Graduate thesis

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The need for treatment in a high dependency unit following major abdominal surgery

Graduate thesis in Medicine

Trondheim, December 2015

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1. Acknowledgements

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2. Abstract

Introduction: Patients undergoing major surgical procedures, such as gastrointestinal cancer surgery, are considered to be at high risk for postoperative complications. Therefore, these patients are routinely monitored in a controlled environment in the early postoperative period, commonly known as a post-anesthesia care unit" (PACU) or "high dependency unit" (HDU). However, admittance to an HDU is expensive and inappropriate use may reduce the capacity for other surgical procedures. Therefore, identifying which patients are in need of a prolonged length of stay (LOS) in an HDU is important. Our goal was to describe the physiological course and need for HDU-specific interventions during the first 24 hours of the postoperative period in patients undergoing major abdominal surgery with an open technique.

Materials and methods: Adult patients undergoing open abdominal surgery between August and November 2015 at St. Olav University hospital (Trondheim, Norway), scheduled to be observed in a high dependency unit (HDU) until the first postoperative day, were consecutively included. HDU-specific interventions were defined as a need for respiratory support, vasoactive medications, fluid replacement therapy > 500 mL/h, or a need for high dose opioids (morphine equivalents > 7.5mg/h i.v.). Data was collected from patient medical records and from the applied anesthesia information management system (AIMS). The Cox proportional hazard model was applied to assess the effects of relevant co-variates on the duration of vasopressor infusion.

Results: Fifty-one patients were included in the study between August and November 2015. About one third of the patients were in need of HDU-specific interventions after the first six postoperative hours, while most of the patients required HDU-specific interventions before this time. The most prevalent intervention was an infusion of norepinephrine. Intraoperative blood loss > 750 mL and increasing age were significantly associated with the time to discontinuation of norepinephrine after surgery.

Conclusion: Our study demonstrates that there is a large variation in the need for HDU-specific treatment after major elective abdominal surgery, especially after the first six hours of the postoperative period. Further development of prediction models is warranted to help assess the need for HDU interventions in patients undergoing major surgery.

3. Introduction

Patients undergoing major surgical procedures, such as surgery for gastrointestinal cancer, are considered to be at high risk for postoperative complications, which may significantly increase the length of hospital stay and overall mortality [1]. Therefore, these patients should be closely monitored in the early postoperative period. This is usually done in units commonly referred to as "post-anesthesia care units" (PACU) or "high dependency units" (HDU) [2, 3]. This allows close follow-up and monitoring by specially trained staff in the period where such high-risk patients are the most vulnerable [4]. In an HDU, patients may receive intensive treatment in order to optimize hemodynamic and respiratory parameters, which have been shown to reduce complication-rates and length of hospital stay [5]. High dose opioids for postoperative pain management may be more safely titrated in an HDU compared to a surgical ward. This also applies to the use of vasopressor drugs, which may be more safely administered when invasive arterial blood pressure monitoring is available [6].

However, admittance to an HDU is expensive and inappropriate use may reduce the capacity for other surgical procedures. Therefore, identifying which patients are in need of a prolonged HDU length of stay (LOS) is useful. A study by Betten and co-workers [7] found that in patients undergoing surgery for rectal cancer, most of the patients were in need of HDU-specific interventions during the first 6 postoperative hours. After this time point, a third of the patients required HDU-interventions for shorter periods of time, while another third required HDU-interventions for more than ten consecutive hours.

The aim of our study was to apply similar methodology as Betten and co-workers to a more varied group of major surgical procedures, in order to possibly generalize the results. Our goal was to describe the physiological course and need for HDU-specific interventions during the first 24 hours of the postoperative period in patients undergoing major open abdominal surgery. We also wanted to investigate possible differences between predefined groups of surgical procedures, such as gastrointestinal, urological and aortic surgery. Furthermore, we wanted to identify patient factors that might predict the need for a prolonged stay in an HDU, by the use of regression analysis applying the Cox proportional hazard model.

4. Materials and methods

Data was collected at St. Olav University Hospital (Trondheim, Norway), which is a 1000-bed tertiary care hospital that serves a population of approximately 700 000 people in middle Norway [8]. The study was approved by the Regional Ethics Committee middle Norway (REC central), reference number 2015/64. Written consent was obtained from all study participants prior to inclusion. The study is part of an ongoing two-center trial registered at clinicaltrials.gov (NTC 02563652).

Adult patients (>18 years) undergoing open abdominal surgery between August and November 2015, who were scheduled to be observed in a high dependency unit (HDU) until the first postoperative day, were consecutively included. Exclusion criteria were pregnancy, patients with cognitive or psychiatric disorders, and patients who were Jehovah's witnesses.

All patients received a thoracic epidural before the induction of general anesthesia. General anesthesia was maintained with fentanyl and desflurane during surgery, and an arterial line was placed in the radial artery in all patients. After induction of anesthesia, all patients received an epidural infusion (4-12 ml/h) of bupivacaine (1 mg/ml), fentanyl (2 µg/ml) and epinephrine (2 µg/ml), which was maintained in the postoperative period. The dose of bupivacaine was increased to 2 mg/ml in patients with insufficient pain control in the postoperative period, and/or additional opioids (morphine or ketobemidone) were administered intravenously. The use of vasopressors and fluid therapy in the postoperative period was guided by individually pre-defined values for minimum mean arterial pressure (MAP) and hourly urine output, set by the anesthesiologist in charge of patient care.

Demographic data was collected from patients' medical records (DocuLive, Siemens Nixdorf Information Systems, Oslo, Norway), including data on comorbidity according to the Charlson Comorbidity Index [9]**.** Physiological data and HDU-specific interventions were collected from the AIMS applied (Critical care manager, Picis, Wakefield, MA, USA).

HDU-specific interventions were defined as:

1. Invasive or non-invasive respiratory support.
2. Intravenous fluids or blood products, exceeding 500 ml/hour.

3. Use of vasoactive medications, such as norepinephrine.
4. Treatment of pain with intravenous (i.v.) opioids in a dose of more than 7.5 mg/h morphine equivalents.

Data points in the AIMS were recorded at intervals of 1, 2, 5 or 15 minutes, depending on the frequency set by the care providers (default was 15 minutes). The frequency of measurements was set to 1 minute in most patients after arrival in the HDU unit. The physiological data recorded included mean arterial blood pressure (MAP), systolic blood pressure, diastolic blood pressure, heart rate, oxygen saturation, respiratory rate and mode of ventilation (i. e. respiratory support). Fluid replacement therapy (ml/hour), blood loss and loss of other body fluids, administration of blood products (red blood cells, blood plasma or thrombocytes), dose of epidural (ml/hour), and dose of i.v. norepinephrine were recorded. Dosing of norepinephrine was classified in categories of 0.05 µg/kg/minute (i. e. <0.05, 0.05 - 0.09, 0.1 – 0.14 etc.).

Samples of blood and urine were taken before start of surgery, and at six and 24 hours after start of surgery, for later analysis of inflammatory markers and oxidative stress and their possible relation to the outcomes chosen in this study.

Data was extracted and processed applying the software Matlab (The Mathworks, Natick, MA, USA) and the software Excel (Microsoft Corporation, Redmond, WA, USA). Statistical analysis, including survival estimates and regression analysis, was performed using the software R version 3.0 [10] and STATA version 13 [11]. The Kaplan-Meier survival estimate was calculated based on the time-to-event for the end-point ‘time to discontinuation of norepinephrine’ (minutes) after end of surgery. The Cox proportional hazard model was applied to assess the effects of relevant co-variates on the ‘time to discontinuation of norepinephrine’. The proportion of patients in need of HDU-specific interventions at any time, and to which degree, was visualized by applying the R-package ‘TraMineR” [12]. Tables were created applying the R-Package “xtable” [13].

5. Results

Fifty-one patients were included in the study, of which all were included in the final analysis. The majority of patients received surgical treatment due to a diagnosis of cancer (n=40, 78%). The main groups of surgery were gastrointestinal (n=36, 71%), urological surgery (n=8, 16%) and open surgery for abdominal aortic aneurysm (n=7, 14%). The spectrum of surgical procedures is shown in Table 1. The most prevalent procedure was open bowel resection (n=9, 18%), followed by open surgery for abdominal aortic aneurysm (n=7, 14%), radical cystectomy with ileal conduit (n=7, 14%) Whipple's operation (n=6, 12%) and liver resection (n=6, 12%).

Table 1 Surgical procedures

	No (%)
Gastrointestinal	**36 (71)**
Open bowel resection	9 (18)
Whipples operation	6 (12)
Liver resection	6 (12)
Low anterior resection of the rectum (LAR)	5 (10)
Gastrectomy	2 (4)
Hartmann's operation	2 (4)
Abdominoperineal resection of the rectum (APR)	1 (2)
Oesophageal resection	1 (2)
Retroperitoneal lymph node dissection (RPLND)	1 (2)
Open extirpation of intraabdominal pheochromocytoma	1 (2)
Open splenectomy	1 (2)
Distal pancreatic resection	1 (2)
Urological	**8 (16)**
Radical cystectomy with ileal conduit	7 (14)
Nephroureterectomy	1 (2)
Vascular surgery	**7 (14)**
Open surgery for abdominal aortic aneurysm	All

Baseline demographic data are presented in Table 2. The median age was 69 years (range 39-84 years). Patient gender was close to equally distributed. Forty-four of the patients (86%) had current comorbidity according to the Charlson comorbidity index, of which most had a Charlson score of 2-3 points (n=26, 51%). Fifteen patients (29%) had a Charlson score of 4 or

more, mainly due to the reason that the presence of metastatic tumors gives a score of six. The median duration of stay in an HDU was 26.5 hours (25q-75q: 23-47 hours).

Table 2 Baseline patient characteristics

Age, median (25q-75q)	69 (57-73.5)
Male sex, No. (%)	28 (55)
Weight in kilograms, mean (SD)	78 (14)
Current smoker, No. (%)	5 (9.8)
Previous smoker, No. (%)	19 (37)
Never smoked, No. (%)	27 (53)
Previous abdominal surgery, No. (%)	25 (49)
Comorbidity, Charlson	
Charlson < 2, No. (%)	10 (20)
Charlson 2-3, No. (%)	26 (51)
Charlson > 3, No. (%)	15 (29)

Clinical data for the per-operative and postoperative period is shown in Table 3.

Table 3 Baseline perioperative clinical data

	No. (%)	Median (IQR)
Per-operative fluid balance (ml)		
Blood loss	All	600 (615)
Received transfusion of RBC	9 (18)	500 (750)
Received transfusion of plasma products	17 (33)	400 (400)
Isotonic fluids	All	4600 (2539)
Postoperative fluid balance (ml)		
Blood loss	27 (53)	340 (354)
Received transfusion of RBC	5 (9.8)	500 (0)
Isotonic fluids	50 (98)	3139 (1418)
Per-operative analgesics		
Epidural infusion (ml/h)	All	8 (0)
Fentanyl i.v. (mg)	All	0.35 (0.23)
Postoperative analgesics		
Epidural infusion (ml/h)	All	8 (2)
Morphine or ketobemidone i.v.(mg)	30 (59)	13.25 (14.5)

5. 1 HDU-specific interventions

The individual need for different HDU-specific interventions during the first 24 hours of the postoperative period is shown in Figure 1, in which one sequence bar corresponds to one patient. No patients received respiratory support during the postoperative period. Only three patients (5.9%) were not in need of any HDU-interventions. During the first six postoperative hours, all of the remaining patients were in need of one or more interventions, while only approximately one third of the patients (n=18, 35%) needed this intervention at 12 hours. The number of patients in need of one or more HDU-specific intervention was the same at 6 and 12 hours, mainly the need for an infusion of norepinephrine.

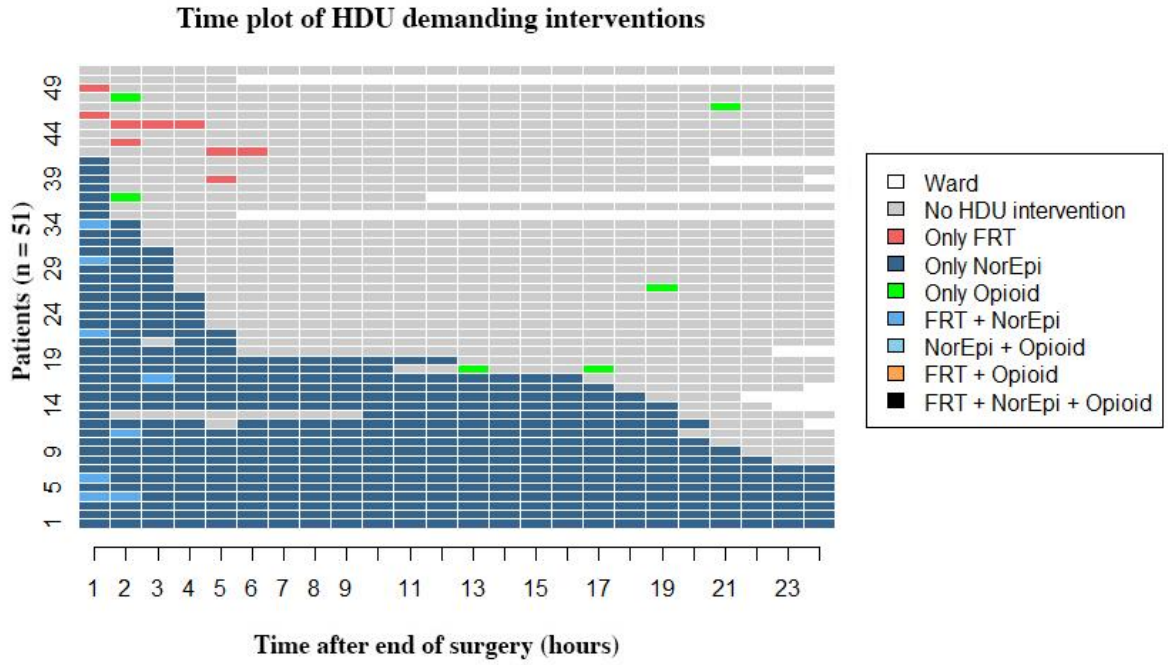

Fig. 1 High dependency unit (HDU) specific interventions given during the first 24 hours of the postoperative period in patients receiving major surgical treatment. Each horizontal bar represents one individual patient (n = 51), and a specific color is given for each intervention, or combination of interventions. Time zero is time at arrival in the HDU. The patients are ordered by the time to discontinuation of norepinephrine.

After 16 hours the need for interventions markedly decreased, and at 24 postoperative hours only seven patients were still receiving HDU-specific treatment in the form of infusion of norepinephrine.

The proportion of patients receiving HDU-specific interventions for a period exceeding 6 hours was approximately the same for the three predefined groups of surgery. The proportion was highest in the aortic surgery group at 43% (n=3), 38% (n=3) in the urological surgery group, and 36% (n=13) in the gastrointestinal surgery group (Figure 2).

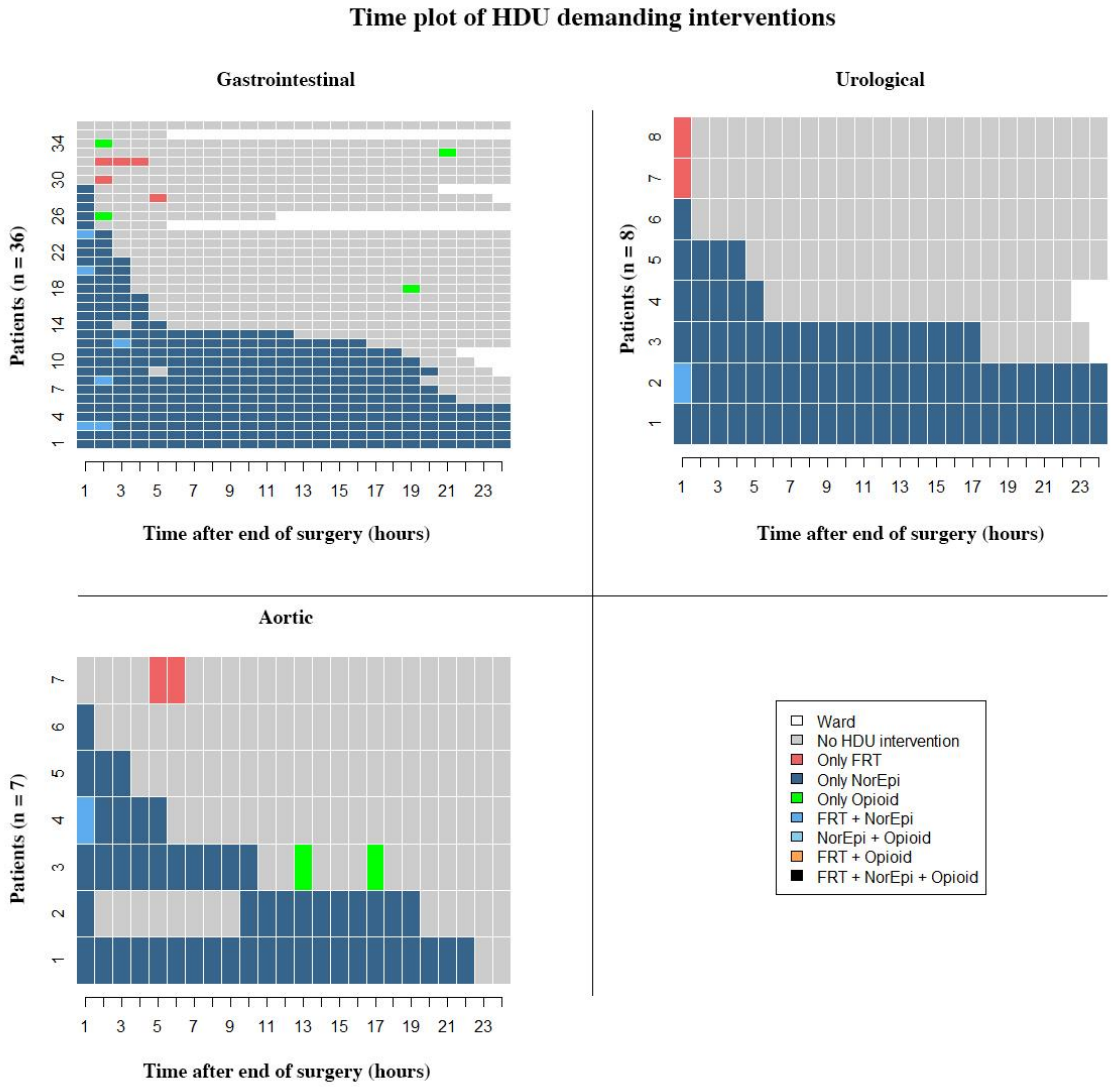

Fig. 2 High dependency unit (HDU) specific interventions given during the first 24 hours of the postoperative period, subdivided by type of surgery. Each horizontal bar represents one individual patient (n = 49), and a specific color is given for each intervention, or combination of interventions. The patients are ordered by the time to discontinuation of norepinephrine.

An intravenous infusion of norepinephrine was by far the most common intervention given, and was the only given intervention for 31 patients (61%). Figure 3 shows the proportions of patients in need of a norepinephrine infusion per hour, and the different doses given. Three of the patients were reintroduced to norepinephrine after it initially being discontinued.

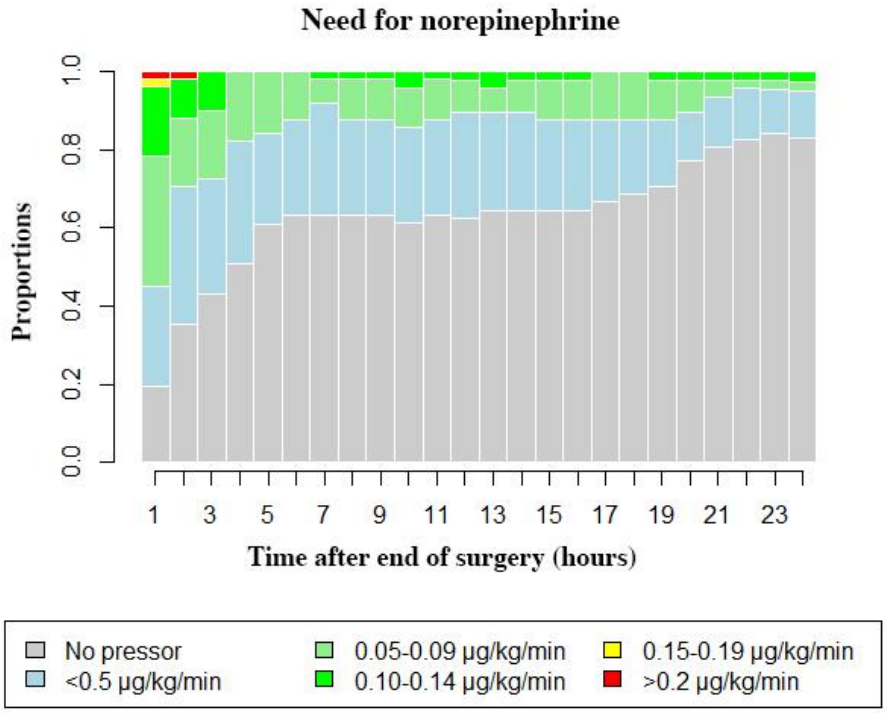

Fig. 3 Prevalence plot depicting the proportion of patients receiving norepinephrine at a specific hour during the first 24 hours postoperatively. Each bar represents a single hour, while the different dose ranges are shown in specific colors.

The first hour after end of surgery, the different doses of norepinephrine are evenly distributed among the patients. Twenty-eight patients (55%) received a dose of norepinephrine of 0.05 µg/kg/min or more at some point in the defined postoperative period, the remaining receiving a lower dose or no infusion at all. Approximately one third of patients (n=18, 35%) needed norepinephrine for more than 6 hours. Overall, there was little change in the dose of norepinephrine given in the time period from 6 to 16 hours postoperatively, apart from a slight increase between 9 and 13 hours.

The proportion of patients receiving fluid replacement therapy (FRT) during the first 24 postoperative hours is demonstrated in Figure 4. Fourteen percent (n=7) of patients received more than 500 ml/h during the first hour, while similar number of patients received 250-500 ml/h and less than 250 ml/h, respectively. Of these, only one patient did not receive any FRT during the duration of the PO period. Overall, one in four patients received more than 500 ml/h at some point during the first 24 hours. The need for HDU-specific FRT (>500 ml/h) decreased steadily the first 6 hours, and after this no patients received FRT exceeding 500 ml/h. The median cumulative volume of FRT given during the first 24 hours of the postoperative period was 3139 ml (IQR = 1418 ml).

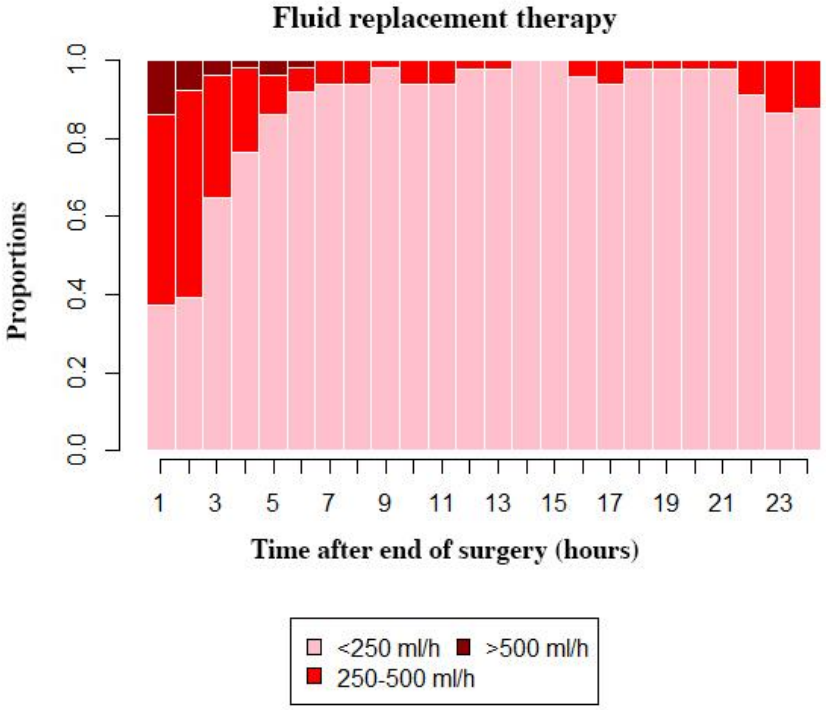

Fig. 4 Prevalence plot depicting the proportion of patients receiving fluid replacement therapy at a specific hour during the first 24 hours postoperatively. Each bar represents a single hour, while the different fluid ranges are shown in specific colors.

5.2 Postoperative pain management

All patients received a thoracic epidural infusion in the postoperative period, with a mean infusion rate of 8 mg/h. Thirty-one patients (61%) received a dose of $\geq$ 1 mg/h of morphine or ketobemidone at some point during the postoperative period, while only seven patients (14%) received a dose of more than 7.5 mg/h within a given hour. Only one patient was given a dose of 10 mg/h or more within a given hour. The median cumulative dose administered during the first 24 hours of the PO period was 13.25 mg (IQR = 14.5).

Figure 5 shows the proportions of patients receiving intravenous opioids in the first 24 hours of the PO period. Overall, it shows that the need for such interventions at any given hour was low but stable, with less than 15-20% of patients receiving any dose of opioids $\geq$ 1 mg/h. The percentage of patients receiving intravenous opioids was highest during the second postoperative hour, with 18% (n=9) receiving a dose of $\geq$ 1 mg/h.

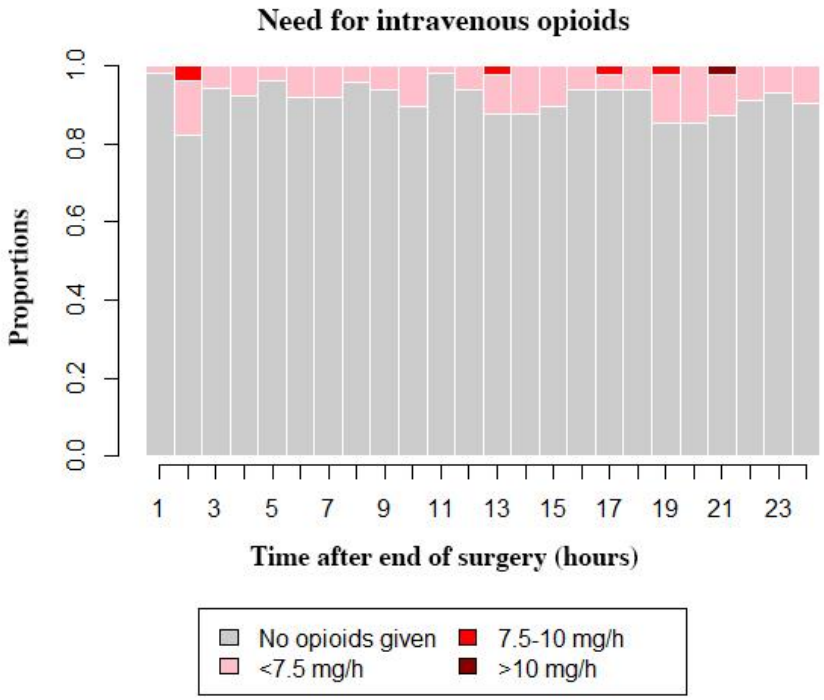

Fig. 5 Prevalence plot depicting the proportion of patients receiving intravenous opioid treatment at a specific hour during the first 24 hours postoperatively. Each bar represents a single hour, while the different dose ranges are shown in specific colors.

5.3 Statistical analysis

Clinical factors considered relevant for the degree of postoperative circulatory instability were included in the Cox regression model, i.e. age, sex, per-operative blood loss, per-operative FRT and time in surgery. The time to discontinuation of norepinephrine was the primary outcome in this model (i.e. the event of interest). The results of the regression analysis are shown in Table 4. Since a longer time to experiencing the event will reduce the hazard ratio for the given covariate, a low hazard ratio signifies an increased risk of receiving prolonged infusion of norepinephrine in this case. The model states that age was significantly associated with the duration of the postoperative norepinephrine infusion. Patients aged above 60 years demonstrated a significantly longer time to event compared with the control group (i.e. patients <50 years). Patients between 70-80 years of age had a hazard ratio (HR) of 0.17 (95% confidence interval: 0.06 – 0.46), indicating that patients in this age group were approximately six times (1/0.17) more likely to stay on norepinephrine postoperatively. The amount of per-operative blood loss was also found to be significantly associated with the duration of norepinephrine infusion, a per-operative blood loss exceeding 750 mL exhibiting increased risk of prolonged infusion of norepinephrine (HR = 0.32, 95% CI: 0.14 – 0.75).

Time in surgery, per-operative FRT and sex were factors found to have no statistically significant effect on duration of norepinephrine infusion after controlling for age and blood loss. The overall pattern of time to discontinuation for all patients is shown applying the Kaplan-Meier estimator in figure 6.

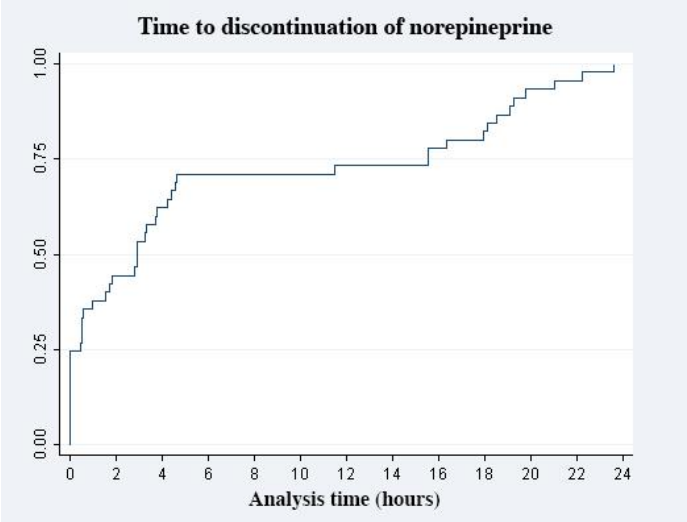

Fig. 6 Kaplan-Meier estimator showing time to discontinuation of norepinephrine after surgery.

Table 4 Cox regression analysis of time to discontinuation of norepinephrine.

	HR[a]	95% CI[b]	*P*-value
Time in surgery, per hour increase	0.94	0.67 - 1.33	0.736
Per-operative blood loss, > 750 mL	0.32	0.14 - 0.75	0.009
Per-operative FRT, <4 L	Ref.		
Per-operative FRT, 4-7 L	0.74	0.35 - 1.57	0.431
Per-operative FRT, > 7 L	0.87	0.22 - 3.45	0.845
Male sex	1.44	0.75 - 2.75	0.268
Age, < 50 years	Ref.		
Age, 50-60 years	0.70	0.20 - 2.44	0.580
Age, 60-70 years	0.24	0.09 - 0.67	0.006
Age, 70-80 years	0.17	0.06 - 0.46	< 0.001
Age, > 80 years	0.22	0.06 - 0.89	0.034

[a] Hazard ratio (HR) estimated from Cox proportional hazard regression model. [b] Confidence interval of the estimated HR.

6. Discussion

Our study demonstrates that the need for HDU-specific interventions in the first 24 hours of the postoperative period in patients undergoing major open abdominal surgery varies and is mainly dependent on the need for an infusion of norepinephrine. Our main finding is that only about one third of patients required such interventions for longer than six hours. This proportion remained stable before declining after 16 hours. We also found that during the first six hours of the PO period, all but three patients needed one or more HDU-interventions. Adjusting for possible confounding factors, we found that age and intraoperative blood loss were significantly associated with the duration of vasopressor use in the postoperative period.

Our study included patients undergoing major open gastrointestinal, urological and aortic surgery. A similar pattern can be observed in the individual surgical categories as in the cohort as a whole. In the aortic surgery group, however, the percentage of patients in need of such interventions longer than six hours was higher (43%) compared to the other two groups. Open surgical repair of an abdominal aortic aneurism (AAA) is a major procedure associated with high morbidity, especially cardiorespiratory complications, and prolonged ICU length of stay [14]. These patients also have an increased prevalence of concurrent cardiovascular disease. This may explain the difference, as the gastrointestinal surgery group is compiled from several different surgical procedures which also include procedures associated with a lesser degree of surgical trauma, such as small bowel resection.

Of the HDU-specific interventions given, an intravenous infusion of norepinephrine was the most frequent. More than eighty percent of patients received norepinephrine at the start of the PO-period, but only approximately one third of the patients needed this for more than 6 hours. It was the only intervention given for over half of the patients. A previous study conducted in the Netherlands by Bos et. al. [15] showed that 25.7% of patients admitted to an intensive care unit after colorectal surgery were treated with vasopressors in the acute postoperative phase, compared to 41.8% for patients undergoing surgery for esophageal cancer. A recent study by Betten and co-workers carried out at our center [7] observed that forty percent of patients admitted to an HDU after surgery rectal cancer received norepinephrine at the start of the PO period. This suggests that the type of surgical procedure may influence the need for vasopressor in the immediate postoperative period.

In our cohort, the percentage of patients receiving a norepinephrine infusion at the start of the postoperative period was much greater, and the variability was small between the different types of surgery. The use of intravenous vasopressors in a postoperative setting is influenced by a number of factors, including the degree of per - and postoperative blood and fluid loss, the FRT regime applied, the pre-defined minimum MAP-value set for each patient and the degree of surgical trauma. The magnitude of the systemic inflammatory response syndrome (SIRS) [16, 17], involving inflammatory cytokines such as IL-6, interleukin 1 (IL-1) and tumor necrosis factor α (TNF-α), reflect the degree of tissue trauma, and are known to have a major role in the inflammatory response to surgical trauma [18, 19]. Activation of the inflammatory system may induce respiratory and circulatory instability, the latter owing to vasodilation and increased microvascular permeability [17]. The degree of SIRS induced by surgery may therefore influence the need for interventions such as vasopressor therapy and FRT in the HDU in the immediate PO period. We observed that excessive blood loss was associated with an increased risk of being in need of a prolonged infusion of norepinephrine in our cohort. It has been shown in patients undergoing surgery for rectal cancer that a high degree of blood loss enhances the stress response to surgery and the risk for surgical complications [20], and that patients receiving blood transfusions for intraoperative blood loss have a marked induction in the pro-inflammatory cytokine IL-6 [21].

A considerable number of patients in our study underwent surgical procedures associated with an extensive degree of surgical trauma, such as Whipple's procedure, open liver resection and open surgery for an AAA. A relatively high median blood loss and a high proportion of extensive surgical procedures in our cohort may indicate that many patients experienced a high degree of SIRS in the immediate postoperative period. This might be an explanation of why four in five patients received vasopressor therapy at the start of the postoperative period in our study.

The median volume of FRT given to each patient in the per-operative period was 4.6 litres, and 3.1 litres in the first 24 hours of the postoperative period. This corresponds to a standard or "liberal" postoperative fluid regimen guided by conventional perioperative measures such as arterial blood pressure or urinary output [22, 23]. A more restrictive FRT-regimen has been proposed by several studies [24, 25], but has not been conclusively demonstrated to improve outcome after surgery [26, 27]. A goal-directed approach guided by physiological parameters such as cardiac output (CO) has also been applied [23]. The large degree of variance in total

fluid therapy between the patients in our study might reflect a lack of standardization in volume therapy, and might suggest that fluid therapy as a marker is not currently well suited to discern the need for HDU-treatment. Only thirteen patients (25%) were in need of more than 500 ml/h (defined as HDU-specific) at some point during the first six postoperative hours.

Admittance to an HDU after general or epidural anesthesia and major surgery is recommended by several guidelines for postoperative care [2, 3]. Our findings show that patients undergoing major open abdominal surgery do not have a uniform need for a 24 hour stay in an HDU after surgery. Being able to identify which patients who are in need for a prolonged HDU length of stay would be beneficial, as a 24 hour stay in an HDU is expensive (approximately 1200 euros for one patient at our hospital). Utilizing an 'early warning score' to differentiate between patients in need for HDU-admittance has been proposed for patients undergoing emergency surgical procedures [28]. Factors that may predict the need for postoperative intensive care include preoperative factors such as age, ASA class and high risk surgery, and intraoperative factors such as arterial oxygen saturation, hypotension and tachycardia [29, 30]. Different models and scoring systems based on these and other factors have been developed to predict the need for HDU-admission after surgery [29, 31].

The decision to discharge patients from the HDU to a surgical ward is at our hospital made by caregivers based on clinical evaluation. The Association of Anesthetists of Great Britain and Ireland has published guidelines for postoperative management, including discharge criteria from an HDU [2]. The use of strict discharge criteria may reduce delays in the decision making process, which has been shown to be an important factor in delaying discharge from the HDU [31]. The fact that about two thirds of the patients in our study did not have any need for HDU-specific interventions after 6 hours, and that the median duration of the HDU-stay was almost 27 hours, may be an argument that an earlier discharge may have been warranted for some of the patients. The application of a prediction model combined with the use of specific discharge criteria from the HDU in this patient group would be beneficiary and a promising area for further research.

Attempting to identify which patients who were in need of a prolonged HDU length of stay, we analyzed both demographic and intraoperative patient variables applying Cox regression. The endpoint was defined as the event 'discontinuation of norepinephrine', as this event was

synonymous to ‘end of need for HDU-interventions’ for most patients in our study. Thus, by testing variables affecting the duration of norepinephrine infusion, the results will mainly reflect the overall time-dependent need for HDU-interventions in our cohort. Per-operative blood loss (mL), time in surgery (hours) and per-operative FRT (litres) were used as surrogate markers for the degree of surgical trauma inflicted on the patient, as these factors might correlate with the extensiveness of the surgical procedure. Increasing age carried a decreasing hazard ratio (HR), indicating that old age increases the likelihood of needing vasopressors for a prolonged period of time postoperatively. Patients between 70 and 80 years were approximately six times more likely to stay on norepinephrine postoperatively compared with those < 50 years of age. The concept of ‘frailty’ might be relevant to these findings. Frailty is defined as a state of vulnerability to poor resolution of homeostasis that arises with aging due to decline in physiological systems, and undermines the ability to respond to stressors [32, 33]. As frailty is a state acquired with increasing age, it might be suggested that the degree of ‘physiological frailty’ has an impact on the postoperative period and the need for HDU-specific interventions. A study by Wunch and co-workers found that there was an association between age and the admission to an intensive care unit (ICU) postoperatively in patients undergoing major gastrointestinal surgery [34]. We propose that the varying degrees of physiological frailty in the postoperative period may be a factor that can be included in future prediction models for postoperative care of surgery patients, along with other relevant factors. As discussed earlier, the degree of intraoperative blood loss has been shown to enhance the stress response to surgery, and increase the risk for surgical complications. The median intraoperative blood loss in our cohort was 600 ml. Our findings demonstrate that a higher than normal blood loss during surgery is associated with a prolonged need for HDU-specific interventions in the postoperative period.

Our study has several limitations that need to be addressed. Firstly, the decision of discharging a patient from the HDU was based on caregivers’ judgement, often taking ward capacity and available beds in the HDU into account. This might have influenced HDU length of stay for some patients. However, patients receiving an infusion of norepinephrine or fluid replacement therapy exceeding 500 ml/h would not have been discharged to a surgical ward, and inter-individual variations in discharge criteria is not likely to have influenced our main findings in any degree. A set of discharge criteria specific for the study patients might have compensated for this source of error, but was not feasible in this study due to its limited resources and the need for training a large number of HDU personnel. Secondly, the use of

fluid replacement therapy and vasopressors are interrelated, and there might have been variations in the clinical approach to managing postoperative hypotension between both anesthesiologists and caregivers. There was no standardized FRT protocol or guideline in place at the HDU at the time this study was conducted. The predefined MAP-value set for each patient by the anesthesiologist in charge might have been higher in older patients, and as a result there might have been a higher threshold for discontinuing the norepinephrine infusion in older patients. Additionally, hemodynamic parameters were recorded at different intervals depending on the manual setting in the AIMS. This implies that in some patients, changes in circulatory or respiratory status or changes in norepinephrine infusion rate in between data points might have been missed. It also creates a difference in precision within the data set, as some patients' recordings were more accurate than others. However, even the highest recording interval found in our data set secures valid observations every 15 minutes, which is probably better than what could have been achieved with manual recordings. Lastly, our definition of FRT > 500 ml/h and intravenous opioids > 7.5 mg/h as 'HDU-specific interventions' could be debated.

To conclude, we found that the majority of patients undergoing major open abdominal surgery required a stay in an HDU unit the first six hours of the PO period. One third of the patients had this requirement for more than six hours. The remaining two thirds of patients did not have any need for such interventions after six hours. Applying Cox-regression analysis we found that intraoperative blood loss and increasing age was significantly associated with the time to discontinuation of norepinephrine after surgery.

7. References

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