Abstract. Cataract is a blinding-caused disease and affects millions of individuals worldwide. Although conventional phacoemulsification (CPCS) has been widely used for treatment of cataract, the incidence of cataract-caused blindness still increased year by year. Recently, femtosecond laser technology has been expanded to various clinical applications, including cataract surgery. The present study evaluated the curative effect of bromfenac sodium (BS) after femtosecond laser-assisted cataract surgery (FLACS) and analyzed the mechanism of action. A total of 90 patients were randomly divided into five groups: Group I, conventional phacoemulsification treatment (CPCS) + dexamethasone (DEX)/tobramycin (TOB); group II, CPCS + bromfenac sodium (BS); group III, Femtosecond laser-assisted cataract surgery (FLACS) + DEX/TOB; group IV, FLACS + BS; and group V, FLACS + pranoprofen. Aqueous humor was collected from these patients post-surgery. For in vitro studies, Sra01/04 cells were irradiated using UV, followed by the collection of culture media and cell lysates. Prostaglandin E$_2$ (PGE$_2$) levels, an indicator of inflammation, were measured using ELISA both in vivo and in vitro. In addition, cyclooxygenase (COX) and cleaved caspase-1 p20 expression levels were analyzed using western blotting. The findings suggested that BS was more effective and safer compared with glucocorticoids (GCs) after cataract surgery. BS can protect against post-operative inflammation by inhibiting PGE$_2$ production. Under in vitro conditions BS prevented the SRA01/04 cells from undergoing apoptosis after UV treatment and also suppressed PGE$_2$ release from UV-irradiated SRA01/04 cells by modulating COX-2 expression. Furthermore, BS may have an inhibitory effect on the inflammatory form of cell death. Overall, these results indicated that BS could replace existing GCs as a reliable drug for a perioperative period of cataract surgery. It was also identified that the inhibitory effect of BS on PGE$_2$ production was mediated via the regulation of COX-2.

Introduction

Cataract is defined as the formation of a dense and cloudy area in the crystalline lens of the eye (1). Visual impairment due to cataract affects ~40,000,000 of individuals worldwide and has become a major cause of blindness (2). Conventional phacoemulsification (CPCS) has been considered as the most prevalent and effective surgical procedure for cataract in recent decades (3). However, while this method has been widely used, more than 20 million patients experience blindness due to bilateral cataracts, especially in developing countries (4). In 2001, for the first time, femtosecond laser technology was introduced in clinical practice, and it was used for flap creation in laser in-situ keratomileusis (5). Since this introduction, femtosecond laser technology has been expanded to various clinical applications, including cataract surgery (6). Femtosecond laser-assisted cataract surgery (FLACS) is more reliable compared with CPCS (7). For instance, more circular and centered capsulorhexis can be created by FLACS to reduce the intraocular lens (IOL) tilt, as well as decentration during IOL implantation (8). FLACS also allows for more effective control of the post-operative astigmatism via the creation of improved quality corneal incisions (9). Moreover, femtosecond laser-assisted pre-fragmentation of the crystalline lens can improve the phacoemulsification power and time consumption during the surgery (10). However, multiple complications such as inflammation and miosis have been reported in several patients with cataract treated by FLACS (11).

Clinically, both glucocorticoids (GCs) and non-steroidal anti-inflammatory drugs (NSAIDs) are used frequently due to their well-known anti-inflammatory effects (12). As these agents have different mechanisms of action, combination...
therapy with GCs and NSAIDs may provide extra benefits; this method has been routinely used for patients undergoing cataract surgery (13). Bromfenac sodium (BS), a potent NSAID, has been observed minimal adverse events in number studies, although it was found the risk of corneal compromise when use of BS to preexisting corneal disease (14). The present study evaluated the curative effect of BS after cataract surgery with the replacement of GCs, and the mechanisms of action by treatment of the patients with BS were clarified.

Materials and methods

Clinical donors. A total of 90 patients (men, 45; women, 45; age, 50-89; mean age, 67.74±9.34 years) from The Fourth Affiliated Hospital of China Medical University (Shenyang, China) between August 2014 and January 2015 were enrolled in the present study. All the experiments were approved by the Ethics Committee of The Fourth Affiliated Hospital of China Medical University (approval no. ChiCTR-TRC-14005114) and informed consent was signed by every study participant.

The patient population did not include corneal diseases, intraoperative complications and other types of eye diseases, such as inflammation, uveitis and glaucoma, or any other pathologies. Patients receiving systemic or topical anti-inflammatory therapy within 1 month before surgery were also excluded. The study participants were randomly divided into five groups: Group I, CPCS + 0.1% dexamethasone treatment (DEX; Nitto Medic Co., Ltd.)/0.3% tobramycin (TOB; Nitto Medic Co., Ltd.); group II, CPCS + 0.1% BS treatment (Senju Pharmaceutical Co., Ltd.); group III, FLACS + 0.1% DEX/0.3% TOB; group IV, FLACS + 0.1% BS; and group V, FLACS + 0.1% pranoprofen (Senju Pharmaceutical Co., Ltd.). Each of the study groups (I-V) consisted of a total of 22, 22, 19, 24 and 23 patients, respectively. No significant differences in the surgical data of these groups such as age, sex, eye type and nucleus degree of the lens (based on the Emery-Little classification) (15) were observed. Additional clinical information for these patients is presented in Table I.

Surgical treatment. A total of ~150 µl of aqueous humor was collected from patients undergoing routine and FLACS. The specimens were collected at the beginning of the surgery and stored at -80°C until used. Cataract surgery was performed by one surgeon and an assistant. Before the surgery, the pupils were dilated using a combination of 0.5% tropicamide (Mydrin-P; Santen Pharmaceutical Co., Ltd.) with 5% phenylephrine hydrochloride eyedrops (Neosynesin, Kowa Co., Ltd.), followed by anesthesia and washing using 4% lidocaine/epinephrine hydrochloride eyedrops (Neosynesin, Kowa Co., Ltd.). Then, record the visual acuity for each patient to read from the top to bottom and from the left to right of the chart after ensure the illumination on the testing chart. a single drop of saline was instilled in the right eye of the chart. The severity of the pain was scored from 0 to 4, where 0=no pain/best outcome and 4=worst outcome/most pain.

Clinical outcomes. Corrected distance visual acuity (CDVA) was measured 1 month before and after the surgery (17). In brief, position the patient at a distance of 6 meters from the chart after ensure the illumination on the testing chart. Ask the patient to read from the top to bottom and from the left to right of the chart. Then, record the visual acuity for each eye separately. The conversion of decimal acuity values to logMAR was used for the calculation of CDVA. Aqueous flare, intraocular pressure (IOP) and corneal thickness measurements were performed postoperatively at 1, 7, 30 and 60 days using FM-600 Laser Flare Meters (KOWA Company, Ltd.), NT-530P Non-Contact Tonometer (Nidek Co., Ltd.) and Pentacam (Oculus GmbH), respectively. Macular thickness was measured using the Spectralis OCT BluePeak module (Heidelberg Engineering, Inc.). The equipment was set as a 3D scan mode (Frequency, 40,000 times/sec; Depth, 2.0 mm; Range, 8.8x8.8 mm²) and data analysis was automatically performed using HEYE X 2 image management software system (Heidelberg Engineering, Inc.). The severity of the pain was scored from 0 to 4, where 0=no pain/best outcome; 1=mild pain/no need for drug intervention/does not affect normal life; 2=moderate pain/affects normal life; 3=severe pain/unable to live a normal life/appropriate to drug intervention and 4=worst outcome/most pain.
diameter measurement was performed by the same doctor under normal room light illumination. The pupil diameters of patients were measured using a ruler in the horizontal and vertical directions. The measurement was repeated three times and the average was taken. The pupil reduction ratio after the surgery was calculated as: (Pupil diameter before surgery-pupil diameter after surgery)/pupil diameter before surgery x 100. To measure the size of macular thickness, we reconstruct a surface map as a false-color topographic image and divided into 9 map sectors as shown in below. The central subfield macular thickness (CSMT) was defined as the average of the mean thickness within the central 1,000 µm ring. The inner macular ring and the outer macular ring were separated into four quadrants with the diameters of 3,000 and 6,000 µm, respectively. The macular thickness was calculated as the mean standard ± deviation in these total 9 regions.

**Cell culture and UV B treatment.** SRA01/04 (cat. no. RCB1591; RIKEN), a human lens epithelium-derived cell line, was cultured in DMEM (FUJIFILM Wako Pure Chemical) supplemented with 20% heat-inactivated FBS (MP Biomedicals, LLC) and 1% penicillin-streptomycin (Nacalai Tesque, Inc.) in a 5% CO₂ humidified incubator at 37°C. Cells were seeded in 96-well plate at a density of 5x10⁵ cells/ml 1 day before the experiment, which was followed by overnight incubation at 37°C. Cells were washed twice with pre-warmed PBS and treated with UV irradiation at room temperature for 30 sec using a CL-1000M UV lamp (Thermo Fisher Scientific, Inc.). Most of the resulting wavelengths were in UVB range (0-315 nm). The used UVB energy sources were at 0, 20, 40, 60 and 80 mJ/cm². Sra01/04 cells were irradiated for 40, 60 and 80 mJ/cm². Sra01/04 cells were irradiated for 30 sec in the absence or presence of different concentrations (0-80 µg/ml) of BS at 37°C. PBS was replaced with fresh DMEM post-UV irradiation.

**MTT assay.** Viability of SRA01/04 cells was determined using a MTT assay based on mitochondrial reduction of MTT to formazan. Cultured medium was replaced with 200 µl MTT-containing fresh medium after the treatment. MTT (FUJIFILM Wako Pure Chemical) solution (7.5 µg/ml) was added into each well (20 µl/well) followed by incubation at 37°C for 1.5 h. Then, 150 µl culture supernatant was removed from each well and the formazan crystal was lysed by adding 100 µl MTT stop solution (0.4% HCl, 10% Triton X-100 in Isopropanol). After 12-h incubation at 37°C, the absorbance was measured at 570 nm, with 655 nm as reference wavelength, on a microplate reader (Bio-Rad Laboratories, Inc.).

**ELISA.** The Prostaglandin E₂ (PGF₂) production in the aqueous flare and culture supernatants after UV exposure was measured using a PGE₂ Expression ELISA kit (cat. no. 500141, Cayman Chemical Company) as per the manufacturer's instructions. Human interleukin IL-1β/IL-1F2 DuoSet ELISA kit (cat. no. DY20105, R&D Systems, Inc.) and Cytotoxicity lactate dehydrogenase (LDH) Assay kit (cat. no. CK12, Dojindo Molecular Technologies, Inc.) were used to detect the release of IL-1β and LDH, respectively, according to the manufacturer's instructions.

**Reverse transcription-quantitative PCR (RT-qPCR).** Total RNA from SRA01/04 cells was isolated using TRIzol® reagent (Invitrogen; Thermo Fisher Scientific, Inc.) followed by the reverse transcription of extracted RNA at 37°C for 1 h and inactivation of the reaction at 95°C for 5 min using a miScript II RT kit (QIAGEN GmbH) in a fluorescence thermal cycler (Bio-Rad Laboratories, Inc.). In brief, the qPCR amplification conditions consisted of pre-denaturation for 3 min at 94°C, followed by a total of 30 cycles of denaturation for 30 sec at 94°C, annealing at 58°C for 30 sec and extension for 60 sec at 72°C. The expression of related genes was measured using a SYBR Green PCR reagent kit (Applied Biosystems; Thermo Fisher Scientific, Inc.) with the following primer sets on an ABIiViiA7 RT PCR system (Thermo Fisher Scientific, Inc., Waltham, MA, USA). The relative expression of target genes was normalized to β-actin. Expression of β-actin was used as internal control for the analysis of other genes while the 2-ΔΔcq method was used for data analysis (19). The primers sequences were as following: COX-1 forward, 5'-CTC TCT AAG TCT CGG TCT CGG-3' and reverse, 5'-AGT GGA AGG GCC GCT AAG-3'; COX-2 forward, 5'-ACGTCTGAACTATCTCTG CC-3' and reverse, 5'-AGATTAGTCGGCGTAGTCG-3'; and β-actin forward, 5'-GTGGGGCCGCCCAAGCCACCA-3' and reverse, 5'-CTCTTTAATGTCACCGAGTTTC-3'.

**Western blotting.** SRA01/04 cells were homogenized in RIPA lysis and extraction buffer (Thermo Fisher Scientific, Inc.).
Bicinchoninic acid Protein assay kit (FUJIFILM Wako Pure Chemical) was used for determining protein concentrations. In total, 20 µg each sample were separated by 15% SDS-PAGE and transferred to PVDF membrane (Immobilon-P; EMD Millipore). Then, 5% skim milk was used to block membranes for 1 h at room temperature, and membranes were incubated with primary antibodies against cleaved human caspase-1 p20 (cat. no. AG-208-0042-C100; AdipoGen), COX-1 (cat. no. 4841; Cell Signaling Technology, Inc.) and COX-2 (cat. no. 12282; Cell Signaling Technology, Inc.; all 1:1,000 dilutions) overnight at 4˚C. GAPDH (cat. no. 5174; Cell Signaling Technology, Inc.; 1:1,000) was used as an internal control. The secondary horseradish peroxide-conjugated anti-rabbit IgG antibody (Cell Signaling Technology, Inc.; cat. no. 5127; 1:5,000) was incubated at room temperature for 1 h. Protein band intensity was analyzed using Luminata Forte Western horseradish peroxidase Substrate (EMD Millipore) with a Bio-Rad ChemiDoc XRS+ imaging system and Image Lab Software Version 6.0.1 (Bio-Rad Laboratories, Inc.).

Statistical analysis. All experiments were conducted with at least three independent replicates. Data are presented as the mean ± standard deviation using GraphPad Prism 5.0 (GraphPad Software, Inc.). The comparisons of paired samples (preoperative vs. postoperative measurements of the same patient) in Figs. 1 and 2 were assessed using a repeated measures ANOVA, which was used to analyse matched samples. Differences among multiple groups were assessed with one-way ANOVA followed by Bonferroni post hoc test or Scheffe's multiple comparison test (SPSS 22.0; IBM Corp.), which was used to analyse unpaired samples. The relations between categorical variables in Tables I and II were analyzed with the χ² test. In addition, Fisher's exact test was used to detect differences in levels of cataract between the groups. P<0.05 was considered to indicate a statistically significant difference.

Results

Beneficial effects of BS on the perioperative period of cataract surgery. No statistically significant differences in the clinical outcomes including CDVA, aqueous flare, IOP, central corneal thickness (CCT) and macular morphology (Table I) among the patients were identified before the surgery. Based on the data in Table II, it was found that the pupil diameter was increased by BS treatment (group II) before the CPCS, as compared with NSAID treatment (group I). However, the pupil diameter was significantly reduced by DEX/TOB treatment when the patients were receiving FLACS (group III). More important, BS treatment strongly improved pupil reduction, as group IV indicated. It was also observed similar protective effect of pranoprofen on pupil reduction as BS. Additionally, cumulative dissipated energy (CDE) in the patients who received FLACS was significantly reduced compared with the patients who received CPCS (Table II), indicating that energy delivered induced less damage in the FLACS group compared with the CPCS group. Moreover, no surgical complications in any of the study subjects after the surgery were demonstrated. Compared with the results of the patients visual acuity before surgery, no significant difference was observed in the visual acuity in patients of each group 1-week post-surgery, suggesting the surgical procedure was successful (Fig. 1A). However, aqueous flare was observed in all the groups 1 day after the surgery (Fig. 1B). Moreover, reduction of the
aqueous flare was observed in the BS-treated groups but not in the NSAID-treated groups after 7 days of treatment. It was also found that the aqueous flare was significantly inhibited by BS compared with NSAIDs after 30 days of treatment. Furthermore, significantly higher IOP was observed in GC-treated groups 30 days after surgery as compared with BS-treated subjects (Fig. 1C). It was demonstrated that the CCT value gradually returned to the pre-operative state, although FLACS treatment significantly increased CCT a day after the operation (Fig. 1D).

Protective effects of BS on surgical complications. There were no significant changes of CSMT between each group at 1-week after surgery (Fig. 2A). However, it was observed that BS exerted a protective effect on the expansion of CSMT on days 30, 45 and 60 post-surgery (Fig. 2A). Moreover, on day 30, the average thickness size of the outer macular ring in FLACS was inhibited by BS (Fig. 2B). It was also found that the inner macular ring AT demonstrated a similar trend to CSMT (data not shown). Thus, BS also reduced the inner macular ring AT in CPCS and FLACS groups.

It has been reported that FLACS can induce the hyper-production of PGE$_2$, which is one of the major causes of the miosis (20). Therefore, PGE$_2$ levels were measured in each group after the surgery. A higher concentration of PGE$_2$ was detected in the aqueous humor of DEX/TOB-treated FLACS group (group III) compared with that of CPCS group (group I). Additionally, compared with the DEX/TOB-treated patients (group III), either BS treatment (group IV) or pranoprofen treatment (group V) significantly suppressed PGE$_2$ production after the patients received FLACS (Fig. 2C). After FLACS surgery, no severe pain (more than level 2) was found in the patients. As Fig. 2D illustrates, most of patients treated by BS did not felt any pain. However, ten patients received DEX/TOB
and 5 patients treated by BS felt mild pain after FLACS surgery. As compared with these two groups, more severe pain (level 2) was found in 3 patients who received pranoprofen treatment. Furthermore, there were 8 patients distributed in level 0 of pain and 12 patients presented in level 1 of pain in pranoprofen group, respectively. Collectively, these results demonstrated that BS has a higher protective effect on pain compared with pranoprofen during the surgery (Fig. 2D).

Protective effects of BS on the perioperative period of cataract surgery via modulating COX.

To identify the mechanism underlying the protective effects exerted by BS on the perioperative period of cataract surgery, the present study established an in vitro model via the irradiation of SRA01/04 cells with UV. As demonstrated in Fig. 3A, the apoptosis of SRA01/04 cells occurred in a time-dependent manner post UV irradiation. Additionally, it was identified that ~50% of cells died after exposure to 60 mJ/cm² UV irradiation. As shown in Fig. 3B, protective effect of BS on UV-induced SRA01/04 cells apoptosis was analyzed by MTT assay (A). Concentrations of PGE₂ in the supernatant were measured using ELISA (B). Data are presented as the mean ± SD (n=3). *P<0.05 vs. group I; ns, P>0.05 vs. group I. FLACS, Femtosecond laser-assisted cataract surgery; CPCS, conventional phacoemulsification treatment; CDE, cumulative dissipated energy.

Table II. Clinical patient data.

| Group | n | Pupil diameter before FLACS (mm) | Pupil diameter before CPCS (mm) | Pupil reduction ratio | Concentration of PGE₂ in aqueous humor (pg/ml) | CDE (%) | Femtosecond laser action time ± SD (sec) | Suction time ± SD (sec) | Intraocular pressure (mmHg) |
|-------|---|-------------------------------|-------------------------------|----------------------|--------------------------------|--------|--------------------------------|----------------------------|-----------------------------|
| I     | 22| 7.7±0.76                      | 12.05±4.67                    | 12.95±4.25           |                                          |        |                                           |                            |                             |
| II    | 22| 8.2±0.50                      | 13.16±3.85                    | 11.89±4.43           |                                          |        |                                           |                            |                             |
| III   | 19| 7.64±0.69                     | 51.84±6.67                    | 9.42±4.49            | 35.16±4.51                     | 206.8±92.79 |                                           |                            |                             |
| IV    | 24| 7.68±0.56                     | 18.41±4.45                    | 7.44±4.73            | 34.5±6.19                       | 190.3±85.68 |                                           |                            |                             |
| V     | 23| 7.72±0.61                     | 18.54±4.32                    | 7.42±4.56            | 37.1±6.12                       | 193.3±86.13 |                                           |                            |                             |

Figure 3. Protective effect of BS on UV-irradiated SRA01/04 cells. (A) To optimize the experimental conditions, SRA01/04 cells were exposed to UV (60 mJ/cm²) as indicated, followed by detection of cell viability using MTT assay. (B) Protective effect of BS on UV-induced SRA01/04 cells apoptosis was analyzed by MTT assay. (C) Concentrations of PGE₂ in the supernatant were measured using ELISA. PGE₂, Prostaglandin E₂; BS, bromfenac sodium; UV, ultraviolet.
exposure to UV for 30 sec, and that most of the cells died after exposure to UV for 40 sec (Fig. 3A). Moreover, the results suggested that BS prevented SRA01/04 cells from apoptosis in a dose-dependent manner when the cells irradiated with UV for 30 sec (Fig. 3B). Similarly, it was also demonstrated that the PGE₂ level in the supernatant was increased by UV exposure compared with non-UV irradiated cells, and this was significantly reversed by BS treatment in a dose-dependent manner (Fig. 3C).

The mRNA expression level of COX-2, but not COX-1, was significantly upregulated by UV irradiation (Fig. 4A). In addition, the protein expression level of COX-2 was significantly increased by UV irradiation (Fig. 4B). The results also indicated that BS treatment significantly inhibited the expression of COX-2 at both transcription and protein level (Fig. 4).

Discussion

CPCS has been routinely used for the treatment of patients with cataract in the last decade (21). Tissue injuries such as endothelial cell loss and macular edema are frequently induced during surgery (22). Previous studies have reported that the use of FLACS has fewer complications and is more reliable compared with CPCS (23). The present results suggested that there was no difference in CDVA, as well as aqueous flare, between CPCS groups and FLACS groups. Moreover, there was no significant difference in IOP between these groups before or after the surgery, suggesting that the IOP rise after surgery was not associated with several docking attempts, vacuum time and treatment time; these results were consistent with Kerr et al (24). In GC-treated groups, it was found that the IOPs of two patients were not within the normal range (12-22 mmHg) 30 days post-surgery. Furthermore, both aqueous flare and IOP were significantly reduced by BS treatment 30 days after the surgery. Therefore, the present results indicated that CCT was increased by FLACS with BS treatment, which can be interpreted by the frequent use of BS before the surgery.

Macular edema appears usually postoperatively after 1-6 weeks, with a peak in the 4-6th week, and this is considered a major factor for vision impairment after cataract surgery (25). Wittpen et al (26) have reported that NSAIDs can protect against the occurrence of macular edema and maintain the CCT. The present findings further support this observation and suggest that BS treatment can effectively prevent macular edema in the eyes after cataract surgery. The present results also provided supporting evidence for the effectiveness and safety of BS. Thus, BS may be used as an alternative to GC and it has protective effects on the complications of cataract surgery.

PGEs, a type of lipid autacoids derived from arachidonic acid, have been implicated in a variety of inflammatory diseases such as rheumatoid arthritis or allergic asthma (27). PGE₂ is one of the most abundant PGEs in mammals, and is synthesized by COX-1 and -2 (27). Previous studies have reported that overproduction of PEG is observed in the aqueous humor of patients after cataract surgery and can cause a reduction in the size of the pupils (20,28,29). PGE₂ concentration is significantly reduced in NSAIDs-treated patients as these drugs can directly bind and inhibit the active site of COXs (30). The results of the present study demonstrated that BS, as an NSAID drug, strongly suppresses PGE₂ production in patients and in UV-induced cells. However, it should be noted that COX-2 expression, but not COX-1, was inhibited by BS treatment, suggesting that BS mitigates miosis via modulating COX-2.

In addition to PEG₂-related inflammation, it has been shown that pyroptosis can play a role in the formation of cataract (31). Pyroptosis, a type of inflammatory cell death, is induced by inflammasome activation, which causes rapid rupture of the cell membrane and the release of pro-inflammatory factors, such as IL-1β, IL-18 and LDH (32). In line with these observations, the results of the present study demonstrated that SRA01/04 cells apoptosis was caused by UV irradiation, indicating the presence of UV-induced pyroptosis. The anti-pyroptotic effects on UV-irradiated cells were observed.
when treatment of cells with BS. To the best of our knowledge, the present study was the first report the inhibitory effects of BS on pyroptosis.

In conclusion, the present study evaluated the curative effect of BS during the perioperative period of cataract surgery and examined its action mechanisms. It was demonstrated that BS was more effective and safer compared with GC after cataract surgery. Furthermore, BS can protect against postoperative inflammation by inhibiting PGE$_2$ production. In vitro BS prevented SRA01/04 cells apoptosis after UV treatment and also suppressed PGE$_2$ release from UV-irradiated SRA01/04 cells by modulating COS-2 expression. Collectively, the present results suggested that BS could replace the existing GC as a reliable drug for perioperative period of cataract surgery.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors’ contributions

JingsongZ designed this study. LL, JiangyueZ, JW, YQ and JingsongZ conducted the experiments. LL, JingsongZ and JW analyzed the data. LL and JingsongZ wrote the manuscript. JingsongZ edited the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

All the experiments were approved by the Ethics Committee of the Fourth Affiliated Hospital of China Medical University (approval no. ChiCTR-TRC-14005114) and written informed consent was obtained from the participants.

Patient consent for publication

Not applicable.
Competing interests

The authors declare that they have no competing interests.

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