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Research paper

Comparisons of different methods of anesthesia and analgesia on the levels of glycometabolism rate-limiting enzymes in erythrocytes and plasma glucose and stress hormones in patients undergoing esophagus surgery ☆

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Abstract

Objective: To compare the effects of different methods of anesthesia and analgesia on the activities of phosphofructokinase(PFK), glucose-6-phosphate dehydrogenase(G-6PD) and aldose reductase(AR) in erythrocytes and levels of plasma glucose and stress hormones in patients undergoing esophagus surgery. **Methods:** Sixty-two patients scheduled for esophagus surgery were randomly divided into three groups: group Ⅰ ($n = 20$) receiving only general anesthesia(GA) followed by intravenous patient controlled analgesia(PCA) with fentanyl 15 μg/kg. The other two groups receiving both general anesthesia combined with thoracic epidural anesthesia (GEA) and either intravenous PCA with fentanyl 15 μg/kg (group Ⅱ, $n = 21$) or thoracic epidural analgesia(TEA) with 0.125% ropivacaine and 0.0002% fentanyl mixture(group Ⅲ, $n = 21$) after the operation. Venous blood samples were collected for measurements of PFK, G-6PD and AR activities in erythrocytes and plasma glucose, cortisol, epinephrine and norepinephrine before induction (T_1), 60 min following the incision (T_2), 60 min(T_3) after operation, on the 1st(T_4) and 2nd postoperative day(T_5). **Results:** The activities of PFK decreased($P < 0.01$ or $P = 0.004$) and the activities of G-6PD and AR increased($P < 0.01$) in groups Ⅰ and Ⅱ on T_4 compared with those on T_1. Between the two groups, the activities of these enzymes in group Ⅱ changed less than those of group Ⅰ ($P < 0.01$ or $P < 0.05$). These enzymes activities changed slightly in group Ⅲ on T_4($P > 0.05$). There were significant differences between group Ⅲ and the other two groups($P < 0.01$ or $P < 0.05$). The levels of plasma glucose increased significantly on T_2($P < 0.01$), reached peak values on T_4($P < 0.01$) and fell on T_5 in the three groups. Compared to those of groups Ⅰ and Ⅱ, the values of plasma glucose in group Ⅲ were lower on T_4 and T_5($P < 0.05$ or $P < 0.01$). The cortisol concentration in each group increased significantly at T_2($P < 0.01$ or $P < 0.05$), and remained elevated on T_5($P < 0.01$ or $P < 0.05$), while on T_2 and T_3 the cortisol levels of group Ⅰ were higher than that of groups Ⅱ and Ⅲ ($P < 0.05$). The levels of group Ⅲ were lower than those of the other groups on T_4 and T_5($P < 0.01$ or $P < 0.05$). The levels of epinephrine and norepinephrine were also significantly higher in group I than those of the other two groups on T_2($P < 0.01$ or $P < 0.05$), and their levels in group Ⅰ and Ⅱ were higher than that of group Ⅲ on T_4. The patients of the three groups obtained satisfactory pain relief, with all Vidual Analogue Scale(VAS) scores less than 3. VAS scores of group Ⅰ were much greater 4h after operation. Group Ⅲ VAS scores were the lowest 24h after operation. However, the number of times patients pressed the bolus switch was higher in group Ⅱ ($P < 0.01$). **Conclusion:** Compared with GA and intravenous PCA, general anesthesia combined with thoracic epidural anesthesia and analgesia obtain better pain relief and could markedly alleviate the stress response and improve these erythrocyte glucose metabolism changes after esophagus surgery.

Key words: Anesthesia; Analgesia; Phosphofructokinases; Aldose reductase; Glucose-6-phasephate dehydrogenase; Cortisol; epinephrine; norepinephrine

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INTRODUCTION

The endocrine, metabolic, and inflammatory responses to injury and infection consist of a variety of physiological changes, collectively called the surgical stress response. This process is considered to be detrimental to restoring homeostasis and returning the organism to a normal state of health and activity. Although the endocrine and metabolic changes have been extensively studied[1], little attention has been paid to the function or the bioactivity changes in cells resulting from a major stress. Erythrocytes play an important role in human body. They have three major glycometabolism pathways; glycolysis, the pentose phosphate and polyol pathways. PFK, G-6PD and AR are glycometabolism rate-limiting enzymes of the three pathways. Our previous studies found that the activities of PFK in erythrocytes were depressed, while the activities of G-6PD and AR were significantly elevated on the 1st postoperative day in patients after esophagus surgery. We supposed that these changes were related to oxidative damage, part of a dramatic stress response[2,3]. The stress response to major thoracic surgery may be inhibited by epidural anesthesia. Thus the aim of this study was to compare the effects of general anesthesia with and without TEA and compare the effects of intravenous PCA or postoperative TEA on the activities of PFK, G-6PD and AR in erythrocytes and on plasma glucose, cortisol, epinephrine and norepinephrine levels in patients undergoing esophagus surgery.

MATERIALS AND METHODS

After institutional approval and informed consents were obtained, 62 adult patients of ASA Ⅰ-Ⅱ undergoing esophagus surgery were randomly divided into three groups: group Ⅰ(n = 20) receiving GA followed by intravenous PCA with fentanyl. The two other groups receiving both GEA, and either intravenous PCA with fentanyl(group Ⅱ, n = 21) or TEA with ropivacaine and fentanyl mixture(group Ⅲ, n = 21). The age, weight and gender in the three groups were comparable. Patients with endocrine diseases or metabolic disorders were excluded.

On arrival at the operating room, an epidural catheter was inserted between T_{7-8} before the operation in group Ⅱ and Ⅲ. After a test dose of 5 ml of 1% lidocaine, an initial dose of 0.25% ropivacaine 3-5 ml was administered epidurally to confirm a sensory block up to T_4, and the block was tested before induction of GA. The induction and maintenance of GA were similar to those in group Ⅰ. GA was induced with 0.1 mg/kg midazolam, 1 mg/kg propofol, 2 μg/kg fentanil and 0.1 mg/kg vecuronium and was maintained with 4-6 μg/kg fentanyl thirty min after making the incision,4 μg /mg/(kg • h) propofol and 10 μg/(kg • min) atracurium was administered. Epidural spaces was administered 0.25% ropivacaine every 1.5 h in group Ⅱ and Ⅲ.

PCA devices were connected into patients after surgery. Patients in groups Ⅰ and Ⅱ were both provided with intravenous PCA, with 15 μg/kg fentanyl, total amount: 200 ml, loading dose: 15 μg fentanyl, infusion rate: 4 ml/h, bolus amount: 4 ml, lockout time: 30 min. In group Ⅲ, postoperative pain treatment was achieved by epidural bolus doses of 4 ml of the mixture 0.125% ropivacaine plus 2 μg/ml fentanyl, a lockout interval of 30 min, and a background epidural infusion of 4 ml/h mixture. VAS scores were recorded at 4 h, 12h, 24h and 48h after the operation and the total number of times the bolus switch was pressed was also recorded.

Venous blood samples were collected before induction (T_1), 60 min following the incision(T_2), 60 min after operation(T_3), on the 1st(T_4) and 2nd postoperative day (T_5). Blood samples were centrifuged at 2,000 rpm to separate erythrocytes and plasma. The methods of detecting PFK, G-6PD and AR activities in erythrocytes were the same as previous described[3]. Plasma was stored at -70℃ for the later detection of epinephrine and norepinephrine, and -20℃ for subsequent cortisol analysis. Cortisol was measured with a chemiluminescence immunoassay. Catecholamines were measured by high-pressure liquid chromatography, using electrochemical detection, and glucose was measured using a glucose oxidase method.

Data are presented as means±SD. Statistical analysis was performed using SPSS 11.5 for Windows software package. Differences between groups means were analyzed using ANOVA, within-group comparison of variables were made by paired T tests. A probability of $P < 0.05$ was considered to be significant.

RESULTS

The activities of PFK decreased($P < 0.01$ or $P = 0.004$) and the activities of G-6PD and AR increased($P < 0.01$) in groups Ⅰ and Ⅱ on T_4 compared with those on T_1. Between the two groups, the activities of these enzymes in group Ⅱ changed less than those of group Ⅰ ($P < 0.01$ or $P < 0.05$). These enzymes activities changed slightly in group Ⅲ on T_4($P > 0.05$). There were obvious differences between group Ⅲ and the other two groups ($P < 0.05$ or $P < 0.01$) with all three enzymes(***Table 1-3***).

The levels of plasma glucose were significantly elevated on T_2($P < 0.01$), reached peak values on T_4 ($P < 0.01$) and fell on T_5 in all three groups. Compared to the values of groups Ⅰ and Ⅱ, the values of plasma glucose in group Ⅲ were significantly lower on T_4 and T_5($P < 0.05$ or $P < 0.01$)(***Table 4***).

The cortisol concentration in each group increased significantly at T_2($P < 0.01$ or $P < 0.05$), and remained elevated on T_5($P < 0.01$ or $P < 0.05$), while on T_2 and T_3 the cortisol level of group Ⅰ was markedly higher than that of groups Ⅱ and Ⅲ ($P < 0.05$). The levels of group Ⅲ were significantly lower than those of the other two groups on T_4 and T_5($P < 0.01$ or $P < 0.05$)(***Table 5***).

Similarly epinephrine and norepinephrine levels were much higher in group Ⅰ than those of other two groups on T_2($P < 0.01$ or $P < 0.05$), and the levels of groups Ⅰ and Ⅱ were markedly higher than that of group Ⅲ on T_4(***Table 6,7***).

Table 1 **The changes of PFK activity** (U/g/Hb, $\bar{x} \pm sd$)

Group	T_1	T_2	T_3	T_4	T_5
Group Ⅰ	1.88 ± 0.54	1.69 ± 0.68	1.66 ± 0.71	0.95 ± 0.28$^{**\#\#\triangle}$	1.77 ± 0.54
Group Ⅱ	1.86 ± 0.72	1.83 ± 0.94	1.93 ± 0.89	1.30 ± 0.59$^{**\#}$	1.61 ± 0.44
Group Ⅲ	1.80 ± 0.54	1.75 ± 0.55	1.95 ± 0.57	1.70 ± 0.66	1.59 ± 0.61

Compared with T_1, $^{**}P < 0.01$; compared with group Ⅲ, $^{\#}P < 0.05$, $^{\#\#}P < 0.01$; compared with group Ⅱ, $^{\triangle}P < 0.05$.

Table 2 **The changes of G-6PD activity** (U/g/Hb, $\bar{x} \pm sd$)

Group	T_1	T_2	T_3	T_4	T_5
Group Ⅰ	8.10 ± 1.55	8.42 ± 1.47	8.70 ± 1.58	10.29 ± 1.45$^{**\#\#\triangle}$	8.58 ± 1.44
Group Ⅱ	8.05 ± 1.34	8.33 ± 1.86	8.45 ± 1.24	9.23 ± 1.09$^{**\#}$	8.52 ± 1.33
Group Ⅲ	8.06 ± 1.60	8.08 ± 1.54	8.06 ± 1.12	8.21 ± 1.65	8.38 ± 1.17

Compared with T_1, $^{**}P < 0.01$; compared with group Ⅲ, $^{\#}P < 0.05$, $^{\#\#}P < 0.01$; compared with group Ⅱ, $^{\triangle}P < 0.05$.

Table 3 **The changes of AR activity** (U/g/Hb, $\bar{x} \pm sd$)

Group	T_1	T_2	T_3	T_4	T_5
Group Ⅰ	0.177 ± 0.015	0.176 ± 0.017	0.176 ± 0.017	0.213 ± 0.026$^{**\#\#\triangle\triangle}$	0.183 ± 0.027**
Group Ⅱ	0.172 ± 0.011	0.174 ± 0.012	0.172 ± 0.012	0.193 ± 0.019$^{**\#}$	0.173 ± 0.009
Group Ⅲ	0.174 ± 0.017	0.175 ± 0.019	0.173 ± 0.019	0.177 ± 0.023	0.176 ± 0.016

Compared with T_1, $^{**}P < 0.01$; compared with group Ⅲ, $^{\#}P < 0.05$, $^{\#\#}P < 0.01$; compared with group Ⅱ, $^{\triangle\triangle}P < 0.01$.

Table 4 **Plasma glucose concentration** (U/g/Hb, $\bar{x} \pm sd$)

Group	T_1	T_2	T_3	T_4	T_5
Group Ⅰ	4.88 ± 0.44	6.47 ± 1.26**	7.41 ± 1.58$^{**\#}$	8.00 ± 1.94$^{**\#\#}$	6.05 ± 1.98$^{**\#\#}$
Group Ⅱ	5.03 ± 0.77	6.00 ± 0.73**	6.64 ± 0.79**	7.54 ± 1.10$^{**\#}$	5.58 ± 1.56$^{\#}$
Group Ⅲ	4.90 ± 0.76	5.93 ± 0.82**	6.51 ± 0.91**	6.64 ± 1.05**	5.04 ± 1.72

Compared with T_1, $^{**}P < 0.01$; compared with group Ⅲ, $^{\#}P < 0.05$, $^{\#\#}P < 0.01$.

Table 5 **Levels of plasma cortisol** (U/g/Hb, $\bar{x} \pm sd$)

Group	T_1	T_2	T_3	T_4	T_5
Group Ⅰ	187.4 ± 48.9	225.9 ± 66.2$^{\#}$	266.6 ± 76.1$^{**\#}$	340.1 ± 65.2$^{**\#\#}$	275.3 ± 84.6$^{**\#\#}$
Group Ⅱ	178.5 ± 39.0	186.8 ± 45.1	225.4 ± 54.1**	313.0 ± 74.5$^{**\#}$	231.9 ± 46.3$^{**\#}$
Group Ⅲ	177.8 ± 52.1	190.2 ± 54.5	224.7 ± 65.4**	257.2 ± 85.8**	191.7 ± 50.8*

Compared with T_1, $^{**}P < 0.01$; compared with group Ⅲ, $^{\#}P < 0.05$, $^{\#\#}P < 0.01$.

Table 6 **The plasma epinephrine concentration** (nmol/l, $\bar{x} \pm sd, n = 10$)

Group	T_1	T_2	T_3	T_4	T_5
Group Ⅰ	0.99 ± 0.24	2.28 ± 0.68$^{**\#\triangle}$	2.34 ± 0.94$^{**\#\#}$	2.25 ± 0.44$^{**\#}$	1.44 ± 0.38**
Group Ⅱ	0.99 ± 0.30	1.59 ± 0.78**	1.70 ± 0.59**	2.14 ± 0.37$^{**\#}$	1.35 ± 0.29*
Group Ⅲ	1.07 ± 0.24	1.54 ± 0.70*	1.40 ± 0.45	1.76 ± 0.42**	1.30 ± 0.32

Compared with T_1, $^{**}P < 0.01$; compared with group Ⅱ, $^{\triangle}P < 0.05$, $^{\triangle\triangle}P < 0.01$;compared with group Ⅲ, $^{\#}P < 0.05$, $^{\#\#}P < 0.01$.

Table 7 **The plasma norepinephrine concentration** (nmol/l, $\bar{x} \pm sd, n = 10$)

Group	T_1	T_2	T_3	T_4	T_5
Group Ⅰ	1.28 ± 0.69	1.97 ± 0.93$^{**\#\#}$	2.30 ± 0.99$^{**\#}$	5.31 ± 3.21$^{**\#}$	3.74 ± 1.75**
Group Ⅱ	1.01 ± 0.33	1.32 ± 0.43*	1.81 ± 0.69**	5.04 ± 1.79$^{**\#}$	3.94 ± 1.61**
Group Ⅲ	1.06 ± 0.60	1.27 ± 0.49	1.43 ± 0.46*	2.88 ± 1.71**	3.05 ± 1.76**

Compared with T_1, $^{**}P < 0.01$; compared with group Ⅲ, $^{\#}P < 0.05$, $^{\#\#}P < 0.01$.

DISCUSSION

In this study, we investigated whether TEA or intravenous PCA and GEA or GA have beneficial effects on perioperative plasma hormones and activities of erythrocyte glycometabolism enzymes.

Epinephrine and norepinephrine are the most quickly released stress hormones which can be affected by anesthesia and analgesia techniques. Our data showed that the plasma epinephrine and norepinephrine levels of patients receiving general anesthesia combined with epidural anesthesia and thoracic epidural analgesia (GEA+TEA) were significantly lower than those of patients receiving general anesthesia and intravenous analgesia(GA+PCA) and GEA+PCA, as were the levels of plasma cortisol. Furthermore, these plasma hormones in GEA+PCA were slightly lower than those in GA+PCA. The results were in accordance with other studies that demonstrated significant attenuation of stress response after epidural blockade[4,5]. This is mainly contributed to local anesthetics or opioids blocking transmission in somatic or sympathetic nerves that have been locally traumatized[1]. However, only preincisional establishment of epidural anesthesia with local anesthetics can prevent the stress response and maintain mediator concentrations at preoperative values. Once the stress response is initiated, postincisional administration of epidural anesthesia can only attenuate the response. This is the reason why epidural analgesia with local anesthetics or opioids should be continued into the postoperative period to maximally reduce the stress response. Use of epidural analgesia in the postoperative period may be critical, as the stress response is maximal immediately after surgery and may continue for as long as 5 days postoperatively. Although the duration of epidural analgesia necessary to provide maximal benefit is unknown, use of epidural analgesia with local anesthetic for only 24 h can suppress the catabolic component of the stress response(nitrogen balance, muscle amino acid composition) for as long as 5 days[6]. In contrast, use of intravenous PCA for postoperative analgesia relieves pain, but the stress response is unaltered. Thus, use of epidural anesthesia followed by epidural analgesia with local anesthetic results in the greatest observed reduction of the perioperative stress response.

In the present study hyperglycemia persisted not only during the operation, but also on the 2nd postoperative day. Epinephrine, norepinephrine and cortisol are hormones that promote elevated blood glucose levels. In addition, periopertive hyperglycemia is also associated with insulin resistance[7,8]. Many factors, including pain, can induce insulin resistance. Greisen et al[9] reported that acute pain could degrade insulin sensitivity while pain relief could recover it. In our study, the VAS scores at 12h and 24h were lowest in the GEA+TEA group, which suggested that epidural blockade might not only relieve pain but also be beneficial to glucose metabolism. Our previous studies found that the activity of PFK in erythrocytes is depressed, while the activities of G-6PD and AR are significantly increased on the 1st postoperative day in patients undergoing abdominal or thoracic surgery. Compared with GA, GEA could moderate these changes[2,3]. In the present study our results confirmed the previous findings. Furthermore, in this study we found postoperative analgesia could also affect these enzymes activities. Postoperative TEA might have less effect on the activities of enzymes than intravenous PCA, so we supposed that GEA+TEA might result in less of a surgical stress effect on erythrocyte glycometabolism.

Our previous study suggested that the depressed activity of PFK on the 1st postoperative day was consistent with trauma resulting in the release of reactive oxygen species(ROS). Asahina et al[10] found H_2O_2 could depress the activity of PFK, especially under hyperglycemic conditions, decreasing activity by 39%. Kashiwagi et al[11] also observed H_2O_2 could promote the activity of G-6PD by 4-7 times. We speculated that the pentose phosphate pathway was activated so as to produce more NADPH, a coenzyme of GSH. GSH then acted as an antioxidant, protecting erythrocyte from oxidative damages. Cytokines such as TNF-α and IL-1 can induce leukocyte respiratory bursting and pro-duce excessive ROS[12,13]. Epidural local anesthetics could act to decrease the release of TNF- α and IL-1[14,15]. Excessive catecholamines also result in the production of ROS[16,17]. This could explain why the effect of surgery on the activities of these enzymes was so attenuated in group Ⅲ patients.

Normal plasma glucose has no effect on the activation of polyol pathway, while hyperglycemia could have had an effect on the 1st postoperative day[18]. He et al[19] found glucose could induce AR gene expression and activate the enzyme, and the longer the duration of the high glucose levels, the greater the AR activity. In the present study the postoperative elevation of plasma glucose levels paralleled the increased AR activity, with the smallest changes being seen in the Group Ⅲ patients. Sorbitol is the endpoint in the polyl pathway and it may contribute to oxidative damage in the stress response. Thus, in this way hyperglycemia contributes to the adverse effect of oxidative damage.

In conclusion, compared with general anesthesia and intravenous analgesia, general anesthesia combined with epidural anesthesia and analgesia could markedly alleviate the stress response, obtain better pain relief and

improve the erythrocyte glucose metabolism changes that occurred after esophagus surgery.

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