Fluid optimisation in pancreas surgery

JENKO MATEJ[1], POŽAR-LUKANOVIĆ NEVA[1], MLADEN PERIĆ[2], SPINDLER-VESEL ALENKA[1]

1 University Medical Centre Ljubljana, Department of Anaesthesiology and Surgical Intensive Therapy, Zaloška 7, Ljubljana, Slovenia
2 Department of Anesthesiology, Resuscitation and Intensive care, University Hospital Centre Zagreb, • Kišpatićeva ul. 12, Croatia

Corresponding author:
Alenka Spindler-Vesel
University Medical Centre Ljubljana, Department of Anaesthesiology and Surgical Intensive Therapy,
Zaloška 7, Ljubljana, Slovenia
alenka.spindler@guest.arnes.si

ABSTRACT

Background. Optimal intravascular blood volume, cardiac output and sufficient oxygen supply is a mainstay in major abdominal surgery. Adequate haemodynamic management can improve a favourable outcome and shorten the duration of hospital stay.
Our study anticipated different fluid and vasoactive drug consumption and less complications during the pancreatic surgery in the group of patients where extended haemodynamic monitoring was applied.
Materials and methods. 59 adult patients, ASA 2-3, undergoing elective pancreas surgery, were included in the study. In 29 patients in the study group (SG – extended haemodynamic monitoring), cardiac index (CI), mean arterial pressure (MAP) and nominal stroke index (SI) were maintained within 80% of baseline values with actions following study protocol. Patients' groups were homogenous, even when divided into 4 subgroups (control group (CG) and without epidural catheter (EC), CG and with EC, SG and without EC, SG and with EC).
Intraoperative variables (amount of fluids, vasopressors, surgery duration) and hospitalisation duration, wound healing, reoperation, mortality and other complication were recorded on the postoperative days 3, 5, 8, 15 and on hospital discharge.
Results. There was no difference in ASA health status, intraoperative management and duration of hospitalisation in 4 subgroups. There is a significant difference in intraoperative use of vasopressor support between 4 subgroups (Fisher exact test, p=0,032). All patients in SG with EC required vasopressors. Number of patients with major complications were not statistically different between groups. Pulmonary embolism, postoperative food intolerance and myocardial infarction have occurred only in CG.
Conclusion. In our study there was no difference in overall fluid and vasoactive drug demand. Although in the studied subgroup of patients with additional epidural anaesthesia there was significantly increased demand for vasoactive drugs. The incidence of complication was low in both groups, however, some of major complications occurred only in CG.

Keywords: haemodynamic monitoring, fluid optimisation, postoperative outcome, pancreatic surgery

INTRODUCTION

Careful management of oxygen delivery by providing adequate intravascular blood volume and cardiac output is a mainstay in major abdominal surgery. According to changes in haemodynamic parameters, fluid replacement therapy and vasoactive drugs are used (1, 2).
Relative intraoperative hypovolemia could result from several factors: drugs used for general anaesthesia, the effects of local anaesthetics if regional anaesthesia is combined with general anaesthesia, systemic inflammatory response to surgical trauma, which is proportional to the duration of operation and the extent of tissue damage (3, 4, 5, 6, 7).
Most patients undergoing pancreatic surgery are elderly and have several comorbidities. Adequate haemodynamic management is of great importance as it can improve a favourable outcome and shorten the duration of hospital stay (8, 9, 10, 11, 12, 13).
Our study compared two groups of patients undergoing elective pancreatic surgery: a control group in which standard haemodynamic monitoring was used, and a study group in which extended haemodynamic monitoring was applied.
Our study anticipated different fluid and vasoactive drug consumption during the procedure, less complications due to inadequate oxygen delivery in the group of patients were extended haemodynamic monitoring has been applied.
Our aim was to answer the following questions: Does the study group with extended haemodynamic monitoring receive significantly larger amount of intraoperative fluids and , does it receive significantly more vasopressor therapy? As secondary goal, we were looking for differences in postoperative complications. Since epidural analgesia was partly used in the group with extended haemodynamic monitoring as well in the group without it, related haemodynamic implications with subgroup analysis are shown as a tertiary goal.
The study has been approved by the National Medical Ethic Committee of the Republic of Slovenia (KME 127/05/12).

MATERIALS AND METHODS

Our study included 59 adult patients undergoing elective pancreas surgery, ASA (American society of Anaesthesiologists) grade 2-3.
In the prospective study group (SG) 29 patients (extended haemodynamic monitoring) were included. Data for control group (CG) were obtained from patients' documentation. Detailed study protocol is seen in Figure 1.
A member of our research team acquired an informed consent and provided information to all patients on the day prior to surgery. Preoperative protocol was the same in all our patients.
The anaesthetic technique did not differ between the two groups.
Upon admission an iv line was inserted, patients received midazolam (1-2 mg). A thoracic epidural catheter was inserted in left lateral position (Th7-8) and a test dose of 3 ml of 2 % lidocaine was given. In case of contraindications or patient refusal the placement of epidural catheter abandoned.

An arterial line was inserted into radial artery. In study group, extended haemodynamic monitoring of fluid loading, cardiac output and changes of peripheral vascular resistance by analysing the arterial curve was provided by LIDCO Rapid (LiDCO, UK).

In both groups unilateral BIS monitor (Medtronic, USA) was used to evaluate the depth of anaesthesia by means of EEG measurement of cortical activity.

Baseline values of nominal stroke index (SI), cardiac index (CI), mean arterial pressure (MAP) and regional oxygen saturation (rSO2) were recorded in the study group and BIS in both groups.

Upon induction to anaesthesia, all patients were given up to 250 ml of crystalloid solutions (antibiotics and other therapy included).

Induction of general anaesthesia was conducted with a slow injection of fentanyl (3-5 mcg/kg) or sufentanil (0.3-0.5 mcg / kg), followed by a bolus of propofol (1-2 mg/kg) or etomidate (0.2 mg/kg) and rocuronium (0.6 mg/kg).

Patients were intubated, a nasogastric tube, a urine catheter with a temperature probe and central venous line were inserted.

Maintenance of general anaesthesia was achieved by using inhaled volatile agent sevoflurane in air/oxygen mixture (FiO2 0.04). Sevoflurane concentration was titrated according to BIS values.

Patients with an epidural catheter received a bolus of 15 ml of 0.25 % levobupivacaine epidurally, with supplementation of sufentanil 15 g. An epidural block was efficient if no supplemental analgesia was needed during operation (analgesia level Th1-L2). One to two hours after an epidural bolus of local anaesthetic, a continuous epidural infusion was started (0.125% levobupivacaine 200 ml, morphine 4 mg, clonidine 0.075 mg; infusion rate 5 ml/h, bolus 5 ml, lock out time 30 minutes) and continued postoperatively as patient-controlled epidural analgesia (PCEA).

In patients without epidural catheter, an intravenous infusion of patient-controlled analgesia (PCA) with piritramide was started at the beginning of laparotomy closure (infusion rate 1.5-2 mg/h, bolus 1,5-2 mg, lock out 30 minutes).

Muscle relaxation was monitored and rocuronium (10-20 mg) was supplemented according to TOF values. All patients received an antiemetic (granisetron 1 mg and dexamethasone 8 mg) during operation. The depth of anaesthesia was adjusted to maintain BIS values between 40-55. Protocol for intraoperative fluid replacement is shown in Figure 2.

At the end of the operation, in both groups the muscle block was reversed with sugamadex (2-4 mg/kg) or neostigmin (2,5 mg) and atropine (1 mg), according to TOF values.

After the surgery, patients were transferred to postoperative recovery and thereafter to Abdominal Surgery's HDU.

In both groups BIS values, the duration of operation, blood loss, intraoperative fluid and blood supplementation and urine output were recorded.

Hospitalisation duration, readmission to HDUs, ICU treatment, wound healing, reoperation, mortality and other complications (gut anastomosis dehiscence, sepsis, pneumonia, acute respiratory infection, pleural effusion, myocardial infarction, lung embolism, cerebrovascular insult, intraabdominal infection, urine infection...) were recorded on the postoperative days 3, 5, 8, 15 and on hospital discharge (14).

STATISTICAL ANALYSIS

SPSS statistics program, version 22 (IBM, NY, USA) was used to calculate general characteristics of included patients and intraoperative differences among groups. Chi square tests and Kruskal - Wallis tests were used where appropriate. Results with p value < 0,05 were considered statistically significant.

For the graphical interpretation of results of 15 days follow up Medplot software was used (http://shiny.mf.uni-lj.si/medplot/) (15). For additional statistical analysis of major complications, logistic regression with the Firth correction was used to estimate the association between each of the outcome variables (listed in table 6) and the selected covariate (use of haemodynamic monitoring), using the measurements obtained at the selected evaluation occasion (15th day after surgery).

RESULTS

Patients were randomized in 2 groups, 30 patients in CG and 29 patients in SG. Gender and ASA health status distribution are shown in Table 1 and Table 2. Subgroups with epidural were considered separately

Table 1: Distribution of patients' gender among test groups.

Group	No of included patients	Distribution of patients by gender	
		Female	Male
CG, without epidural (1)	7	4	3
CG, with epidural (2)	23	11	12
SG, without epidural (3)	10	4	6
SG, with epidural (4)	19	12	7
Total	59	31	28

CG – control group, SG – study group

Table 2: Distribution of patients according to ASA health status.

Group	ASA 1	ASA 2	ASA 3	ASA 4
CG, without epidural (1)	0	3	2	2
CG, with epidural (2)	0	11	12	0
SG, without epidural (3)	0	5	5	0
SG, with epidural (4)	2	7	10	0
Total	2	26	29	2

CG – control group, SG – study group

Table 3: Characteristics and intraoperative variables of patients included. (Kruskal - Wallis or Mann-Whitney U test were used where appropriate). Group as follows: Control group, without epidural (1), control group with epidural (2), study group, without epidural (3), study group with epidural (4).

Variable	group	median	IQR	P value (adjusted)
Intraoperative crystalloid solution (ml)	Control group	1500	1000	0,138
	Study group	2000	1000	Standardized Test Statistic: 1,332
				Mann-Whitney U test
Intraoperative colloid solution (ml)	Control group	1000	875	0,446
	Study group	1000	750	Standardized Test Statistic: 0,761
				Mann-Whitney U test
RBC transfusion (ml)	Control group	0	566	0,372
	Study group	0	596	Standardized Test Statistic: 0,891
				Mann-Whitney U test
Total intraoperative fluids (ml)	Control group	2577	1631	0,267
	Study group	3032	1093	Standardized Test Statistic: 1,109
				Mann-Whitney U test
Age (years)	1	72	72 - 78	0.172
	2	64	57 - 76	Kruskal – Wallis test
	3	62	59 - 77	
	4	59	46 - 66	
Body weight (kg)	1	66	57 - 75	0.602
	2	76	66 - 86	Kruskal – Wallis test
	3	71	65 - 75	
	4	73	60 - 76	
Body height (cm)	1	170	166 - 175	0.648
	2	165	159 - 172	Kruskal – Wallis test
	3	158	158 - 171	
	4	160	155 - 176	
Intraoperative crystalloid solution (ml)	1	1550	1500 - 1600	0.482
	2	1500	1000 - 2000	Kruskal – Wallis test
	3	2000	1050 - 2250	
	4	2000	1100 - 2000	
Intraoperative colloid solution (ml)	1	1250	1000 - 1500	0.522
	2	1000	500 - 1500	Kruskal – Wallis test
	3	1000	750 - 1500	
	4	1500	1000 - 1500	
RBC transfusion (ml)	1	142	0 - 285	0.102
	2	0	0 - 570	Kruskal – Wallis test
	3	535	0 - 574	
	4	0	0 - 595	
Total intraoperative fluids (ml)	1	2942	2600 - 3285	0.432
	2	2527	2000 - 3675	Kruskal – Wallis test
	3	2842	2500 - 3800	
	4	3150	2650 - 3600	
Total intraoperative diuresis (ml)	1	350	200-500	0.764
	2	325	200-450	Kruskal – Wallis test
	3	400	300-600	
	4	300	200-400	
Total blood loss (ml)	1	650	300-1000	0.317
	2	950	500-1200	Kruskal – Wallis test
	3	800	400-900	
	4	500	500-1000	
Duration of hospital stay (days)	1	22	8-36	0.246
	2	10	8-14	Kruskal – Wallis test
	3	13	11-15	
	4	9	8-14	

Control group, without epidural (1), control group with epidural (2), study group, without epidural (3), study group with epidural (4).

to avoid any bias. However, groups were homogenous, even when divided into 4 subgroups.

Female and male genders were equally distributed among groups. (Chi-square test, p= 0,625).

There was equal distribution of patients in SG and CG according to their ASA health status (Chi square, p=0,243). There was no difference in ASA health status in 4 subgroups (Fisher exact test p=0.168)

Personal characteristics and intraoperative variables are shown in Table 3. As above, patients were also divided into subgroups regarding epidural catheter (without epidural and LIDCO monitoring [1], with epidural, without LIDCO monitoring [2], without epidural, with LIDCO monitoring [3], with epidural and LIDCO monitoring [4]). No significant differences in intraoperative management were observed. Duration of hospitalisation was similar among 4 subgroups. There was no difference in hospital stay in comparison of SG and CG alone (Mann-Whitney U test, p= 0,855).

Intraoperative use of vasopressor support was monitored as shown in Table 4. Considering only SG and CG, the difference was not significant (Chi square, p=0,08). If 4 subgroups were considered (CG and without epidural [1], CG and with epidural [2], SG and without epidural [3], SG and with epidural [4]), difference was statistically significant (Fisher exact test, p=0,032). All patients in SG with epidural required vasopressors.

Postoperative 15 days' follow-up of some of the observed variables is shown in Chart 1. We have observed some patients with

Table 4: No. of patients with intraoperative vasopressors.

Group No. (see text for details)	**Control group**		**Study group**	
	Without epidural	With epidural	Without epidural	With epidural
Intraoperative vasopressors required No. of patients (%)	4 (57.1%)	19 (82.6%)	8 (80%)	19 (100%)
No vasopressors required				
No. of patients (%)	3			
(42.9%)	4			
(17.4%)	2			
(20%)	0			
(0)				
Sum of patients required vasopressors*	23 (76%)		27 (93%)	

* Chi square, p=0,08 (no significant difference)

Table 5: Number of major complications that have significantly affected time and course of patients' hospitalisation.

Group	**No major complications (No. of patients)**	**one or more major complications during hospital stay (No. of patients)**	**P value (Chi-square)**	**List of complications**
CG	25	5	1	1 occurrence of pulmonary embolism, 1 acute myocardial infarction, 2 dehiscence of anastomosis, 2 episodes of delirium
SG	25	4		1 occurrence of ventricular tachycardia, 2 dehiscence of anastomosis, 1 episode of delirium

CG – control group
SG – study group

Table 6: Logistic regression with the Firth correction showing the association between the outcome variables and the presence of haemodynamic monitoring on 15th day after surgery.

Variable	**Odds ratio**	**95% conf. interval**	**P value**
Severe pain (additional therapy required)	3.2	0.16 to 476	0.45
RBC transfusion	1	0.0055 to 194	0.99
Foley catheter inserted	0.42	0.071 to 1.9	0.27
Presence of nausea	0.33	0.0022 to 6.5	0.48
Food intolerance	0.33	0.0022 to 6.5	0.48
Rise in creatinine level (>20%)	0.33	0.0022 to 6.5	0.48
Newly ATB therapy	0.24	0.042 to 0.98	0.047*
Oxygen supplementation required	0.13	0.00097 to 1.5	0.11

*statistically significant difference

multiple complications. Transient rise in creatinine levels were observed in 2 patients in study group and in 1 patient in control group. The renal function of the patient in control group returned to preoperative level 2 months after the hospital discharge. Complications that have significantly affected time and course of patients' hospitalisation are presented in Table 5. One patient in control group had 2 major complications (acute myocardial infarction and dehiscence of anastomosis). Some complications, that were present 15th day from surgery, analysed with logistic regression by their significance are shown in Table 6.

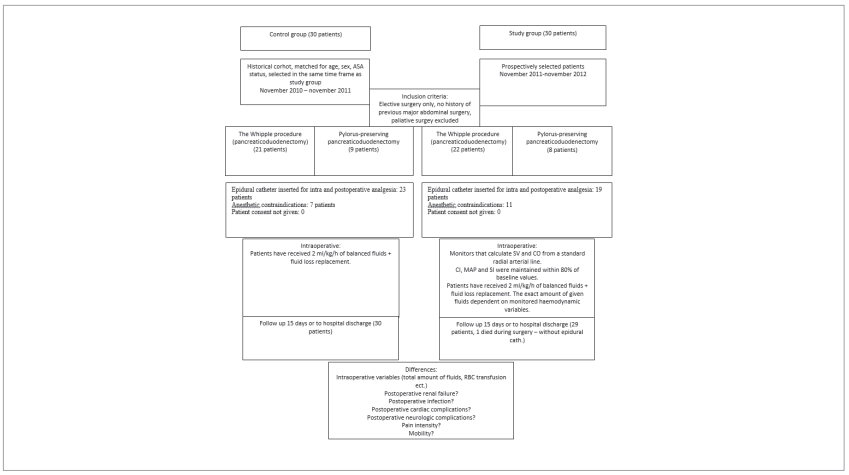

Figure 1: Study protocol

DISCUSSION

Fluid optimisation and vasopressors use

The amount of fluids given during major surgery, as pancreas surgery, is unexpected. Pearse proved that early fluid optimisation during major surgery reduced complications, hospital stay and increased colloids and vasoactive drugs consumption (8). In present study there were no differences in perioperative fluid administration, as well as hospital stay. However, detailed subgroup analysis revealed that all patients with additional epidural anaesthesia in study group needed more vasoactive drugs, which was statistically significant. For hip replacement in spinal anaesthesia fluid optimised patients received significantly more crystalloid fluids and vasoactive drugs (14). Similar observation was made for hip replacement in general anaesthesia. The group of patients, that were optimised with fluids, received more colloids and less crystalloids. Inotropes were used more frequently (16).

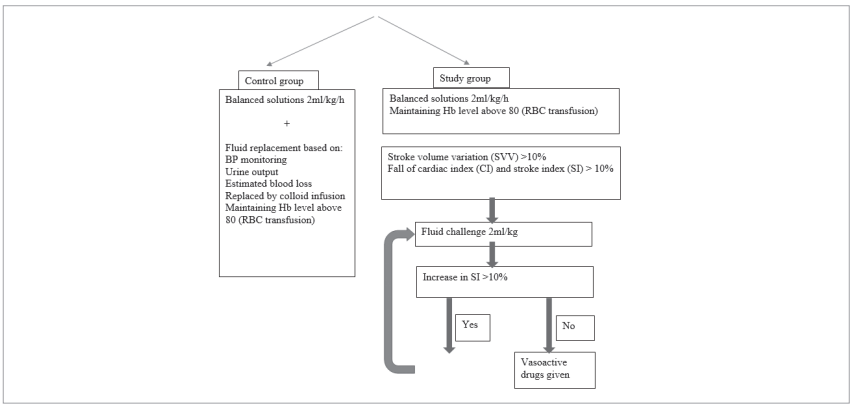

Figure 2: Intraoperative fluid loss management
Lungs were ventilated with a tidal volume of ≥ 8 ml/kg ideal body weight. Normothermia (36- 37°C) and normocapnia (5-5.5kPa) were maintained.

Postoperative complications and length of stay

The difference in observed major complications (acute myocardial infarction, dehiscence of anastomosis, pulmonary embolism, postoperative delirium, cardiac arrhythmia) was not significantly different between groups. However, there were two major complications, postoperative pulmonary embolism and myocardial infarction, both occurred in control group. Myocardial damage is otherwise frequent in patients after major surgery. In high risk patients, fluid optimization improved results in surgical therapy, but it may trigger acute myocardial damage (18).
Incidence of gut anastomosis dehiscence

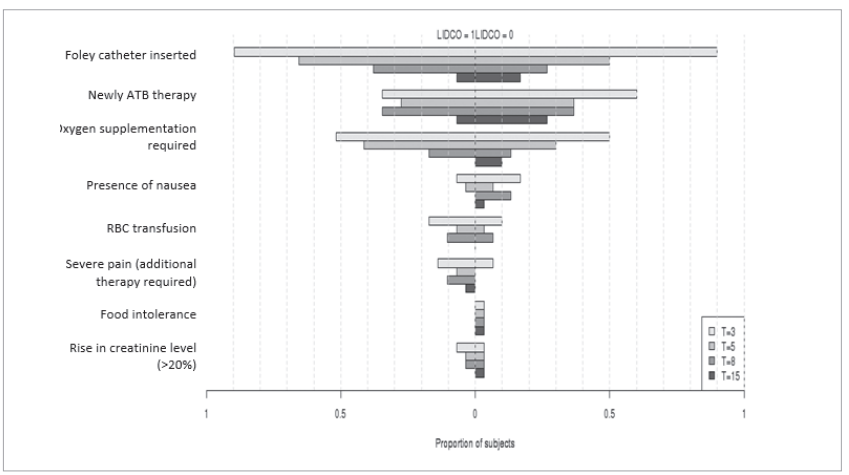

Chart 1: Results of 15 days follow up are shown (3rd, 5th, 8th and 15th postoperative day). The relative proportion of subjects with positive variable in SG and CG are shown. Created with Medplot, http://shiny.mf.uni-lj.si/medplot/.

is increased if anaemia, blood loss, transfusion and prolonged surgery are present. There is also influence of hypotension, use of vasoactive drugs, type of anaesthesia and fluid optimisation (17). In present study there was no difference in gut anastomosis dehiscence incidence; that could be the result of similar perioperative fluid, vasoactive drug and transfusion administration.

Early mobilisation is important for postoperative recovery, but is limited with orthostatic intolerance, present in 50 % of patients in six hours after major surgery, probably due to hypovolemia besides dysregulation of vasomotor tone. Fluid optimisation can only improve functional hypovolemia. Bundgaard-Nielsen et al. report, that fluid optimisation improved stroke volume, but could not decrease the prevalence for orthostatic intolerance (19). It was due to impaired cardiovascular response, that prolonged hormonal response for mobilisation and hospital stay (19).

Increased need for antibiotics in control group 15th day after surgery (as can be seen in Chart 1) may indicate increased risk for postoperative infections. However, detailed analysis has shown variety of reasons for starting therapy, from firm indications such as positive intraoperative abdominal swabs to only moderate rise in CRP value.

In already mentioned Cecconi research study group of patients had significantly fewer minor complications (hypotension, anaemia, infections) and less cardiovascular complications (14). Also the study of Habicher proved less postoperative bleeding and decreased incidence of morbidity (16).

In contrast Phana and co-workers in gut resection surgery did not find any differences in incidence of complications and hospital stay between optimised and not optimised patients (20). Also, Cecconi found no difference between groups in hospital stay (14). On the other hand, Habicher report shorter HDU and hospital (16).

Increased mortality and hospital stay could be also due to low mean arterial pressure, low BIS value and MAC, as was shown by Sessler and co-workers (21). In present study BIS was maintained between 40 and 55 and MAP with fluid boluses or vasopressors. This may be the reason that we did not find any differences in mortality and hospital stay in our group of patients.

In prospective, randomized, multicentre investigation by Scheeren, individualized fluid optimization was studied. More colloids administration and less wound infection were observed in fluid optimized group of patients. This fluid protocol based on stroke volume variation and stroke volume. Probably this approach decreases postoperative organ dysfunction (22). Overall, the expected decline in morbidity was not confirmed in our study (23,24).

We have not preformed any smaller prestudy that could serve as simulation for power analysis. However, we can discuss the effect size of results, specifically comparison of total amount of infused fluids during surgery. There is no difference between study group and control group. Estimated r2 based on Standardized Test Statistic (Table 3) is 0,02. Related probability of superiority is 58% (25,26). In other words, less than 3% of variability of the amount of infused fluids can be interpreted because of intraoperative haemodynamic monitoring. Variability among patients in our case is much larger than effect of haemodynamic monitoring and only very significantly larger sample might show correlation.

The study has important limitations. After the surgical procedure, researchers were only observers, the attending surgeons treated patients. Antimicrobial therapy was their decision, based on clinical and laboratory findings, no special study protocol was used.

CONCLUSION

In our study there was no difference in overall fluid and vasoactive drug demand. Although in the studied subgroup of patients with additional epidural anaesthesia there was significantly increased demand for vasoactive drugs. The incidence of complication was low in both groups and with no statistically significant differences among groups; however, some major complications (pulmonary embolism, acute myocardial infarction) occurred only in control group.

REFERENCES

1. Shoemaker WC, Appel PL, Kram HB, Waxman K, Lee TS. Prospective trial of supranormal values of survivors as therapeutic goals in high-risk surgical patients. Chest. 1988;94(6):1176-86
2. Giglio MT, Marucci M, Testini M, Brienza N. Goal-directed haemodynamic therapy and gastrointestinal complications in major surgery: a metaanalysis of randomised controlled trials. Br J Anaesth. 2009;103:637-46.
3. Drobin D, Hahn RG. Time course of increased haemodilution in hypotension induced by extradural anaesthesia. Br J Anaesth. 1996;77:223-6.
4. Buttenschoen K, Buttenschoen DC, Berger D, Vasilescu C, Schafheutle S, Goeltenboth B et al.Endotoxemia and acute-phase proteins in major abdominal surgery. Am J Surg. 2001;181:36-43.
5. Mijawaki T, Maeda S, Koyama Y, Fukuoka R, Shimada M. Elevation of plasma interleukin-6 level is involved in postoperative fever following major oral and maxillofacial surgery. Oral Med Oral Pathol Oral Radiol.1998;85:146-151.
6. Wortel CH, van Deventer SJH, Aarden LA, Lygidakis NJ, Buller HR, Hoek FJ et al. Interleukin-6 mediates host defence responses induced by abdominal surgery. Surgery 1993;114:564-569.
7. Foex BA, Lamb WR, Roberts TE, Brear SG, Macartney I, Hammer M et al. . Early cytokine response to multiple injury. Injury. 1993;24:373-376
8. Pearse R, Dawson D, Fawcett J, Rhodes A, Grounds RM, Bennett ED. Early goal-directed therapy after major surgery reduces complications and duration of hospital stay. A randomised, controlled trial (ISRCTN38797445). Crit Care. 2005;9:R687-93.
9. Wilson J, Woods I, Fawcett J, Whall R, Dibb W, Morris C et al. Reducing the risk of major elective surgery: randomised controlled trial of preoperative optimisation of oxygen delivery. BMJ. 1999,318:1099-103.
10. Sandham JD, Hull RD, Brant RF, Knox L, Pineo GF, Doig CJ et al. A randomized, controlled trial of the use of pulmonary-artery catheters in high-risk surgical patients. N Engl J Med. 2003,348:5-14.
11. Walsh SR, Tang T, Bass S, Gaunt ME. Doppler-guided intra-operative fluid management during major abdominal surgery: systematic review and metaanalysis. Int J Clin Pract. 2008;62:466-70.

12. Abbas SM, Hill AG. Systematic review of the literature for the use of oesophageal Doppler monitor for fluid replacement in major abdominal surgery. Anaesthesia. 2008;63:44-51.
13. Gurgel ST, do Nascimento P Jr. Maintaining tissue perfusion in high-risk surgical patients: a systematic review of randomized clinical trials. Anesth Analg. 2011;112(6):1384-91.
14. Cecconi M, Fassano N, Langiano N, Divella M, Costa MG, Rhodes A et al.Goal-directed haemodynamic therapy during elective total hip arthroplasty under regional anaesthesia. Crit Care. 2011;15(3):R132.
15. Ahlin Č, Stupica D, Strle F, Lusa L: A Web Application for Dynamic Summary and Analysis of Longitudinal Medical Data Based on R. PLoS ONE 10(4):e0121760.
16. Habicher M, Balzer F, Mezger V, Niclas J, Müller M, Perka C et al.Implementation of goal-directed fluid therapy during hip revision arthroplasty: a matched cohort study. Perioper Med.2016;5:31.
17. Van Rooijen SJ, Huisman D, Stuijvenberg M, Stens J, Roumen RM, Daams F et al.. Intraoperative modifiable risk factors of colorectal anastomotic leakage: Why surgeons and anesthesiologists should act together. Int J Surg. 2016; 36:183-200.
18. Gillies MA, Shah AS, Mullenheim J, Tricklebank S, Owen T, Antonelli J et al. Perioperative myocardial injury in patients receiving cardiac output-guided haemodynamic therapy: a substudy of the OPTIMISE Trial. Br J Anaesth. 2015;115:227-33.
19. Bundgaard-Nielsen M, Jans Ø, Müller RG, Korshin A, Ruhnau B, Bie Pet al. Does goal-directed fluid therapy affect postoperative orthostatic intolerance?: A randomized trial. Anesthesiology. 2013;119:813-23.
20. Phan TD, D'Souza B, Rattray MJ, Johnston MJ, Cowie BS. A randomised controlled trial of fluid restriction compared to oesophageal Doppler-guided goal-directed fluid therapy in elective major colorectal surgery within an Enhanced Recovery After Surgery program. Anaesth Intensive Care. 2014;42:752-60.
21. Sessler DI, Sigl JC, Kelley SD, Chamoun NG, Manberg PJ, Saager L et al.Hospital stay and mortality are increased in patients having a "triple low" of low blood pressure, low bispectral index, and low minimum alveolar concentration of volatile anesthesia. Anesthesiology. 2012;116:1195–203.
22. Scheeren TW, Wiesenack C, Gerlach H, Marx G. Goal-directed intraoperative fluid therapy guided by stroke volume and its variation in high-risk surgical patients: a prospective randomized multicentre study. J Clin Monit Comput. 2013;27:225-33.
23. Forni LG. Fluid therapy and acute kidney injury: A question of balance? Signa Vitae. 2016;11(Suppl 2):17–21.
24. Žličar M. Current concepts in fluid therapy and non-invasive haemodynamic monitoring. Signa Vitae. 2017;13(21):53–5.
25. Colquhoun D. An investigation of the false discovery rate and the misinterpretation of P values. R Soc Open Sci. 2014;1–15.
26. Fritz CO, Morris PE, Richler JJ. Effect size estimates: Current use, calculations, and interpretation. J Exp Psychol Gen. 2012;141(1):2–18.