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Original article

Effect of Somatostatin on hepatic blood flow: preliminary results

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Abstract

Background: **Somatostatin (SOMATO) administration affects hepatic blood flow (HBF); however, its clinical effect remains ill-defined. The aim of this study is to assess the clinical effects of SOMATO administration on HBF during major abdominal surgery by comparing HBF in patients with and without intra-operative SOMATO admin-istration.**

Methods: **This retrospective analysis used data from two separate prospective studies including patients undergoing pancreaticoduodenectomy and was approved by the Ghent University Hospital ethical committee. All patients received total intravenous an-esthesia, using target-controlled infusion, and guided by a depth of anesthesia monitor. Schnider model was used for propofol, and Minto model was used for remifentanil. All patients received goal-directed hemodynamic therapy guided and recorded by Pul-sioFlex monitoring (Getinge Group). Portal vein blood flow and arterial hepatic blood flow were measured using ultrasound transit time flow measurements (Medi-Stim®). Both PVF and HAF were indexed using cardiac index. Patients were divided in two groups, receiving SOMATO (group S) versus control group not receiving SOMATO (group C). The Shapiro-Wilk test was used for testing normal distribution. Statistical testing was done using a Welch T-test or a Wilcoxon test.**

Results: **From 6/2017 to 10/2020, a total of thirty-seven patients were analyzed. Twenty-five patients received SOMATO (group S) whereas twelve patients did not (group C). In Group S, PVFi was significantly reduced in patients receiving SOMATO compared to the control group (p = 0.005). HAFi was similar in both groups. The net effect on total HBFi was significantly lower in group S (p = 0.027). Hemodynamic parameters did not differ between both groups.**

Conclusions: **SOMATO significantly reduced PVFi in the surgical patients while HAFi remained similar in both groups. As a result, total HBFi was significantly lower in SO-MATO-treated patients.**

Keywords: **Somatostatin, liver circulation, hepatic blood flow.**

Introduction

Hemodynamic changes during major liver surgery and liver transplantation have a ma-jor role in postoperative morbidity and mortality. On one hand, adequate portal blood flow is necessary for perfusion of the liver to stimulate liver repair and regeneration. On the other hand, hyper perfusion of the liver may cause liver insufficiency and even failure may develop[1–3]. To improve outcome in surgical patients, goal-directed hemodynamic therapy (GHDT) is frequent-ly used. Optimization of perioperative hemodynamics using GDHT reduces mortality and length of the hospital stay. The aim of GDHT is to attain standardized hemodynamic targets for cardiac output and stroke volume, by following a treatment protocol[4]. Treatment algorithm mostly includes fluid optimization and vasoactive medication to improve patient hemodynam-ics[5].

The hepatic vascular system is unique among other organs by its dual blood supply. The hepatic vascular system is dynamic and characterized by a high volumes circulation of low-pressure blood flow. The portal blood flow (PVF) is the sum of blood through the mesenteric organs and is determined by the total mesenteric blood flow. It provides two-

thirds of the blood flow to the liver. The remaining one third of the blood supply is provided by hepatic artery, which originates directly from the aorta via the celiac trunk. The hepatic artery contains therefore well oxygenated blood, this contrasts with portal vein blood, which comes from the mes-enteric organs and is less oxygenated. In general, 50% of the hepatic oxygenation is provided by the hepatic artery and 50% is provided by the portal vein[6,7]. The sum of PVF and hepatic arterial flow (HAF) results in total hepatic blood flow (HBF).

Several pharmacological agents could influence HBF, such as somatostatin (SOMA-TO). SOMATO is a natural peptide hormone, which regulates various functions of the body, among which the gastrointestinal and the endocrine system, by its inhibiting characteristics. It also affects neurotransmission and cell proliferation. It is well known in the treatment of vari-ceal bleeding, due to his vasoconstrictive effect of the splanchnic vessels[8,9]. This effect is through an inhibitory effect on the release of the vasodilator glucagon but also by a local mes-enteric vasoconstrictive effect[10,11]. In pancreatic surgery, it is used to prevent pancreatic compli-cations after surgery. During pancreatic resection, SOMATO analogues administrated prophy-lactically depending on surgical risk factors[12]. Studies suggest that SOMATO may reduce peri-operative complications, especially pancreatic fistula. This reduction can be explained by the reduction of pancreatic secretion by SOMATO and to protect the pancreatic anastomosis[13]. Generally, the use of SOMATO is safe. Known side effects of this drug are steatorrhea, diar-rhea, malabsorption, gastrointestinal cramps and occasional nausea[11,13]. Previous studies have suggested that SOMATO may affect HBF in the presence of portal hypertension[8,14,15]. The clinical effects of SOMATO administration on HBF however remain ill-defined[16].

The aim of this study was to assess the clinical effects of SOMATO administration on HBF during major abdominal surgery by comparing HBF in patients with and without intra-operative SOMATO administration.

Material and methods

Study design and patients

The study was approved by the ethical committee of the University Hospital of Ghent (BC-08919 E02, Prof. Dr. Deron, 09/02/2022). Written informed consent was obtained from all participants. Data was obtained from two previous prospective trials with similar methodolo-gy[17,18].

Inclusion and exclusion criteria were similar in both trials. Adult patients of both genders (18-80 years old) undergoing pancreaticoduodenectomy in the University Hospital of Ghent were included. Only patients with an American Society of Anesthesiologists (ASA) score of I to III were eligible. Exclusion criteria consisted of patients with renal insufficiency (Serum creatinine > 2mg/dl), severe heart failure (EF <25%), hemodynamic instable patients, atrial fibrillation, sepsis, body mass index > 40, severe coagulopathy (INR >2), thrombocytopenia, end stage liver disease and pregnant or breastfeeding women. This study contained preliminary results and was additional to previous studies which were aimed to assess the clinical effects of propofol and norepinephrine on hepatic blood flow. One study assessed the effect of propofol versus sevoflurane, only patients who received propofol were selected for this database[7,18]. Patients were divided into two groups according to the surgical indication for SOMATO ad-ministration. Soft pancreatic texture or small pancreatic duct were defined as an indication for SOMATO due to potential role in reducing risk for postoperative fistula. Group S, receiving prophylactic SOMATO analogues, was compared to a control group (group C).

Anesthetic procedure

All patients received standard of care using a departmental written protocol. All patients re-ceived standardized monitoring. A thoracic epidural catheter was placed before induction for postoperative analgesia. Epidural analgesia was initiated at the end of surgery and after the ex-perimental measurements, to avoid any effect on HBF. General anesthesia was provided by total continuous infusion using propofol and remifentanil. Induction was obtained with remifentanil target-controlled infusion (TCI) (Minto model) with an effect site concentration start-ing at 5 ng ml -1 and titrated according to blood pressure and heart rate (HR). Propofol TCI (Schnider Model) was started at an effect site of 5.0 mcg ml -1 and titrated according to depth of anesthesia, which was measured using Bispectral Index Monitoring (BIS). A target BIS value between 40-60 was considered to be an adequate depth of anesthesia. The effect site concentra-tion of remifentanil was titrated between 3 to 7 ng ml-1 according to hemodynamic changes. After losing consciousness rocuronium 1mg kg-1 bolus was given followed by intubation. Neuromuscular blockade was ensured during the procedure by intermittent boluses of rocu-ronium. An additional bolus of rocuronium was administered before each measurement to en-sure adequate neuromuscular blockade during the observations. After intubation, a lung re-cruitment was performed, and mechanical ventilation initiated. Mechanical ventilation was standardized in all patients with a tidal volume of 8 - 10 ml kg-1 according to ideal

body weight, with a respiratory rate 14 – 16 per minute and PEEP 5 cmH_2O. Ventilation was adjusted ac-cording to arterial blood gas samples. All patients received individualized perioperative GDHT which was done according to the departmental written protocol (figure 1). Following this flowchart, a baseline infusion with crystalloids of 3 ml kg-1 h-1 was provided. We ensured fol-lowing hemodynamic goals: a cardiac index (CI) > 2 L min-1 m-², mean arterial pressure (MAP) > 60 mmHg and pulse pressure variation (PPV) < 12%. Additional boluses of 200 ml of col-loids were administered depending on the PPV. In case CI was increased to more than 2 L min-1 m-² in combination with hypotension (MAP <60mmHg) norepinephrine was started. The starting dose of norepinephrine infusion was 0.1 mcg kg-1 min-1 and titrated according to the MAP. To temporarily bridge the latency of effect the norepinephrine infusion, boluses of ephedrine 3 mg were administered when HR was less than 60 beats per minute or phe-nylephrine 100 mcg, if HR > 60 beats min-1.

Hemodynamic variables were guided and recorded by PulsioFlex® (Maquet, Getinge Group, Germany). Standardized approach of fluid was performed by a GDHT.

Before pancreatectomy SOMATO was administered in group S at an infusion rate of 250mcg/h, after slowly administering an initial bolus of 250 mcg. The initial bolus of SOMA-TO induces a transient hypertensive period, measurements were fulfilled afterwards. Measure-ments were performed after pancreatectomy, at baseline before starting or raising of norepi-nephrine infusion.

Postoperative analgesia was ensured by a multimodal approach. After opening of the abdominal cavity, clonidine 150 mcg and magnesium 2 g were administered. Furthermore, we gave para-cetamol 1g intravenously and ropivacaine epidurally during closing of the abdomen. Post op-erative nausea and vomiting was prevented using dexamethasone 5 mg and ondansetron 4 mg. Reversal of neuromuscular blockade was provided by the administration of sugammadex.

Measurements and calculations

Standard invasive monitoring for pancreatic surgery included arterial line, central venous line and PiCCO catheter (Maquet, Getinge Group, Germany). Under general anesthesia, ultra-sound-guided placement of a central venous access was gained in the right jugular vein. The systemic arterial pressure was measured by an invasive access in left radial artery. A 5-Fr PiC-CO catheter was placed under ultrasound guidance in the left femoral artery. Before placing the PiCCO catheter, we ensured no atheromatous plaques were observed in the artery.

Measurements of HBF were performed by the surgeon using ultrasound transit time flow measurements (TTFM, Medi-Stim AS, Oslo, Norway)[19–21]. According to the size of the vessel, probe sizes were chosen by the surgeon ranging from 2 mm to 12 mm. HBF was measured in the HAF and PVF. Flow measurements were indexed to CI. Order to prevent influence of positive pressure ventilation of the measurements, apnea was obtained during the observations. The following parameters were registered during the measurement: HR, MAP, central venous pressure (CVP), CI. Hemodynamic goals were successfully obtained by the application of GDHT as described above. Post-induction hypotension was covered by the administration of boluses of ephedrine and phenylephrine as mentioned earlier. All measurements were per-formed during steady-state administration of SOMATO.

Outcome measures

The primary endpoint was to assess the effect of SOMATO on HBF. The secondary objective of the study was to assess the effect of SOMATO on

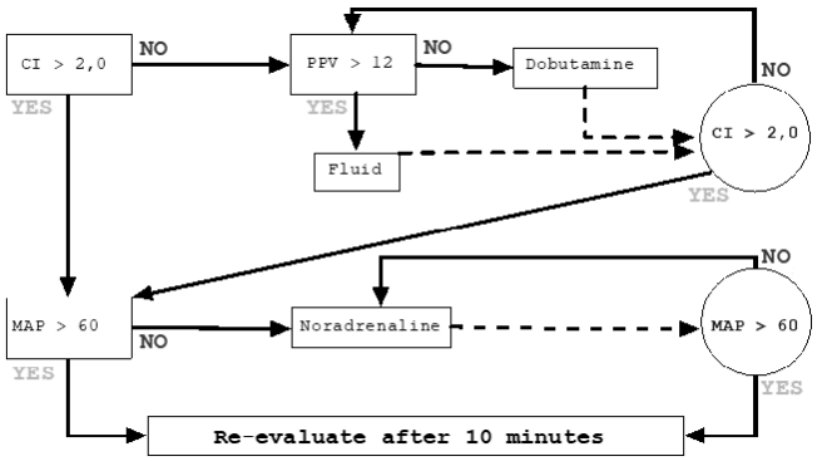

Fig. 1 — Goal-directed hemodynamic therapy.

systemic hemodynamic variables. The following variables were evaluated: MAP, CVP, CI, PPV and HR.

Statistical analysis

Patients were divided into groups depending on administration of SOMATO (group S, n = 25) or not (Group C, n = 12). After testing for normal distribution using the Shapiro-Wilk normali-ty test, a paired sample t-test will be used for the primary and secondary objective. In case no normal distribution of data was seen, appropriate non-parametric test (Mann-Whitney U test) was used. All significance levels was set at 0,05. All statistical tests was done using studio R (Team, R, R-studio Users manual; 2018).

Results

Patient characteristics

From June 2017 to October 2020, a total of thirty-seven patients were included. Patients were post- hoc divided into Group S and Group C depending on surgical indication of administration of SOMATO. Twenty-five patients received SOMATO (group S) whereas twelve patients did not (group C). Patient characteristics were comparable between the groups and are summarized in Table I.

Hepatic blood flow measurements

Data is summarized in Table II. In group S, PVFi was significantly reduced in patients receiv-ing SOMATO (300 ml min-1 m-2) compared to the control group (418 ml min-1 m-2) ($p < 0.01$). HAFi was similar in both groups. In group S, a median of 173 ml min-1 m-2 was measured which is similar to group C (219 ml min-1 m-2). The resulted net effect on total HBFi was sig-nificantly lower in group S (459 ml min-1 m-2 vs 635 min-1 m-2) ($p < 0.05$).

Hemodynamic variables

MAP, HR, CVP, CI and PPV were compared between both groups and listed in Table III. He-modynamic goals were successfully obtained by the application of GDHT as described above. Post-induction hypotension was covered by the administration of boluses of ephedrine and phenylephrine as mentioned earlier. All measurements were performed during steady-state ad-ministration of SOMATO. SOMATO had no effect on systemic hemodynamic variables.

Discussion

The results of the current study showed that, in patients under strict GDHT, administration of SOMATO resulted in significantly reduced total HBF. This reduction was mediated by a sig-nificantly reduced PVF, while HAF remained unchanged. By the application of GDHT, all patients achieved hemodynamic targets which resulted in no systemic hemodynamic differences between both groups.

An understanding of the influence of anesthetics and medication used peri-operative on the he-patic vascular system may provide methods for

Table I. — Patient characteristics.

Variable	Total group (n = 37)	Group S (n = 25)	Group C (n = 12)
Male/Female ratio	19/18	10/14	9/4
Age (years)	59.2 (11.4)	57.5 (12.2)	62.4 (9.4)
Length (cm)	170 (8.31)	169 (8.03)	171 (8.95)
Weight (kg)	72.4 (11.8)	73.8 (12.6)	69.6 (10.2)
BMI (kg cm^{-2})	25.1 (3.48)	25.7 (3.36)	23.8 (3.49)
Systolic BP (mmHg)	130 (16.8)	132 (17.3)	126 (15.8)
Diastolic BP (mmHg)	76.5 (7.99)	78 (7.4)	73.7 (8.55)
HR (bpm)	73.9 (9.49)	72.4 (9.54)	76.6 (9.1)
Smoker (F/N/Y)	9/19/9	7/11/6	2/8/3
Duration of surgery (min)	542 (91.7)	559 (80.5)	511 (106)
Data are expressed in mean (SD); No statistically significant differences between the groups; Welch T-test BMI Body Mass Index. HR Heart Rate; F Former smoker; N Non-smoker; Y Smoker.			

Table II. — Hepatic blood flow data.

Variable	Total group (n = 37)	Group S (n = 25)	Group C (n = 12)	P
PVFi (ml min^{-1} m^{-2})	331 (193)	300 (126)	418 (210)	0.005
HAFi (ml min^{-1} m^{-2})	180 (151)	173 (152)	219 (150)	NS
HBFi (ml min^{-1} m^{-2})	527 (249)	459 (207)	635 (235)	0.027
Values are median (interquartile range), ml min-1 m-2. PVFi indexed portal venous flow, HAFi indexed hepatic arterial flow, HBFi indexed hepatic blood flow, Wilcoxon rank sum test. Significant differences are marked as *, NS not significant.				

Table III. — Hemodynamic data.

Variable	Total Group (n = 37)	Group S (n = 25)	Group C (n = 12)	P
MAP (mmHg)	75.2 (10.2)	75.6 (10.8)	74.4 (9.2)	NS
HR (bpm)	77.1 (11.4)	74.8 (11.0)	81.9 (11.2)	NS
CVP (mmHg)	4.92 (2.9)	4.88 (2.93)	5.0 (2.95)	NS
CI ($L.min^{-1}.m^{-2}$)	2.83 (0.81)	2.79 0.89)	3.01 (0.65)	NS
PPV (%)	9.92 (3.28)	9.32 (2.98)	11.2 (3.64)	NS
Data are presented as mean (SD); Welch t-test was used; MAP Mean arterial pressure, HR Heart rate, CVP Central venous pressure, CI Cardiac index, PPV Pulse pressure variation, NS not significant.				

preventing hepatic injury and improve outcome in major liver surgery. In this study we observed the effect of SOMATO on HBF during GDHT.

SOMATO has been used for the treatment of acute variceal bleeding. Although the exact mech-anism is unknown, studies suggest this positive effect of SOMATO is caused by selective splanchnic vasoconstriction. Since esophageal varices is caused by cirrhosis, most study are performed in cirrhotic patients[8,9,15,16]. We were aimed to assess the effect of SOMATO in he-modynamic stabilized patients undergoing major abdominal surgery, typical pancreatic surgery.

The splanchnic vasoconstriction of SOMATO is due to decreased release of glucagon but also by local mesenteric vasoconstriction. As the PVF is the sum of total mesenteric blood flow, this reduction of mesenteric flow leads to a decrease in PVF, which our study confirmed. One of the mechanisms to maintain adequate liver is the hepatic arterial buffer response. This response can buffer up to 60% of decreased PVF by increasing HAF. In our study no change was ob-served in the HAF. As result, total HBF was significant lower in patients receiving SOMA-TO[7,22]. Knowing this, SOMATO can be used as flow reducer during liver surgery and liver transplantation in case of hyperperfusion.

Our study was performed during pancreaticoduodenectomy. This procedure provides adequate access to the hepatic vessels to perform our observations. No surgical interventions were per-formed on these vessels during measurements, which decreased the risk of bias. Although me-ta-analysis shows a relevant reduction of the incidence of pancreatic fistula and postoperative complications in patient receiving SOMATO,[23] the prophylactic use of SOMATO in pancreat-ic surgery remains controversial. On the other hand, the administration of SOMATO is rela-tively safe without significant adverse reactions.

Our study has several limitations. First, the decision for the administration is made by the sur-geon depending on the texture of the pancreas. Soft pancreatic texture is identified as a risk fac-tor for the development anastomotic leakage[24]. This subjective decision made by the surgeon might be a selection bias. Secondly, the choice of probe size and angle of insonation should be mentioned as possible errors in flow measurement. Since ultrasound is observer-dependent, reproduction of measurement could show variations. Although in our study flow measurement was performed by only two different surgeons, there is also an intra-observer variation. Previ-ous study shows a variation in measurement of 24% in both inter- and intra-observer. No dif-ference was seen between inter- and intra-observer variation[25]. Thirdly, the preliminary results of this retrospective analysis has only a small sample size. Larger prospective trials are neces-sary to conform these findings. Fourthly, there was no possibility of performing a group matching, since the administration of somatostatin was due to surgical indication. Also the indi-cation is an subjective interpretation of potential risk factors.

In conclusion, SOMATO significantly reduced PVF in the surgical patients while HAF re-mained similar in both groups. As a result, total HBF was significantly lower in SOMATO-treated patients. No effects were observed in systemic hemodynamic variables. These results showed that administration of SOMATO during pancreatic surgery, resulted in a reduction of total HBF, which is mediated by a reduction in PVF.

*Abbreviations:*ASA: American society of anesthesi-ologist; BMI: Body Mass Index; CI: Cardiac index; CVP: Central venous pressure; GDHT: Goal-directed hemodynamic therapy; HAF: Hepatic arterial flow; HAFi : Hepatic arterial flow indexed to cardiac index; HBF: Hepatic blood flow; HBFi : Hepatic blood flow indexed to cardiac index; HR: Heart rate; INR: International normalized ratio; MAP: Mean arterial pressure; PVF : Portal vein flow; PVFi : Portal vein flow indexed to cardiac index; SOMATO: somatostatin;TCI: Target-controlled infusion; TTFM: Transit-time flow measurement.

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