Characteristic	Per patient analysis			Per bleeding site analysis
	Stage I $n = 8$	Stage II $n = 39$	All patients $n = 47$	All $n = 63$
SBSS bleeding severity per patient				
1	1 (12.5)	9 (23.1)	10 (21.3)	13 (22.0)
2	6 (75.0)	16 (41.0)	22 (46.8)	27 (45.2)
3	1 (12.5)	14 (35.9)	15 (31.9)	22 (30.9)
4	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.6)
Hemostatic technique before patch application*				
Cautery	3 (37.5)	15 (38.5)	18 (38.3)	26 (38.3)
Clips	1 (12.5)	9 (23.1)	10 (21.3)	15 (21.3)
Suture or ligature	0 (0.0)	7 (17.9)	7 (14.9)	8 (14.2)
Other	0 (0.0)	1 (2.6)	1 (2.1)	1 (1.6)

SBSS = severity bleeding surface scale.
* Multiple techniques could be applied in a single patient. In some patients, listed hemostatic techniques were not attempted before the patch.

Safety outcomes

Overall, 28 patients (59.6%) experienced 44 adverse events, of which 11 were identified during postprocedural required imaging but had no clinical implications (Table 4). Of the patients experiencing adverse events, the median (with IQR) number of adverse events per patient was 2.0 (1.0, 2.0) in the stage I cohort, 1.0 (1.0, 2.0) in stage II and 1.0 (1.0, 2.0) combined.

There were seven patients (14.9%) who experienced a SAE. The SAEs were as follows: perihepatic abscess requiring radiological drainage ($n = 1$); abdominal abscess resulting from fistula from a primary sigmoid carcinoma requiring surgical resection ($n = 1$); biloma requiring radiological drainage and an endoscopic retrograde cholangiopancreatography and papillotomy with placement of stents ($n = 1$); gastric perforation due to late thermal injury from open microwave ablation, requiring relaparotomy ($n = 1$); hepatic failure with ascites requiring multiple radiological drainages ($n = 1$); pneumonia requiring intravenous antibiotics resulting in prolonged hospitalization ($n = 1$); and postprocedural bile leak requiring radiological drainage and an endoscopic retrograde cholangiopancreatography with stent placement ($n = 1$).

A possible device-related adverse event occurred in three patients, one of which was a serious device-related adverse event. The possibly device-related adverse events included one patient with a biloma and one patient with postprocedural hematoma. The above-mentioned event of perihepatic abscess was assessed as serious and resolved without sequelae after 4 d. All device-related adverse events were considered possibly related to the device because exclusion of a causal relationship could not be established. There were no events that were probably related to the device or with a causal relationship with the device. There were no reoperations for rebleeding or device issues. There were no deaths reported during the conduct of the study.

Post procedure imaging

There were 46 patients who underwent 6-wk imaging (44.8 ± 8.6 d postsurgery), of which 43 underwent routine ultrasound imaging and three underwent clinically indicated CT. A biloma was diagnosed in all three clinically indicated CT scans.

Among the 43 patients with routine non–clinically indicated ultrasound imaging, evidence of biloma was reported in seven patients as possible biloma ($n = 3$), suspicion of partly biloma ($n = 1$), fluid collection being seroma or biloma ($n = 1$), fluid collection being hematoma/biloma ($n = 1$), and biloma ($n = 1$). Evidence of a hematoma was found in four patients from routine ultrasound and evaluated as fluid collection partly hematoma ($n = 1$), fluid collection ($n = 1$), small hematoma ($n = 1$), and encapsulated hematoma ($n = 1$). These events were incidental findings on postoperative imaging; none were confirmed as biloma or hematoma since no percutaneous or operative drainage was required. No events required any further intervention and events resolved by themselves over time.

There were no patients with device encapsulation, rolled-up device, or evidence of pseudoaneurysm.

Device usability

The usability questionnaire was completed by 15 surgeons for all 47 surgeries (Supplemental Table S1). The results indicated high user satisfaction with a mean SUS of 86.2 ± 9.8 and with a "neutral", "agree", or "strongly agree" response in over 90% for all 27 device-specific questions. Specifically, an "agree" or "strongly agree" response was given in 100% of questionnaires to statements "GATT-Patch can be used intuitively", "GATT-Patch is easy to be used/handled", "I feel confident that GATT-Patch stops a bleeding", and in 98% to the statement "I feel confident that GATT-Patch can be used safely".

Discussion

In this first-in-human evaluation of GATT-Patch in patients undergoing elective open liver surgery, GATT-Patch use resulted in a very high rate (97.4%) of hemostasis within 3 min, with a low rate of SAEs, noninferior to existing hemostatic agents. Moreover, 83% of the bleeding sites reached

Table 4 – Adverse events based on clinical and imaging findings.

Adverse event	All $n = 44$	Clinical events $n = 33$	Imaging findings without clinical implications $n = 11$
Atrial tachycardia	1 (2.1)	1 (2.1)	0 (0.0)
Abdominal abscess	1 (2.1)	1 (2.1)	0 (0.0)
Abdominal pain	1 (2.1)	1 (2.1)	0 (0.0)
Ascites	1 (2.1)	1 (2.1)	0 (0.0)
Fluid collection possible/suspicion of biloma/bile leakage	10 (21.3)	3 (6.4)*	7 (14.9)†
Constipation	1 (2.1)	1 (2.1)	0 (0.0)
SARS Cov-2 (COVID 19)	2 (4.3)	2 (4.3)	0 (0.0)
Cystitis	1 (2.1)	1 (2.1)	0 (0.0)
Decreased appetite	1 (2.1)	1 (2.1)	0 (0.0)
Decubitus ulcer	1 (2.1)	1 (2.1)	0 (0.0)
Delirium	1 (2.1)	1 (2.1)	0 (0.0)
Fluid overload	1 (2.1)	1 (2.1)	0 (0.0)
Gastric perforation	1 (2.1)	1 (2.1)	0 (0.0)
Fluid collection possible/suspicion of hepatic hematoma	4 (8.6)	0 (0.0)	4 (8.6)*,†
Hepatic failure	1 (2.1)	1 (2.1)	0 (0.0)
Interstitial lung disease	1 (2.1)	1 (2.1)	0 (0.0)
Nausea	1 (2.1)	1 (2.1)	0 (0.0)
Perihepatic abscess	1 (2.1)	1 (2.1)*	0 (0.0)
Pneumonia	1 (2.1)	1 (2.1)	0 (0.0)
Portal vein thrombosis	2 (4.3)	2 (4.3)	0 (0.0)
Postop wound infection	1 (2.1)	1 (2.1)	0 (0.0)
Procedural intestinal perforation	1 (2.1)	1 (2.1)	0 (0.0)
Pulmonary embolism	2 (4.3)	2 (4.3)	0 (0.0)
Pyrexia	2 (4.3)	2 (4.3)	0 (0.0)
Surgical incision site swelling	1 (2.1)	1 (2.1)	0 (0.0)
Urethral pain	1 (2.1)	1 (2.1)	0 (0.0)
Urinary tract infection	2 (4.3)	2 (4.3)	0 (0.0)

Data presented as number of patients with an event (percentage). A patient could have had more than one adverse event. All adverse events were adjudicated as a worst-case scenario.

* Possibly device-related, all $n = 1$ per event.

† Events were reported as possible biloma ($n = 3$), suspicion of partly biloma ($n = 1$), fluid collection being seroma or biloma ($n = 1$), fluid collection being hematoma/biloma ($n = 1$), and biloma ($n = 1$). Evidence of a hematoma was reported as fluid collection partly hematoma ($n = 1$), fluid collection ($n = 1$), small hematoma ($n = 1$), and encapsulated hematoma ($n = 1$). These events were incidental findings on postoperative imaging; none were confirmed as biloma or hematoma since no percutaneous or operative drainage was required. No events required any further intervention and events resolved by themselves over time. They were most likely sterile fluid collections.

hemostasis at 30 s, and 93% of bleeding sites achieved hemostasis at 1 min; overall with a mean TTH of 55 s.

Among six trials evaluating performance of hemostatic agents and reporting rates of hemostasis at 3 min, a meta-analysis found that the mean rate of hemostasis was 74.8% (95% CI 65.4%-83.1%).[17-21,23] More specifically for TachoSil, which is considered to be a state-of-the-art hemostatic agent used during liver surgery, three randomized trials were performed in liver surgery and the pooled rate of achieved hemostasis at 3 min was 74.7%.[25] In the largest and most recent trial reported by Genyk *et al.*, the rate of hemostasis at 3 min was 80.7% with TachoSil *versus* 50.6% with Surgicel Original.[18] Compared to these trials, the performance of GATT-Patch in this clinical trial was favorable with quick, reliable, and persistent hemostasis, reaching hemostasis at 30 s in 83% and at 3 min in 97.4% compared to the performance goal of 65.4% ($P < 0.001$), without evidence of rebleeding after surgery.

The incidence of device-related adverse event with GATT-Patch was 6.4%, and the incidence of device-related SAE was 2.1%, comparable to adverse events related to the use of other hemostatic agents,[18-20,26-28] demonstrating that GATT-Patch is associated with acceptable safety outcomes. Specifically, the overall rate of adverse events was similar as seen in other hemostatic agent trials,[18-20,26,28-30] reporting adverse events rates of 42%-100% (*versus* GATT-Patch with 46.8%) with the incidence of device-related adverse events of 0%-18.2% (*versus* GATT-Patch with 6.4%). Of note, all adverse events observed in our study are considered to be common complications of liver surgery. There were no rebleeding events reported in the present study, or reoperations for rebleeding or device issues.

There were four patients who underwent clinically indicated CT that resulted in the diagnosis of biloma ($n = 3$) and an abscess ($n = 1$). In the 43 patients that underwent the scheduled 6 wk follow-up with an ultrasound of the liver, evidence for suspicion of biloma and hematoma was observed in seven and four patients, respectively. These findings on ultrasound imaging were typically reported as perihepatic fluid being visible which could be a biloma or hematoma, but without confirmation that the fluid was a result of bile leakage or hematoma formation. These events of fluid were reported as biloma or hematoma according to the worst-case principle. When evaluating the liver resection area on imaging to identify postoperative fluid, a high rate of imaging findings can be expected. In a previous clinical trial where routine imaging was performed after liver surgery, similar to the scheduled ultrasound of the current trial, postoperative CT scans identified 27% of patients with a fluid collection of 100 mL or more at the resection surface yet only 11% of patients actually underwent any reintervention for resection surface related complications.[31] In our study of GATT-Patch, a similar trend was observed, where the majority of the fluid-related events, for example potential biloma or hematoma, were considered clinically insignificant such that they required no medical action and none were confirmed as biloma or hematoma by percutaneous or operative drainage. Thus, these imaging findings were most likely minor sterile fluid collections, and the rate of occurrence and severity was consistent with published literature and did not result in significant complications.

It should be noted that postoperative bile leakage and potential biloma formation is not unexpected after large liver resections. In fact, bile leakage is one of the most frequent complications after liver resection surgery, even in randomized trials on the use of sealant products to reduce postoperative bile leakage. In the trial by De Boer *et al.*,[31] TachoSil was used to cover the entire resection area to prevent bile leakage; nonetheless, 14% of patients had bile leakage. A meta-analysis of six randomized trials encompassing 970 patients found that the incidence of postoperative bile leak was not reduced when sealants were applied on the liver resection surface.[32] In one of the studies included in the meta-analysis, the rate of bile leakage was as high as 18% among 121 randomized patients.[33] In the current clinical investigation, the GATT-Patch was used as a hemostatic device and not as a sealant, and therefore applied only on a target bleeding site and not the overall resected area, and bile leakage could have occurred from the exposed resection area not covered by GATT-Patch. Nonetheless, the confirmed clinical rate of biloma occurrence in this study (6.4% based on clinically indicated CT scans) is consistent with the published literature.

While a meta-analysis on available hemostatic agents was performed to establish the performance goal of hemostasis achieved at 3 min, a randomized clinical trial will provide further evidence on how safety and performance of GATT-Patch compares with a state-of-the-art hemostatic agent. Nevertheless, the results of this clinical trial were in patients with similar baseline characteristics, indications for surgery, and rates of presence of liver cirrhosis as other hemostatic agent trials.[16-20,28,34] A randomized clinical trial comparing GATT-Patch with TachoSil in patients undergoing elective open liver resection surgery is currently underway (ClinicalTrials.gov identifier: NCT05385952).

Conclusions

The data in this clinical investigation demonstrate that, when compared to a performance goal derived from state-of-the-art hemostatic agents, GATT-Patch for minimal to moderate bleeding shows a higher rate of hemostasis, a short TTH, and acceptable safety outcomes when used during open liver surgery in adults.

CRediT authorship contribution statement

Johannes H.W. de Wilt: Funding acquisition, Investigation, Methodology, Supervision, Writing – original draft, Writing – review & editing. **Cornelis Verhoef:** Investigation, Supervision, Writing – review & editing. **Marieke T. de Boer:** Investigation. **Martijn W.J. Stommel:** Investigation, Writing – review & editing. **Leanne van der Plas-Kemper:** Investigation. **Linda M. Garms:** Investigation. **Charlène J. van der Zijden:** Investigation. **Stuart J. Head:** Formal analysis, Investigation, Methodology, Supervision, Writing – original draft, Writing – review & editing. **Johan C.M.E. Bender:** Conceptualization. **Harry van Goor:** Funding acquisition, Supervision, Writing – review & editing, Conceptualization, Methodology. **Robert J. Porte:** Investigation, Supervision, Writing – review & editing.

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Disclosure

S.J.H. and J.C.M.E.B. report being employees of GATT Technologies at the time of this study and are currently consultants at GATT Technologies. Harry van Goor reports a relationship with Radboud University Nijmegen Medical Center that includes consulting or advisory. None of the other authors report competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary Data

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