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***Observational Study***

**Sequential blood purification therapy for critical patients with** **hyperlipidemic severe acute pancreatitis**

Wang HL *et al.* Sequential blood purification therapy

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**Abstract**

**AIM:** To evaluate the efficacy of sequential blood purification therapy in the treatment of critical patients with hyperlipidemic severe acute pancreatitis (SAP).

**METHODS:** Thirty-one intensive care unit (ICU) patients with hyperlipidemic SAP treated at the Second Affiliated Hospital of Harbin Medical University were divided into either a study group (*n* = 15, July 1, 2012 to June 30, 2014) or a control group (*n* = 16, July 1, 2010 to June 30, 2012) based on the implementation of sequential blood purification therapy or not. The control group received continuous venous-venous hemofiltration (CVVH) on the basis of conventional treatments, and the therapeutic dose of CVVH is 30 mL/kg/h. The study group received sequential plasma exchange and CVVH on the basis of conventional treatments. The anticoagulation regimen of CVVH is the regional citrate anticoagulation. Mortality rate on day 28, rates of systemic and local complications, duration of ICU, and time to target serum lipid level, as well as physiological and laboratory indexes were compared for the two groups.

**RESULTS:** The mortality rate on day 28 was significantly lower in the study group than in the control group (13.33% *vs* 37.50%, *P <* 0.05). The duration of ICU stay was significantly shorter in the study group than in the control group (7.4 ± 1.35 d *vs* 9.19 ± 2.99 d, *P =* 0.042). The time to target serum lipid level was significantly shorter in the study group than in the control group (3.47 ± 0.52 d *vs* 7.90 ± 1.14 d, *P <* 0.0001). There were no significant differences in the rates of systemic complications and local complications between the two groups (60% *vs* 50%, *P =* 0.7224; 80% *vs* 81.25%, *P =* 1.0000). In the comparisons of physiological and laboratory indexes, serum albumin and C-reactive protein were significantly better in the study group than in the control group (37.8 ± 4.6 g/L *vs* 38.9 ± 5.7 g/L; 20.5 ± 6.4 mg/L *vs* 28.5 ± 7.1 mg/L, *P <* 0.05) after treatment,. Other indexes except plateletcrit showed no significant (*P* > 0.05) differences between the two groups.

**CONCLUSION:** Sequential blood purification therapy has good efficacy in the treatment of ICU patients with hyperlipidemic SAP and can improve patients’ prognosis.

**Key words:** Sequential blood purification; Hyperlipidemic severe acute pancreatitis; Plasma exchange; Continuous venous-venous hemofiltration

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**Core tip:** Plasma exchange (PE) and continuous venous-venous hemofiltration (CVVH) has a certain clinical effect in the treatment of hyperlipidemia acute severe pancreatitis, but there is not the standardized combination therapy of PE and CVVH so far. The recent international consensus of pancreatitis launched the 2012 latest revised edition. Based on the 2012 Atlanta International pancreatitis Consensus, we designed a sequential mode of combined application of sequential PE and CVVH for the treatment of hyperlipidemia acute severe pancreatitis. Our sequential blood purification therapy has good efficacy in the treatment of intensive care unit patients with hyperlipidemic severe acute pancreatitis (SAP) and can improve patients’ prognosis. We hope that our study can promote the standardized treatment process of blood purification for hyperlipidemic SAP.

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**INTRODUCTION**

According to the 2012 Atlanta classification of acute pancreatitis (AP), AP is divided into three categories: mild, moderate and severe[1]. In contrast to the low mortality of mild AP, severe AP (SAP) is associated not only with a high mortality rate, but also with a high rate of complications[2]. So far, many treatment strategies for AP have been developed. In addition to common surgical treatment, peritoneal lavage, organ support therapy, and endoscopic retrograde cholangiopancreatography (ERCP), blood purification therapy is also a promising treatment. Despite these therapies, the treatment of SAP is still a great challenge, and its mortality rate can still reach 15%-25%[3]. SAP is characterized by persistent organ failure, and the risk of death is especially higher in the first several days of organ failure (36%-50%)[4-6]. Therefore, there is an urgent need to further improve the survival rate of patients with SAP. Currently, the utility of a paradigm involving a multidisciplinary team typically including general surgeons, gastroenterologists, radiologists and intensive care unit (ICU) physicians is advocated in the clinical treatment of SAP[7]. In the critical care of SAP, organ support technology, especially continuous renal replacement therapy (CRRT), has a key role. At present, the most common causes of AP including gallstone diseases, excessive alcohol consumption, and pregnancy. Compared with AP of common causes, hyperlipidemic AP accounts for only 1%-4%[8,9]. In terms of the etiology of AP, when triglyceride level is above 1000 mg/dL, hyperlipidemic AP is considered. At present, it is believed that hyperlipidemic AP is related to pancreatic tissue (pancreatic ducts and acini cells) injury and microcirculation disturbance caused by free fatty acids that are produced by pancreatic lipase-catalyzed decomposition of triglycerides. With the progression of the disease, the enzymes, fatty acids and inflammatory mediators in pancreatic tissue enter into the systemic circulation and participate in the development of multiple organ dysfunction, thus leading to the failure of one or multiple organs[2,10]. There is evidence that multiple organ failure subsequent to systemic inflammatory response syndrome caused by pancreatic inflammation is the main reason of death in patients with pancreatitis. In the past few years, the use of blood purification technology in the treatment of ICU patients with AP has increased year by year. Continuous venous-venous hemofiltration (CVVH) is one of the most commonly used blood purification procedures in ICU patients, and it can selectively remove inflammatory factors in the body and effectively eliminate the inflammatory cytokine storm. For acute kidney injury (AKI) patients, CVVH can remove toxins in the body and reduce water retention. In patients with hyperlipidemic AP, the application of plasma exchange (PE) allows for rapid and efficient removal of serum lipids, and reduces triglyceride levels and the production of free fatty acids, thus weakening pancreatic self-digestion by trypsin. In addition, PE can improve pancreatic tissue microcirculation and relieve high blood coagulation state, ultimately achieving the goal of treatment of AP. In theory, PE is very beneficial to the treatment of hyperlipidemic SAP[11-13].

So far, there have been many small sample-sized clinical studies confirming that PE and CVVH are conducive to improving mortality in patient with either severe pancreatitis or hyperlipidemic SAP. Moreover, a recent study demonstrated that combined use of PE and CVVH has more advantages in patients with severe pancreatitis[14-16]. However, despite a large number of existing clinical studies, there have been no standardized criteria for the combination of PE and CVVH for SAP, and this has led to conflicting conclusions. In addition, because the samples patients were selected randomly in many previous studies, they could not effectively evaluate the clinical efficacy of the combination therapy of PE and CVVH. The present study was designed to further evaluate the clinical efficacy of PE combined with CVVH in the treatment of ICU patients with hyperlipidemic SAP.

**MATERIALS AND METHODS**

***Patient characteristics***

This study was divided into two stages based on the implementation of sequential blood purification therapy or not. The patients (*n* = 16) treated from July 1, 2010 to June 30, 2012 underwent conventional treatments and CVVH and were included in a control group (group B), and those (*n* = 15) treated from July 1, 2012 to June 30, 2014 received conventional treatments with sequential blood purification therapy and comprised a study group (group A).

Inclusion criteria were: (1) diagnosis of pancreatitis (meeting at least two of the following three criteria): abdominal pain typical of pancreatitis; serum amylase and/or lipase levels ≥ three times the upper limit of normal; evidence of pancreatitis on abdominal imaging; (2) diagnosis of severe pancreatitis: Marshall score ≥ 2; and (3) diagnosis of hyperlipidemic pancreatitis: serum triglycerides > 1000 mg/dL. Exclusion criteria were: (1) pancreatic cancer; (2) gallstones; (3) more than five years of history of heavy drinking (more than 50 g/d); (4) younger than 18 years of age or older than 60 years; and (5) not receiving PE/CVVH within five hours after admission to ICU. Withdrawal criterion was that the patient himself/herself or the authorized person requested to withdraw from the study. Indications for discontinuation of therapy were: (1) disappearance of specific abdominal symptoms; (2) Marshall score < 2; and (3) serum triglycerides < 500 mg/dL[17].

***Research scheme***

The study group received sequential blood purification therapy, which involved the initial PE with freshly frozen plasma (at least 3000 mL per day) until serum triglycerides < 500 mg/dL and subsequent CVVH until the disappearance of specific abdominal symptoms and Marshall score < 2. The control group received conventional treatments and CVVH, *i.e.*, lipid-lowering drugs (simvastatin with fenofibrate, 20 + 200 mg/d[17]) plus CVVH, until the disappearance of specific abdominal symptoms, Marshall score < 2, and serum triglycerides < 500 mg/dL.

***RRT settings***

PE was performed using a FLEX system with the TPE 2000 set *via* a polysulfone filter, and the velocity was set at 30 mL/min. CVVH was performed using a FLEX system with the M100 set *via* an AN69 filter, and the parameters were as follows: therapeutic dose, 30 mL/kg/h; blood flow velocity, 150-180 mL/min; dilution mode, pre-dilution 100%; frequency of filter replacement, 8-12 h (depending on transfilter pressure); permissible transfilter pressure, 0-300 mmHg; anticoagulation regimen, regional citrate anticoagulation (4% sodium citrate and 100 mmol/L calcium chloride); detection range for free Ca2+ ion before filter, 0.25-0.35 mmol/L; and detection range for free Ca2+ ion after filter, 1.12-1.20 mmol/L[18,19].

***Conventional treatments***

Conventional treatments applied to the study group and control group included fasting, fluid resuscitation, oxygen therapy, gastrointestinal decompression, somatostatin, and organ support therapy.

***Clinical parameters***

The primary outcome measure was mortality on day 28[14], and secondary outcome measures [15] were rate of systemic complications, rate of local complications, duration of ICU stay, and time to target serum triglyceride level (< 500 mg/dL). Systemic complications included: (1) pulmonary insufficiency (PaO2 < 8 kPa); (2) renal insufficiency (Cr > 2 mg/dL); (3) shock (SB*P <* 12 kPa); and (4) UGI bleeding > 500 mL/24h. Local complications included pylorus dysfunction, peripancreatic effusion, pancreatic pseudocyst, spleen vein and portal vein thrombosis, colon necrosis, necrotic collection and walled-off necrosis. In addition, physiological and laboratory indexes were also compared after treatment between the two groups. The physiological indexes included BT (°C), HR (beats/min), BP (mm Hg), RR (beats/min), MAP (mmHg), and PaO2 / FiO2. Laboratory indexes included WBC (109/L), plateletcrit (109/L), albumin (ALB) (g/L), ALT (U/L), TBIL (mmol/L), BUN (mmol/L), Scr (mmol/L), Ca (mmol/L), bicarbonate(mmol/L), serum amylase(U/L), urine amylase (U/L), C-reactive protein (CRP) (mg/L), and PCT (ng/mL).

***Statistical analysis***

Measurement data are expressed as mean ± standard deviation, and count data are expressed as number of cases (or percentage). Survival analysis was performed using the Kaplan-Meier method. Mortality on day 28, secondary indexes (systemic complications, rate of local complications, duration of ICU stay and time to target serum triglyceride level), as well as physiological and laboratory indexes after treatment were compared using the *t*-test between the two groups. Statistical analyses were performed using SAS9.1.3 statistical software, and *P* < 0.05 were considered statistically significant.

**RESULTS**

Table 1 shows the baseline characteristics of patients in the study group (group A) and the control group (group B). There were no significant differences in the baseline characteristics between the two groups (*P* > 0.05).

Kaplan-Meier survival analysis showed that the mortality rate on day 28 was 13.33% and 37.50% in the study group and control group, respectively. As time went on, the mortality rate was significantly lower in the study group than in the control group (Figure 1).

For secondary outcome measures, the duration of ICU stay and the time to target serum lipid level were significantly shorter in the study group (group A) than in the control group (group B) (7.4 ± 1.35 d *vs* 9.19 ± 2.99 d, *P =* 0.042; 3.47 ± 0.52 day *vs* 7.90 ± 1.14 d, *P <* 0.0001) (Table 2). The rate of systemic complications was 60% for the study group and 50% for the control group. The rate of local complications was 80% for the study group and 81.25% for the control group. There were no significant differences in the rates of systemic complications and local complications between the two groups (*P* > 0.05) (Table 2).

The comparisons of physiological and laboratory indexes between the two groups are shown in Tables 3 and 4. After treatment, serum ALB and CRP were significantly better in the study group than in the control group (37.8 ± 4.6 g/L *vs* 38.9 ± 5.7 g/L; 20.5 ± 6.4 mg/L *vs* 28.5 ± 7.1 mg/L, *P <* 0.05). Other indexes except PCT showed no significant differences between the two groups.

**DISCUSSION**

Hyperlipidemic SAP is clinically characterized by heavy symptoms, many complications, easy recurrence, and poor prognosis. It is common in obese, young or middle-aged men, most of which have bad living habits such as high fat diet. Evidence has shown that control of serum triglyceride < 500 mg/dL can prevent further progression of pancreatitis[17]. It is well known that hyperlipidemia causes acute pancreatitis mainly through the complex interplay among high serum triglyceride level, increased free fatty acids, reduced activity of trypsin and activated inflammatory factors to eventually lead to pancreatic tissue inflammation. A high level of serum triglyceride destroys the protection function of the pancreas, causes abnormal pancreatic enzyme activation and pancreatic self-digestion, and result in the release of a large amount of various proinflammatory factors, thereby causing a cascade effect[10]. Therefore, lowering serum triglyceride level is the primary goal of early treatment of hyperlipidemic SAP.

To lower high serum triglyceride levels in patients with pancreatitis, oral lipid-lowering drugs (typically fibrates) are usually used in clinical settings. Meanwhile, fat-free parenteral nutrition preparations are often administered. When patients with hyperlipidemic SAP become seriously ill and are transferred to the ICU, physicians may utilize the PE technology to rapidly lower serum triglyceride levels so as to prevent the progression of pancreatic inflammation. When hyperlipemia is effectively relieved, the cause of disease progression and aggravation is effectively eliminated. Previous clinical studies on the use of PE in the treatment of hyperlipidemic SAP have demonstrated that PE has a good curative effect (especially for lowering serum lipid) and is safe[20,21]. The present study compared the time to target serum triglyceride level (<500 mg/dL) between PE and use of oral lipid-lowering drugs and found that the former had certain advantages.

When serum triglyceride levels in pancreatitis patients are effectively controlled, the clinical treatment goal shifts to regulating the body's inflammatory response and volume status. CVVH achieves the purpose of treatment by regulating fluid balance and removing inflammatory mediator and toxins[22]. PE combined with CVVH for treatment of hyperlipidemic SAP can improve the clinical effects of PE alone in terms of rapidly decreasing the body's inflammatory factors and, at the same time, adjusting and optimizing patients’ circulation state[23,24]. For this reason, the present study sequentially utilized PE to lower lipid levels and then CVVH to effectively reduce the SIRS and optimize circulation state. In addition, application of CVVH can clear allergic reaction related antigens and antibodies generated during PE treatment due to the transfusion of allogeneic plasma, and further optimize the therapeutic effect, thus ensuring the safety of the treatment. Fortunately, no allergic transfusion reactions occurred in our patients, thus reducing the impact on the implementation of PE. In view of this, although the rate of systemic complications (60%) in the study group was higher than that in the control group (50%), the duration of ICU stay was significantly shorter in the study group than in the control group (7.4 ± 1.35 d *vs* 9.19 ± 2.99 d, *P =* 0.042).

Although this study is not a randomized controlled trial, its design was different from that of many previous studies with arbitrarily selected patients, in which the duration of blood purification treatment as well as the combination of blood purification therapies are arbitrary. In the present study, a target oriented sequential therapy protocol was used. This allowed us to monitor the relatively complete clinical course of patients with hyperlipidemic SAP, thus ensuring the credibility of subsequent evaluation of disease outcome and prognosis. However, given that hyperlipidemic SAP is relatively not very common[25,26], recruitment of much more patients is somewhat difficult. Future larger sample-sized, randomized controlled multicenter clinical studies are expected. In addition, despite many unpredictable variations in clinical trials and that there were no significant differences in the secondary outcome measures between the two groups, the sequential treatment group was associated with a better survival rate and some significantly improved laboratory indexes such as C-reactive protein (*P <* 0.05), suggesting that the application of sequential blood purification treatment in the management of ICU patients with hyperlipidemic SAP is feasible, effective and safe.

Hyperlipidemia is either one of the causes or a consequence of AP[27-30], and even may be both in some cases. However, there is still controversy over this point of view. The pathogenesis of hyperlipidemia induced AP is still under study, and signaling pathways that have an exact association with hyperlipidemic SAP are being explored. Future treatment of pancreatitis may be based on targeted therapies that can block hyperlipidemia induced pancreatic injury. Currently, there have been no standardized criteria for the selection of blood purification procedures and parameters for ICU patients with different stages of pancreatitis. These will be our future important research topics and directions. It is currently well recognized that the treatment of hyperlipidemic SAP relies greatly on early, rapid lowering of blood lipid levels in combination with routine therapies for AP. For early lipid-lowering effects, plasma exchange has better efficacy than the use of lipid-lowering drugs. The subsequent application of blood filtration technology and conventional treatments for acute pancreatitis is the current good practice for the treatment of ICU patients with AP.

**COMMENTS**

***Background***

Hyperlipidemia is a common cause of acute pancreatitis with leading pancreatic tissue inflammation. The pancreatic tissue inflammation can lead to secondary systemic inflammatory response syndrome and multiple organ failure. Multiple organ failure is the main cause of death in patients with severe acute pancreatitis. Many studies showed that, the plasma exchange (PE) combined with continuous venous-venous hemofiltration (CVVH) in the treatment of severe acute pancreatitis (SAP) had certain clinical benefit. However, many clinical studies did not have the standardized treatment so far. Therefore, we cannot assess the validity of their study.

***Research frontiers***

In the past few years, the use of blood purification treatment of pancreatitis has increased year by year in intensive care unit (ICU). In the treatment of hyperlipidemia pancreatitis aspect, the current research focus is how to reduce the mortality of patients and improve the prognosis of patients with the combined application of PE and CVVH.

***Innovations and breakthroughs***

Based on the 2012 Atlanta International Pancreatitis Consensus, the authors designed a sequential mode of combined application of sequential PE and CVVH for the treatment of hyperlipidemia acute severe pancreatitis. Compared with the past research, we designed a relatively reasonable treatment process for improving hyperlipidemic SAP patients’ prognosis.

***Applications***

This sequential blood purification therapy has good efficacy in the treatment of ICU patients with hyperlipidemic SAP and can improve patients’ prognosis.

***Terminology***

Severe acute pancreatitis is refers to the acute pancreatitis with more than 48 h persistent multiple organ failure (Marshall Score = 2). In the etiology of acute pancreatitis, when triglyceride was higher than 1000 mg/dl, it can consider to that acute pancreatitis was caused by hyperlipidemia. In this case, we call it the hyperlipidemic acute pancreatitis. In addition, PE or CVVH was the common organ support technology in the ICU.

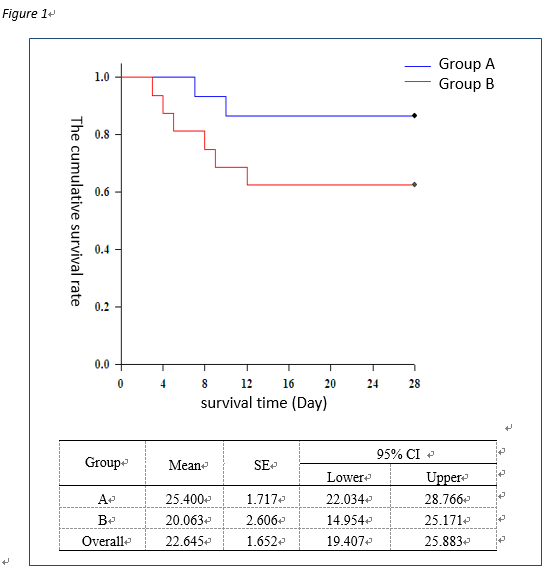
***Peer-review***

This observational study is a very interesting manuscript about sequential blood purification therapy for intensive care unit patients with hyperlipidemic SAP. In this manuscript, the authors evaluated the efficacy of sequential blood purification therapy in the treatment of intensive care unit patients with hyperlipidemic SAP and its impact on prognosis.

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**Figure 1 Kaplan-Meier survival curve.**

**Table 1 The baseline characteristics of patients in the two groups**

|  |  |  |  |
| --- | --- | --- | --- |
|  | Group A  (*n* = 15) | Group B  (*n* = 16) | *P* value |
| Age (yr) | 42.6 ± 9.9 | 40.9 ± 12.6 | 0.6806 |
| BMI (kg/m2) | 27.4 ± 4.1 | 28.5 ± 3.7 | 0.4387 |
| Sex (male/female) | 10/5 | 11/5 | 1.0000 |
| Bacterial culture positive | 3 | 4 | 1.0000 |
| Marshall score | 2.6 ± 1.7 | 2.5 ± 1.4 | 0.8590 |
| APACHE II score | 21.3 ± 2.9 | 22.5 ± 2.1 | 0.1952 |
| Upper gastrointestinal bleeding | 7 | 8 | 1.0000 |
| ARDS | 12 | 13 | 1.0000 |
| Heart failure/pulmonary edema | 3 | 2 | 0.6539 |
| DIC | 1 | 2 | 1.0000 |
| Surgical debridement | 1 | 1 | 1.0000 |
| Use of vasopressors | 15 | 16 | 1.0000 |
| Mechanical ventilation | 10 | 10 | 1.0000 |

BMI: Body mass index; ARDS: Acute respiratory distress syndrome; DIC: Disseminated intravascular coagulation.

**Table 2 Comparison of secondary outcome measures between groups A and B**

|  |  |  |  |
| --- | --- | --- | --- |
| **Variable** | **Group A** | **Group B** | ***P* value** |
| Duration of ICU stay (d) | 7.40 ± 1.35 | 9.19 ± 2.99 | 0.0420a |
| Time to target TG (d) | 3.47 ± 0.52 | 7.90 ± 1.14 | < 0.0001a |
| Systemic complications | 9 (60.00) | 8 (50.00) | 0.7224 |
| Local complications | 12 (80.00) | 13(81.25) | 1.0000 |

a*P <* 0.05, group A *vs* group B.

**Table 3 Comparison of physiological variables between groups A and B**

|  |  |  |
| --- | --- | --- |
|  | Group A  (*n* = 15) | Group B  (*n* = 16) |
| BT (℃) | 37.5 ± 0.6 | 37.3 ± 0.4 |
| HR (beats/min) | 86 ± 14 | 90 ± 19 |
| RR (beats/min) | 16 ± 4 | 18 ± 5 |
| MAP (mmHg) | 70.2 ± 9.3 | 67.9 ± 6.0 |
| PaO2/FiO2 | 179.1 ± 41.9 | 167.7 ± 38.9 |

**Table 4 Comparison of laboratory variables between groups A and B**

|  |  |  |
| --- | --- | --- |
|  | Group A  (*n* = 15) | Group B  (*n* = 16) |
| WBC (109/L) | 11.5 ± 2.3 | 13.1 ± 2.9 |
| PLT (109/L) | 196.5 ± 40.5 | 199.6 ± 58.7 |
| ALBa (g/L) | 37.8 ± 4.6 | 38.9 ± 5.7 |
| ALT (U/L) | 54.3 ± 20.4 | 59.7 ± 23.1 |
| TBIL (mmol/L) | 20.1 ± 3.9 | 25.3 ± 4.2 |
| BUN (mmol/L) | 7.8 ± 2.6 | 9.7 ± 2.8 |
| Scr (mmol/L) | 149.8 ± 30.2 | 139.3 ± 37.5 |
| Ca (mmol/L) | 2.1 ± 0.5 | 2.0 ± 0.3 |
| Serum amylase (U/L) | 74.4 ± 28.3 | 82.1 ± 20.7 |
| Urine amylase (U/L) | 399.7 ± 59.7 | 387.1 ± 51.4 |
| CRPa (mg/L) | 20.5 ± 6.4 | 28.5 ± 7.1 |
| PCTa (ng/mL) | 1.33 ± 0.42 | 1.71 ± 0.61 |

a*P <* 0.05, group A *vs* group B. WBC: White blood cell; ALB: Albumin; ALT: Alanine transaminase; TBIL: Total bilirubin; BUN: Urea nitrogen.