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JNMU
Journal of Nanjing Medical University, 2008, 22(1):47-51
www.elsevier.com/locate/jnmu
Research Paper

Differential effects of controlled hypotension on gastric intramucosal pH and post-operational gastrointestinal functional under two different anesthesia methods

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Received 5 September 2007

Abstract

Objective: To observe the effects of controlled hypotension on gastric intramucosal pH and post-operational gastrointestinal functions using two specific anesthesia methods. Methods: Thirty patients(ASA Ⅱ)scheduled for ectomy of hepatocarcinoma, were randomly assigned to two groups: epidural block combined with intravenous anesthesia group(E group) and inhalation anesthesia group(G group). Gastric $PgCO_2$ and pHi were monitored at different time points, before theintravenous induction of controlled hypotension, after 1 h and 2 h, and 1 h after the termination of controlled hypotension. In the meanwhile, the artery blood gas was analyzed. Results: There was no significant difference in blood gas indexes between E group and G group. However, pHi decreased significantly after 1 h and 2 h of controlled hypotension($P < 0.05$), and during the same periods $PgCO_2$ increased significantly($P < 0.05$ or $P < 0.01$), the time of bowel movement and defecating deferred significantly shorter in G group patients, when compared with E group patients. Conclusion: Epidural block in combination with general anesthesia can improve gastrointestinal blood flow during controlled hypotension and facilitates post-operational recovery of gastrointestinal functions.

Key words: anesthesia; epidural; general anesthesia; controlled hypotension; gastric mucosa

INTRODUCTION

Gastrotonometer can be used to evaluate localized blood flow of visceral vasculature. Gastrointestinal mucosal pH provides an accurate estimation of microcirculatory blood flow and reflects the conditions of gastrointestinal blood infusion and oxidation with considerable sensitivity and specificity. Compared with other conventional approaches, it represents a more timely evaluation of visceral blood flow, oxidation and visceral function. Through extensive sympathetic nerve blockade, epidural anesthesia dilates visceral blood vessels and ameliorates blood flow. Controlled hypotension can reduce intraoperative bleeding as well as tissue blood infusion. The objective of this study is to investigate the effects of various anesthesia methods and controlled hypotension on the visceral blood flow under different anesthesia methods,in order to offer a novel approach for studying controlled hypotesion.

MATERIALS AND METHODS

General Materials

Thirty hepatic cancer patients(ASA Ⅱ, male or female,age 26-60 years, body weight 56-72 kg) undergoing elective surgery were chosen for this study.The study was approved by the Hospital Research Ethics Com-mittee and written informed consent was obtained from all patients before the start of the study. All the patients included had normal hemoglobin, normal hepatic and renal function and no recent medication of NSAID or steroid drugs and no family history of hypertension, cardiovascular diseases, immunological or endocrinological diseases. Patients were randomly divided into two groups, epidural blockade in combination with

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general anesthesia (E Group) and inhalation general anesthesia(G group).

Methods

All patients were fasted for 12 h for food and 6 h for drink prior to surgery, midazolam(0.06 mg/kg) and scopolamine(0.3 mg) were given Intramuscular at 30 min before anesthesia induction. The patients in E group were treated with conventional epidural puncture and intubation at the level of T_{8-9} or T_{9-10} and maintained at supine position. Patients from both groups were moni-tored for their artery blood pressure, and their mean artery blood pressure(MAP) was recorded through a catheter inserted in the radial artery. In addition, patient's heart rate and lead II ECG were continu-ously monitored. Central venous pressure was moni-tored through a catheter inserted into the intrajugular vein. A trial dose of lidocaine (2%, 4 ml) was given to the epidural space, and maintained at T_4-T_{12} by using 2% lidocaine 8-10 ml. 5-9 ml 2% lidocaine was rein-forced or based on individual patient responses. The general anesthesia induction for both groups used intravenous administration of etomidate(0.3 mg/kg), fentanyl(6-8 μg/kg), atracurium (0.8 mg/kg), and both groups were continuously given propofol 2 mg/(kg • h) after trachea intubation and atracurium 8 μg/(kg • min)through pumps. Patients of G group were given isoflurane inhalation for general anesthesia. Nitroglyc-erin was continuously given after the beginning of surgery[initially at 0.3 μg/(kg • min) and gradually increased to 2 μg/(kg • min)] to maintain the MAP at 25%-30% lower than basal level[1]. All patients were given pure oxygen during the operation.

Determination of $PgCO_2$ and pHi

Gastric intubation was performed on patients to introduce the gastrotonometer(TRIP-NGS) tubes. A Tonocap monitor (Datex-Engtrom, Finland) was used to determine gastric $PgCO_2$ and pHi basal levels. Gastric mucosal pHi was continuously monitored, based on which blood was sampled for HCT and Hb determination. The tonocap monitor automatically analyzed gastric gas samples for $PgCO_2$ and simultaneously drawn artery blood for gas analysis. By collecting artery pH and $PaCO_2$ values, the Tonocap monitor automatically calculated all the values, where pHi=pHa+log($PaCO_2$/$PgCO_2$); Pg-aCO_2=$PgCO_2$-$PaCO_2$[2]

Statistical analysis

The quantitative data is expressed as mean ± *s*. The *t* test was employed to compare the difference and *P* values < 0.05 were considered significant. All data analysis were done using SPSS 11.0 package.

RESULTS

General conditions of patients in two groups

There was no difference significantly in general conditions, such as age, sex, body weight, surgery sites and operation time in two groups(Tab 1). No significant difference of amount of liquid infusion and erythrocyte HCT at all the time points was observed.

Tab 1 Comparison of overall conditions of patients in two groups ($\bar{x} \pm s$)

	Sex (male/female)	Age (years)	Body weight (kg)	Operation time (min)
E group	9/6	45 ± 3.6	60 ± 7.9	182.4 ± 48.5
G group	8/7	43 ± 5.2	58 ± 8.2	188.8 ± 39.8

Changes of heart rates in two groups

Patients in both groups showed varying degrees of increased heart rate during controlled hypotension, patients with inhalation anesthesia had significantly higher heart rate compared with patients treated with epidural blockade in combination with general anesthesia (Tab 2).

Tab 2 Changes of heart rates of patients in two groups before, during and after controlled hypotension (bpm, $\bar{x} \pm s$)

		Controlled Hypotension(CH)		
	Before CH	After 1 h	After 2 h	1 h after CH
E group	76.8 ± 8.6	78.5 ± 9.5	80.2 ± 8.8	79.2 ± 8.2
G group	77.2 ± 8.4	84.4 ± 9.8*	86.5 ± 9.6**	82.3 ± 8.4

Compared with before CH, *$P < 0.05$; **$P < 0.01$.

Changes in the mean values of pHa, PaO_2, $PaCO_2$, BE, pHi, and $PgCO_2$ before, during and after controlled hypotension

The comparison results of artery blood gases and gastric mucosal metabolisms were illustrated in Tab 3. No significant difference in artery blood gases was found in both groups. However, pHi of G group patients was significantly lower at 1 h and 2 h after the establish-ment of controlled hypotension($P < 0.05$) than that of group E. $PgCO_2$ of G group was significantly elevated at the same time points($P<0.05$ or $P<0.01$) com-pared with that of group E.

Changes of post-operational gastrointestinal recovery in two groups

The bowel movement, gas passage time[(39.5 ± 7.6) h] and defecation time[(72.6 ± 8.4)h] were significantly shorter in E group compared with those[(45.6± 6.2)h]($P < 0.05$), (79.8 ± 7.5)h($P < 0.05$)] from G group.

DISCUSSION

Controlled hypotension during surgical operation has been a widely adopted in conventional practice. More

Tab 3 Comparison of artery gases and gastric mucosal metabolisms in both groups ($\bar{x} \pm s$)

	Group	Basal	1 h after	2 h after	1 h after termination
pHa	E	7.406 ± 0.032	7.401 ± 0.056	7.389 ± 0.048	7.394 ± 0.046
	G	7.411 ± 0.033	7.396 ± 0.052	7.384 ± 0.036	7.401 ± 0.041
PaO_2	E	432.5 ± 82.3	428 ± 78.6	424.8 ± 81.6	419.6 ± 76.8
(mmHg)	G	421.7 ± 79.6	401 ± 85.4	399 ± 76.3	411 ± 58.9
$PaCO_2$	E	39.6 ± 2.9	39.9 ± 3.1	41.3 ± 2.3	40.9 ± 2.8
(mmHg)	G	40.1 ± 2.2	41.6 ± 1.9	41.9 ± 2.6	40.8 ± 2.4
BE	E	1.6 ± 0.8	1.1 ± 0.6	0.8 ± 0.8	0.6 ± 0.7
	G	1.8 ± 0.6	0.8 ± 0.5	0.2 ± 1.1	0.4 ± 0.9
pHi	E	7.419 ± 0.028	7.421 ± 0.026	7.418 ± 0.033	7.416 ± 0.025
	G	7.426 ± 0.032	7.392 ± 0.036*	7.372 ± 0.015*	7.398 ± 0.013
$PgCO_2$	E	38.87 ± 2.03	37.86 ± 1.98	39.17 ± 2.16	39.82 ± 2.31
(mmHg)	G	39.16 ± 1.96	41.15 ± 4.09*	41.96 ± 2.98**	40.15 ± 2.59

Compared with E group, $^*P < 0.05$; $^{**}P < 0.01$

frequently, the protection of gastrointestinal function during controlled hypotension is overlooked, compared with the awareness of surgeons for blood supplies to vital organs such as the heart, brain and kidney. It is well accepted that the gastrointestinal system is richly perfused and very sensitive to hypoxia and ischemia. Researches have found that the gastrointestinal mucosa is among the first inflicted organs during tissue ischemia and the last organs that ameliorate after cessation of ischemia[3-5]. Reports have shown that exceedingly low pHi value during an operation(as a result of hypoxia/ischemia of gastrointestinal mucosa) results in a slower recovery of gastrointestinal function, a breakage of the gastrointestinal barrier and disruption of the epithelial metabolisms. The gastrointestinal mucosa is therefore more permeable to endotoxins and bacterium, which translocate into the blood stream to cause "endogenous" infections[6], and in severe cases, even more serious complications such as peptic ulcer. Therefore, monitoring of gastrointestinal pH can not only reflect overall hypoxic conditions of the body, but also the oxygenation states of individual organs.

By monitoring the microcirculation with Tonometry, Sielenkamper et al[7] and Gretcher[8] detected that the blood flow of intestinal mucosa increased undergoing the epidural anthesia in rats. Epidural blockade in combination with general anesthesia is widely used because of the com-plimentary nature of these two approaches. Thoracic epidural blockade induces widespread thoracic and abdominal nerve blockade, dilates the resistant and volume blood vessels and ameliorates visceral blood perfusion[9-11], and protects the trauma-induced stress response in patients[12].

Due to the rich blood supply of the liver, surgery is usually more traumatic and blood loss is heavier. In addition, circulation is more prone to fluctuation, resulting in hypotension and arrhythmia[13]. Therefore, controlling blood loss is critical to improve the safety of the operation and anesthesia conditions. Deliberate induction of hypotension is frequently adopted to control blood loss. However, it is very important to maintain stable blood pressure[14]. The organs can be damaged by ischemic injuries once the blood pressure is excessively low. Based on a report by Taniguchi et al[15] an average blood pressure of above 55 mmHg during controlled hypotension will not adversely affect brain tissues-provided the two following criteria were satisfied: ① Sufficient urine production was at least 1 ml/(kg • h) during operation. ②The blood pressure did not drop below the 70% of the pre-operational level. The enforcement of intraoperational monitoring is of critical importance. Typically during liver operation, high variations in water, electrolyte and acid-base balances, and variations in blood flow dynamics occur, especially during portal occlusion and release times. Therefore, it is obligatory to dynamically monitor ECG, peripheral artery pressure(radial artery pressure) and central venous pressure. In the meanwhile, the amount of urine production and blood loss should be meticu-lously recorded and, analysis of blood gases and elec-trolytes should be performed where necessary[16-17].

Most frequently, the monitoring of hypoxic is achieved by measuring the partial pressure oxygen of the arteries, which does not necessarily represent proper oxygenation at the tissue level(or even satisfactory oxygen partial pressure) nor does it reflect increased localized organ perfusion. Therefore, it is of clinical importance that a proper method should be established to represent the status of oxygenation at tissue and cellular levels. Since a direct measurement of oxygen metabolism is prohibitively intricate and will not be feasible as a routine monitoring process clinically in a foreseeable future, we have adopted an indirect measurement, pHi, to reflect the oxygenation state of tissues and monitor the visceral blood flow. This tonometry is currently the only non-invasive method in evaluating visceral blood

flows. By measuring $PgCO_2$, the pHi values can be deduced. Therefore, intramucosal acidosis and reduced visceral perfusion can be detected at an early stage. It has been shown that an elevated local $PgCO_2$ is correlated with poor prognosis in patients undergoing major surgery, suffering severe traumas or being critically ill[18-19]. The tonometry used in this study uses conventional tubes (a type of gastric tube with silicon air bag attached to the end). The air bag is automatically inflated with 5 ml air, which is equilibrated in the gut environment for 10 min before an air sample is measured for CO_2 pressure using infrared lights. The sampling air is then returned to the air bag, equilibrated, and is then ready for the next measurements. Compared with salt-water tonometry, this approach takes less time to equilibrate, provides excellent accuracy, and is less error-prone. It also eliminates many artificial errors and is more reproducible[20]. This technique can detect reduced gastric mucoal perfusion within a short time period(5 min), and can provide a continuous, automatic monitoring for the gut blood perfusion[21].

In summary, our study has shown that during controlled hypotension, even in the absence of changes of the overall body oxygenation index(e.g. PaO_2), the gastrointestinal $PgCO_2$ was significantly elevated and pHi was significantly lowered in the G group patients. These results suggest that pHi is more sensitive in reflecting the oxygenation levels of local tissues compared with other overall indices. In addition, it also somewhat predicts the degree of ischemia and provides an objective sign for early clinical intervention. Moreover, pHi monitoring is non-invasive, easily maneuverable and yields reliable results. It is also capable of dynamic monitoring and may be applied to patients in critical conditions during surgery.

Acknowledgements

This work was supported by a grant from the Foundation of Six Top Talent of Jiangsu province personnel department.

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Molecular targeting in cancer therapy and prevention

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Recent progress made in many biological sciences such as genomics, genetics, and molecular biology has made molecular targeting possible. Although thousands of disease-causing molecules(genes and proteins alike) can theoretically be drug targets, there have been limited cases with successful drug targets that have been moved to clinical practice. Advances in experimental biomedical research have provided many sophisticated methods that can improve our ability to link human diseases with specific genes or proteins and to explore the underlying mechanisms. However, these approaches have not bee well validated for drug targeting. This presentation aims at providing a systemic review on the state-of-art information and technology in the field of drug targeting and its role in the process of drug discovery and drug development. After a brief discussion of the process of modern drug discovery and development, the roles of drug targeting in drug discovery, design, development, and delivery will be reviewed.

The focal points in the first part of the presentation will be the determining the causal relationship between disease and drug targets and the scientific principles for establishing such a relationship and the major approaches to selection of drug targets at various levels, including in vitro, in vivo, and clinical and population studies. The advantages and disadvantages of these methods and major challenges in each of the field will be discussed. In the second part of the presentation, several cutting-edge methods available to drug targeting will be discussed. They include gene silencing technologies, such as RNAi, antisense, and miRNA. In addition, the major challenges in this field will be discussed, especially with respect to off-target effects, biomarkers, species differences, and efficacy and safety issues. As an example, oncogene and tumor suppressor genes play important roles in the development, progression, treatment and prevention of human cancer. Addict to oncogene is one of the major characteristics of human cancer and it is suggested that oncogene can be targeted for both prevention and therapy of human cancers. In this presentation, the biology and role of p53 and MDM2 and their interaction will be discussed. Several novel mechanisms responsible for the gene-drug and gene-chemopreventive agent interactions will be presented. [This work was supported by NIH grants and contracts (R01 CA 80698, R01 CA 112029, R01CA121211, R01CA116804, N01-CM-07111, and N01-CM-47015-45) and DoD grants (W81XWH-04-1-0845 W81XWH-06-1-0063). Many members of Zhang Laboratory and collaborators contributed tremendously to this work.]