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ORIGINAL RESEARCH

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Effect of epirubicin combined with docetaxel on inflammatory factors, cytokines, tumor markers, clinical efficacy and adverse reactions in patients with cervical cancer after surgery

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Abstract

To investigate the clinical efficacy of epirubicin combined with docetaxel in postoperative patients with cervical cancer. A total of 124 postoperative cervical cancer patients were randomly allocated into two groups: the control group (n = 62) and the experimental group (n = 62), using a random number table. Patients in both groups underwent extensive hysterectomy, pelvic nerve-sparing lymphadenectomy, and other surgical interventions as deemed necessary. Postoperatively, the control group received intravenous epirubicin, while the experimental group received intravenous docetaxel in addition to epirubicin. After 3 courses of treatment, the serum levels of interleukin-2 (IL-2), IL-6, IL-4 and interferon γ (IFN-γ) in the experimental group were lower than that in the control group. The levels of IL-2/IL-6, IFN-γ/IL-4, IL-2/IL-4 and IFN-γ/IL-6 were lower than that in the control group. The serum levels of carbohydrate antigen 125 (CA125), carcinoembryonic antigen (CEA), cytokeratin 19 fragment (CYFRA21-1) and squamous cell carcinoma antigen (SCC-Ag) were lower than that in the control group. The disease control rate was 74.19% (46/62), higher than 56.45% (35/62) in the control group. The incidence of adverse reactions was 6.45% (4/62), lower than 19.35% (12/62) in the control group. The combination of epirubicin and docetaxel demonstrates efficacy in the treatment of postoperative cervical cancer.

Keywords

Epirubicin; Docetaxel; Postoperative cervical cancer; Clinical efficacy

1. Introduction

Cervical cancer presents a significant health risk to women worldwide, with its incidence and mortality rates varying according to economic status and geographic location [1]. It ranks as the second most prevalent cancer among women, trailing only endometrial and breast cancers. Annually, an estimated 500,000 new cases arise, with approximately 410,000 occurring in developing nations and 135,000 in China alone [2]. Despite advances in treatment, including widespread cervical cancer management, some patients still experience metastasis, recurrence, and mortality [3]. Factors such as increased human papillomavirus (HPV) infections contribute to a rise in cervical cancer cases, often affecting younger populations [4]. Persistent HPV infection, along with other high-risk factors such as human cytomegalovirus, herpes simplex virus, contraceptive methods, chronic cervical lesions, and lifestyle factors like smoking and sexual behavior, are closely linked to cervical cancer [5].

Symptoms of cervical cancer can manifest at various stages, including abnormal bleeding, vaginal discharge, lower abdominal pain, lower limb swelling and pain, and rectal discomfort, significantly impacting women's well-being and life expectancy. Current treatment strategies for cervical cancer typically consider the clinical stage and individual clinical conditions, which may influence treatment outcomes [6]. Surgical interventions and radiotherapy are commonly employed for patients with tumor stages Ia to Ib and tumor diameters less than 2 cm, with options like pelvic nerve-sparing lymphadenectomy and extensive hysterectomy being considered for preserving reproductive function in young nulliparous patients. In cases of advanced local lesions, radiotherapy may be initiated initially to reduce tumor burden [7–9]. Studies indicate that patients with tumor stages $\geq$IIb often experience decreased long-term survival rates and control rates with radiotherapy alone, leading to local recurrence and distant metastasis, necessitating combination therapies with other drugs for optimal outcomes.

Docetaxel, a novel anticancer drug derived from paclitaxel, exhibits low toxicity and high efficacy. Its mechanism of action involves inhibiting microtubule destruction, thereby inducing tumor cell death [10, 11]. Epirubicin, an antibiotic with potent anti-tumor properties, penetrates DNA base pairs

directly, interfering with the transcriptional process, mRNA production, and DNA/RNA synthesis [12]. Currently, limited research exists on the combined effects of epirubicin and docetaxel on inflammatory factors, cytokines, tumor markers, clinical efficacy, and adverse reactions following cervical cancer surgery [13]. Therefore, this study aims to explore the potential therapeutic value of combining epirubicin and docetaxel in postoperative cervical cancer patients. By investigating this combination therapy, we aim to provide insights into its efficacy, safety and clinical impact.

2. Materials and methods

2.1 Clinical data

A total of 124 patients diagnosed with cervical cancer who underwent surgery between February 2019 and February 2020 at our hospital were enrolled in this study. They were randomly allocated into two groups: the control group (n = 62) and the experimental group (n = 62) using a random number table.

The study inclusion criteria were: (1) confirmed diagnosis of cervical cancer through pathological examination, (2) a projected survival time of more than 6 months, (3) demonstrated high compliance with the proposed treatment, and (4) patients and their families had been informed and provided signed the consent form.

The exclusion criteria were as follows: Patients with blood system diseases, severe organic diseases, immune system disorders, mental or cognitive impairments, heart, liver or kidney dysfunction, prior history of chemotherapy or radiotherapy, or allergic constitutions were excluded from the study.

In the experimental group, the age of the patients ranged between 39 and 76 years, with a mean age of (55.03 $\pm$ 6.48) years. Their body mass index ranged from 19 to 27 kg/m^2 (mean, 23.11 $\pm$ 1.28 kg/m^2), and their tumor diameter ranged from 5 to 8 cm (mean, 6.11 $\pm$ 0.70 cm). Among the participants, 30 cases were classified as Federation International of Gynecology and Obstetrics (FIGO) stage IIb, while 32 cases were classified as IIa. Pathological categories included 31 cases of squamous cell carcinoma and 31 cases of adenocarcinoma.

In the control group, the age ranged from 36 to 71 years, with a mean age of (57.05 $\pm$ 6.74) years. The body mass index ranged from 19 to 27 kg/m^2, with an average of (22.63 $\pm$ 1.50) kg/m^2. Tumor diameter ranged from 4 to 7 cm, with an average of (6.15 $\pm$ 0.70) cm. Among the participants, 29 cases were classified as FIGO stage IIb, while 33 cases were classified as IIa. Pathological categories included 28 cases of squamous cell carcinoma and 34 cases of adenocarcinoma. Baseline data demonstrated balance and comparability between the two groups ($p > 0.05$).

2.2 Surgical procedure

Extensive hysterectomy and pelvic nerve-sparing lymphadenectomy were performed in both groups according to the following surgical procedures: Firstly, laparoscopic dissection of pelvic lymph nodes was conducted. The iliac vessels were exposed, and blunt dissection was performed to fully expose the bladder and rectal spaces. Uterine arteries and veins were clamped using forceps, followed by dissection with an ultrasonic scalpel to strip the parametrial fat structure of the cardinal ligament to obtain the rectal and bladder spaces. Subsequently, dissection of the uterosacral ligaments and ureteral mesentery was performed to expose the bladder and anterior and posterior uterine spaces. The utero-rectal peritoneum was transected, and the uterosacral ligaments were divided and closed. The utero-peritoneum was opened to expose the lateral vaginal space, and the anterior lobe of the cervical ligaments and the apical artery ureter of the utero-urinary catheter were separated. Paravaginal tissues and deep cervical ligaments were then detached. The bladder and anterior and posterior spaces of the uterine ligaments were clamped, and the veins and uterine branches were divided to ensure the patency of the anterior and posterior spaces of the vesicouterine ligament. The uterus and corresponding vaginal side were removed, followed by freeing the bladder on the lateral wall of the vaginal vault to a resectable degree. Absorbable sutures were used to suture the vaginal stump, and pelvic irrigation was performed after suturing. Lastly, a drainage tube was placed.

2.2.1 Control group

In the control group, epirubicin (manufactured by Zhejiang Hisun Pharmaceutical Co., Ltd., with State medical permit number H20183145, strength: 10 mg, Taizhou, Zhejiang, China) was administered *via* intravenous drip at 60–75 mg/m^2.

2.2.2 Experimental group

In the experimental group, docetaxel (manufactured by Beijing Union Pharmaceutical Factory, with State medical permit number: H20093744, strength: 0.5 mL containing 20 mg, Beijing, China) was added to the treatment regimen following the protocol of the control group. Docetaxel was given on the second day of treatment at 75 mg/m^2. It was dissolved in 500 mL of 5% glucose solution and administered intravenously over 2 hours.

Each treatment cycle lasted 21 days, and both the experimental and control groups underwent three treatment cycles.

2.3 Outcome measures

(1) Inflammatory factors: Levels of interferon γ (IFN-γ), interleukin-2 (IL-2), interleukin-4 (IL-4), and interleukin-6 (IL-6) were compared between the two groups before and after 3 courses of treatment. Peripheral venous blood (approximately 4 mL) was collected and centrifuged for 15 minutes (rotation speed: 3500 r/min, radius: 8 cm). Serum separation was achieved using a kit provided by Shanghai Enzyme-linked Biotechnology Co., Ltd. (100190, Shanghai, China), followed by an enzyme-linked immunosorbent assay (ELISA) for assessment.

(2) Cytokines: the ratios of Th1/Th2, IL-2/IL-4, IFN-γ/IL-4, IL-2/IL-6 and IFN-γ/IL-6 values were calculated and compared between the two groups before and after the 3 courses of treatment.

(3) Tumor markers: Levels of carbohydrate antigen 125 (CA125), carcinoembryonic antigen (CEA), cytokeratin 19 fragment (CYFRA21-1), and squamous cell carcinoma antigen

(SCC-Ag) were compared between the two groups before and after 3 courses of treatment. Briefly, peripheral venous blood (approximately 4 mL) was centrifuged for 15 minutes (rotation speed: 3500 r/min, radius: 8 cm), and the serum was separated. CEA and CA125 levels were determined using ELISA kits. Serum CYFRA21-1 levels were measured using a chemiluminescence kit (100211, Shanghai, China) provided by Abbott Laboratories (USA), and SCC-Ag levels were measured using a Chemiluminescent Detector kit provided by Shenzhen Dakota Biotechnology Co., Ltd (111032, Shenzhen, China).

(4) Clinical efficacy comparison: Clinical efficacy was evaluated in both groups following completion of 3 treatment cycles. Evaluation criteria included a tumor diameter reduction of $\geq$50% lasting >4 weeks, the patients conditions were stable between partial responses and progression, and a tumor diameter increase of $\geq$25% or identification of new lesions indicating progression. The disease control rate encompassed complete response, partial response, and stable disease, with complete response and partial response contributing to the objective response rate.

The definitions were as follows: Complete response indicated the disappearance of tumor cells persisting for at least 1 month. Partial response was characterized by a reduction in tumor diameter of at least 60%, persisting for at least 1 month. Stable disease denoted a decrease in tumor diameter ranging from 20% to 60%, persisting for at least 1 month. Progression was defined as a decrease or increase in tumor diameter of $\leq$20% or identification of new lesions. The disease control rate was calculated as the sum of complete response, partial response, and stable disease.

(5) Analysis and Comparison of Adverse Reactions Incidence: Incidence rates of adverse reactions, including gastrointestinal reactions, radiation proctitis, bone marrow suppression, and radiation cystitis, were analyzed and compared between both groups.

2.4 Statistical methods

The data were analyzed using SPSS 27.0 (International Business Machines Corporation, Armonk, NY, USA). Measurement data that adhered to a normal distribution are presented as mean $\pm$ standard deviation ($\pm$sd), while measurement data that did not follow a normal distribution were displayed as median (interquartile range) (M (Q1, Q3)). The *t*-test was used for comparisons involving normally distributed data, whereas the rank sum test was used for non-normally distributed data. Enumeration data were expressed as number and percentage (n (%)). Group comparisons for enumeration data were conducted using the χ^2 test, with $p < 0.05$ indicating statistical significance.

3. Results

3.1 Comparison of inflammatory factors between both groups

Before the treatment, our data showed no significant differences in serum levels of IL-2, IL-6, IL-4 and IFN-γ between both groups ($p > 0.05$), which were then improved in both groups compared to before treatment. Notably, the experimental group had significantly lower levels of these inflammatory factors than the control group ($p < 0.05$). These results are summarized in Table 1.

3.2 Comparison of cytokines between both groups

Before treatment, we observed no significant differences in IL-2/IL-6, IFN-γ/IL-4, IL-2/IL-4 and IFN-γ/IL-6 levels between both groups ($p > 0.05$). However, after treatment, their levels in both groups were found to be lower than before treatment, with the experimental group exhibiting significantly lower levels compared to the control group ($p < 0.05$). These findings are presented in Table 2.

3.3 Comparison of tumor marker indicators between the two groups

Before treatment, there were no significant differences in serum levels of CA125, CEA, CYFRA21-1 and SCC-Ag between the two groups ($p > 0.05$). However, after treatment, the serum levels of CA125, CEA, CYFRA21-1 and SCC-Ag in both groups were lower than before treatment, with the experimental group showing significantly lower levels than the control group ($p < 0.05$). These results are presented in Table 3.

3.4 Comparison of clinical efficacy between both groups

The disease control rate in the experimental group was 74.19% (46/62), which was significantly higher than the control group's rate of 56.45% (35/62) ($p < 0.05$). These findings are detailed in Table 4.

3.5 Comparison of adverse reactions between both groups

The incidence of adverse reactions in the experimental group was 6.45% (4/62), significantly lower than the control group's incidence of 19.35% (12/62) ($p < 0.05$). These results are shown in Table 5.

4. Discussion

Studies have reported associations between cervical cancer incidence and factors such as smoking, sex hormone secretion disorders, HPV infection, early marriage, and early childbearing [14]. The extent and depth of tumor invasion in cervical cancer significantly influence treatment strategies and prognoses. In addition, disease progression, which may occur due to the generation of new blood vessels by tumor cells to promote tumor invasion, prompts adjustments in treatment modalities [15]. In the early stage of cervical cancer, the pelvic lymph node metastasis rate is approximately 15%, and this is often managed with extensive hysterectomy and pelvic nerve-sparing lymphadenectomy. This approach enhances safety and facilitates rapid recovery while preserving normal lymph nodes and reducing damage to surrounding tissues [16, 17]. However, surgical intervention may impact pelvic autonomic

TABLE 1. Comparison of inflammatory factors between both groups (pg/mL, $\bar{x} \pm s$).

Indicator	Experimental group (n = 62)	Control group (n = 62)	*t* value	*p* value
IL-2				
Before treatment	49.14 ± 4.61	49.12 ± 4.97	0.023	0.982
After 3 courses of treatment	27.21 ± 4.98	32.54 ± 3.87	6.654	<0.001
t value	25.445	20.726		
p value	<0.001	<0.001		
IL-6				
Before treatment	20.54 ± 4.59	20.88 ± 4.65	0.410	0.683
After 3 courses of treatment	14.35 ± 4.01	16.32 ± 4.13	2.695	<0.001
t value	7.997	5.773		
p value	<0.001	<0.001		
IL-4				
Before treatment	23.69 ± 4.14	24.51 ± 4.07	1.112	0.268
After 3 courses of treatment	17.34 ± 3.21	19.99 ± 4.55	3.747	<0.001
t value	9.544	5.83		
p value	<0.001	<0.001		
IFN-γ				
Before treatment	52.79 ± 4.48	51.84 ± 4.99	1.115	0.267
After 3 courses of treatment	33.14 ± 4.56	39.39 ± 4.99	7.280	<0.001
t value	24.204	13.557		
p value	<0.001	<0.001		

IFN-γ: interferon γ; IL-2: interleukin-2; IL-4: interleukin-4; IL-6: interleukin-6.

TABLE 2. Comparison of cytokines between both groups ($\bar{x} \pm s$).

Indicator	Experimental group (n = 62)	Control group (n = 62)	*t* value	*p* value
IL-2/IL-6				
Before treatment	2.34 ± 1.13	2.56 ± 1.07	1.113	0.268
After 3 courses of treatment	1.67 ± 0.51	2.01 ± 0.51	3.712	<0.001
t value	4.255	3.654		
p value	<0.001	<0.001		
IL-2/IL-4				
Before treatment	2.17 ± 1.12	2.14 ± 1.09	0.151	0.880
After 3 courses of treatment	1.34 ± 0.39	1.56 ± 0.41	3.922	<0.001
t value	5.511	3.922		
p value	<0.001	<0.001		
IFN-γ/IL-4				
Before treatment	2.35 ± 1.07	2.37 ± 1.03	0.106	0.916
After 3 courses of treatment	1.68 ± 0.58	2.01 ± 0.55	3.251	0.002
t value	4.335	2.428		
p value	<0.001	0.017		
IFN-γ/IL-6				
Before treatment	2.99 ± 0.69	3.21 ± 1.14	1.891	0.061
After 3 courses of treatment	2.09 ± 0.57	2.58 ± 0.69	4.311	<0.001
t value	7.918	4.314		
p value	<0.001	<0.001		

IFN-γ: interferon γ; IL-2: interleukin-2; IL-4: interleukin-4; IL-6: interleukin-6.

TABLE 3. Comparison of tumor marker indicators between the two groups ($\bar{x} \pm s$).

Indicator	Experimental group (n = 62)	Control group (n = 62)	*t* value	*p* value
CA125 (U/mL)				
Before treatment	55.54 ± 4.53	55.21 ± 4.43	0.410	0.682
After 3 courses of treatment	24.69 ± 3.91	33.57 ± 4.69	11.451	<0.001
t value	40.593	26.412		
p value	<0.001	<0.001		
CEA (μg/L)				
Before treatment	8.57 ± 1.89	8.76 ± 1.87	0.563	0.575
After 3 courses of treatment	3.12 ± 0.87	5.98 ± 1.17	15.445	<0.001
t value	20.625	9.923		
p value	<0.001	<0.001		
CYFRA21-1 (mg/L)				
Before treatment	6.61 ± 0.91	6.71 ± 1.21	0.520	0.604
After 3 courses of treatment	2.11 ± 0.31	4.51 ± 0.71	24.393	<0.001
t value	36.857	12.348		
p value	<0.001	<0.001		
SCC-Ag (mg/L)				
Before treatment	5.71 ± 1.01	5.51 ± 1.21	0.999	0.320
After 3 courses of treatment	1.71 ± 0.21	3.91 ± 0.21	58.329	<0.001
t value	30.531	10.259		
p value	<0.001	<0.001		

CA125: carbohydrate antigen 125; CEA: carcinoembryonic antigen; CYFRA21-1: cytokeratin 19 fragment; SCC-Ag: squamous cell carcinoma antigen.

TABLE 4. Comparison of clinical efficacy between both groups.

Group	Case	Complete response	Partial response	Stable	Progression	Disease control rate
Experimental group	62	19 (30.64)	27 (43.54)	10 (16.12)	6 (9.68)	46 (74.19)
Control group	62	12 (19.35)	23 (37.09)	14 (22.58)	13 (20.96)	35 (56.45)
χ^2 value	——		——			4.307
p value	——		——			0.037

TABLE 5. Comparison of adverse reactions between both groups.

Group	Case	Gastrointestinal reactions	Myelosuppression	Radiation proctitis	Radiation cystitis	Overall incidence of adverse reactions
Experimental group	62	1 (1.61)	1 (1.61)	1 (1.61)	1 (1.61)	4 (6.45)
Control group	62	2 (3.22)	2 (3.22)	4 (4.83)	4 (4.83)	12 (19.35)
χ^2 value	——		——			4.592
p value	——		——			0.032

nerves. Studies emphasize tumor compression as a primary cause of death in cervical cancer, leading to vessel invasion, uremia, hemorrhage and cancerous infections. Thus, optimizing treatment plans is essential for reducing pain and improving cervical cancer patient outcomes.

Epirubicin, a non-specific cell cycle agent and broad-spectrum antibacterial drug, has demonstrated efficacy in treating various cancers such as malignant lymphoma, soft tissue sarcoma, gastric cancer, lung cancer and ovarian cancer. Its primary mechanism involves direct interaction with DNA bases, leading to the inhibition of mRNA synthesis and DNA transcription. This action blocks the DNA synthesis pathway and inhibits RNA, while also suppressing the activity of topoisomerase II [18]. On the other hand, docetaxel, a taxane anticancer drug, directly targets tumor cell microtubules, stabilizing their activity and inhibiting cell division, thereby exerting its anti-tumor effects [19]. Additionally, docetaxel can inhibit microtubule depolymerization, enhance tubulin

polymerization, and promote the formation of nonfunctional microtubule bundles [20]. It also enhances radiosensitivity, suppresses tumor proliferation post-radiotherapy, and induces tumor cell death. Several studies, including those by Zhang *et al*. [18], have shown that the combination of epirubicin and docetaxel effectively enhances the anti-tumor effects, consistent with the findings of this study. Furthermore, research indicates that T lymphocyte dysfunction can contribute to cervical cancer progression and is associated with a balance between Th1 and Th2 cells in healthy individuals, regulating each other [21]. Th1 cells secrete IL-2 and IFN-γ, guiding cellular immune responses [22], while Th2 cells secrete IL-4 and IL-6, guiding humoral immune responses [23]. Abnormal levels of Th1 and Th2 cytokines are observed in cervical cancer patients, indicating the potential of these cytokines as markers for assessing disease severity [24]. Moreover, immune disorders can result from bodily damage, leading to Th1 and Th2 cell imbalances [25]. The study's outcomes demonstrate that after treatment, the serum levels of IL-2, IL-6, IL-4 and IFN-γ in the experimental group were notably lower than those in the control group, and the levels of IL-2/IL-6, IL-2/IL-4, IFN-γ/IL-4 and IFN-γ/IL-6 were also lower in the experimental group compared to the control group. These findings suggest that the combination of epirubicin and docetaxel can effectively alleviate inflammatory responses and improve Th1 and Th2 levels in postoperative cervical cancer patients. This result is consistent with that reported in the literature [24].

It has also been pointed out that serum CA125, CEA, CYFRA21-1 and SCC-Ag can be involved in the development and progression of cervical cancer [26]. Among these markers, CA125, a carbohydrate protein tumor marker, is often found in the endometrium, cervix, and other regions, making it useful for cervical cancer diagnosis [27]. Serum CEA, an early tumor marker, has diagnostic value in adenocarcinoma and plays an essential role in tumor growth, metastasis, and invasion as a cell adhesion molecule [28]. Elevated levels of serum CYFRA21-1 are closely associated with tumor stage and size [29]. Meanwhile, serum SCC-Ag serves as a primary indicator of cervical squamous cell carcinoma, reflecting cancer recurrence potential through its regulation of normal and malignant proteolysis [30]. The study's results further demonstrate that after treatment, serum levels of CA125, CEA, CYFRA21-1 and SCC-Ag were dramatically lower in the experimental group compared to the control group, which is consistent with the literature [27]. These findings suggest that the combination of epirubicin and docetaxel effectively reduces tumor marker levels in postoperative cervical cancer patients. Additionally, significant differences in clinical efficacy and adverse reactions were observed between the two groups, indicating that epirubicin combined with docetaxel is effective in treating postoperative cervical cancer patients and reduces the incidence of adverse reactions. The efficacy may be attributed to epirubicin's ability to eliminate tumor cells by inhibiting cell division, metastasis, and DNA polymerase activity, thereby reducing nucleic acid production and inhibiting DNA and RNA synthesis. Moreover, the relatively fewer adverse reactions associated with epirubicin and the alleviation of symptoms by resting and symptomatic treatment demonstrate the treatment's safety profile.

5. Research limitations and future perspectives

This study has several limitations. First, the number and diversity of cases are limited, which may affect the generalizability of the findings. Second, we did not investigate the mechanism of action of epirubicin combined with docetaxel in postoperative cervical cancer patients. Third, this was a single-center study, and the patient selection process might have had some inherent potential biases. Therefore, future research could aim to address these limitations by including a larger and more diverse sample size, investigating the underlying mechanisms, and considering multicenter studies for more comprehensive insights.

6. Conclusions

In conclusion, the combination of epirubicin and docetaxel was found to be effective in treating postoperative cervical cancer patients. It demonstrates efficacy in rectifying cytokine disorders, lowering tumor marker levels, alleviating inflammatory responses, and reducing the occurrence of adverse reactions.

AVAILABILITY OF DATA AND MATERIALS

The authors declare that all data supporting the findings of this study are available within the paper and any raw data can be obtained from the corresponding author upon request.

AUTHOR CONTRIBUTIONS

RL, QQF, YM and JY—designed the study and carried them out; prepared the manuscript for publication and reviewed the draft of the manuscript. RL, QQF and YM—supervised the data collection. RL and QQF—analyzed the data, interpreted the data. All authors have read and approved the manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Ethical approval was obtained from the Ethics Committee of Suzhou Municipal Hospital (Approval no. KL901354). Written informed consent was obtained from a legally authorized representative(s) for anonymized patient information to be published in this article.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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