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Comparison of the Effect of Bromfenac versus Betamethasone Ophthalmic Solutions in Patients with Diabetic Macular Edema

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ABSTRACT

Purpose: To examine the effect of 0.1% bromfenac (BF) ophthalmic solution and 0.1% betamethasone (BM) ophthalmic solution on diabetic macular edema (DME).

Methods: This was a prospective trial. Nineteen patients (mean age of 66.6 ± 10.1 years) with DME and mean retinal thickness within a diameter of 1 mm from the fovea (central subfield thickness: CST) of 250–500 μm were randomized and instilled with BF or BM. CST, best-corrected visual acuity (BCVA), and intraocular pressure (IOP) were measured at 4, 8, and 12 weeks after administration.

Results: CST at baseline ($p = .128$) and that at 4, 8, and 12 weeks of administration was not significantly different between the BF (10 patients) and BM groups (9 patients). In patients with glycated hemoglobin (HbA1c) $< 8.0\%$, CST, compared with baseline, was significantly decreased in the BF group (seven patients) at 8 ($p = .025$) and 12 weeks ($p = .043$) of administration. When compared with the baseline, no significant changes in BCVA were observed at any point in time in either group. Baseline IOP was comparable between the groups. In the BM group, the values of change in IOP from baseline significantly increased at 8 ($p = .025$) and 12 weeks ($p = .044$) of administration, with no significant changes in IOP over the 12 weeks of administration in the BF group.

Conclusions: BF did not affect IOP even after 12 weeks of administration, suggesting its effect in reducing CST in DME with good glycemic control.

Trial registration: University Hospital Medical Information Network (UMIN-CTR); UMIN000026201, February 18, 2017; Japan Registry of Clinical Trials; jRCTs031180308, March 15, 2019

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Introduction

According to the National Health and Nutrition Surveys in 2016, 10 million individuals in Japan were strongly suspected of having diabetes, which was the highest number in history.¹ Although diabetic retinopathy, one of the complications of diabetes, is decreasing due to early detection and appropriate treatment, it is still the third most common cause of acquired blindness and is the major cause of blindness among the working-age population in Japan.² Macular edema associated with diabetic retinopathy (DME) is known to develop regardless of the severity of diabetic retinopathy, and prolongation of DME results in irreversible changes, such as future retinal thinning, atrophy, and deposition of hard exudates, significantly affecting visual functions and greatly influencing patients' quality of life.³ In the treatment of DME, it is important to maintain and improve visual functions by alleviating edema before irreversible retinal changes occur.

Currently, the treatment paradigm for DME includes intravitreal injection of triamcinolone acetonide, a corticosteroid, and vascular endothelial growth factor (VEGF) inhibitors.^{4–7} Intravitreal injection of triamcinolone acetonide, an anti-inflammatory agent, suppresses macular edema by inhibiting inflammatory cytokine production in the eyes. However, the major side effects include elevated intraocular pressure (IOP), cataracts, and infectious endophthalmitis caused by infection during the injection.^{8,9} VEGF inhibitors reduce edema via the inhibition of VEGFs, which are inflammatory substances; however, attention must be given to invasion and infection, as with steroid injection.¹⁰

Currently, approved drug treatments for DME are administered via intravitreal injections. Despite their efficiency, these treatments are invasive, require multiple injections, and are difficult to use in patients with mild DME. Hence, from the viewpoint of early and non-invasive treatments, it is desirable to develop instillation therapies for such patients.

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Bronuck ophthalmic solution 0.1% (0.1% bromfenac sodium hydrate ophthalmic solution, BF) is a non-steroidal anti-inflammatory drug (NSAID), that suppresses prostaglandin (PG) biosynthesis by inhibiting cyclooxygenase (COX). A study in rabbits confirmed that instillation of BF twice a day can maintain the half-maximal inhibitory concentration (IC₅₀) of COX in choroid tissues.¹¹ In a pilot study, Pinna et al.¹² showed that bromfenac ophthalmic solution has the potential to reduce DME. Additionally, BF has been reported to significantly suppress cystoid macular edema (CME) after cataract surgery in patients with diabetes when compared with Eye, Nose Rinderon-A Solution (a mixture of betamethasone and fradiomycin).¹³ Thus, to compare the usefulness of BF for DME with that of ophthalmic steroids, in the present study, we examined Rinderon Ophthalmic, Otic and Nasal Solution 0.1% (0.1% betamethasone sodium phosphate solution, BM) as the control drug.

Materials and methods

This randomized, prospective, specified, single-center trial was conducted from June 2017 to October 2019 at the Diabetes Center, Tokyo Women's Medical University Hospital. The study was conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice. The protocols were approved by the ethics committee (Certified Review Board of the National Center for Global Health and Medicine, NCGM-C-003157-00). The patients provided written informed consent to participate and publish the study.

Patients diagnosed with DME with glycated hemoglobin (HbA1c) levels of less than 10% and mean retinal thickness within a diameter of 1 mm from the fovea (central subfield thickness: CST) of 250–500 μm were offered the option of anti-VEGF treatment and those who refused treatment due to lack of subjective symptoms, financial reasons, and refusal of vitreous injections were included in this study. In addition, the consent form included a section titled "If you wish to discontinue participation in the study," which clearly stated that patients could discontinue participation at their own will, and explained this verbally as well. Patients were also presented with options for adjuvant therapy and we confirmed the patient's willingness at each follow-up visit. Patients with non-DME retinochoroidal diseases, glaucoma and uveitis, retinal photocoagulation or who underwent cataract surgery within the 6 months prior to starting the study, or those who were administered systemic or ocular steroids, or VEGF inhibitors within 1 month prior to starting the study, and hyperbaric oxygen therapy within the 6 months prior to starting the study, or diagnosed with severe myopia of more than -6D , those who had undergone vitrectomy, those who had undergone treatment that might affect DME within a month, those with subretinal fluid confirmed by tomography at the macula using optical coherence tomography (OCT), and cystic opacity that might affect visual acuity improvement were excluded from the study. Additionally, when researchers deemed a patient unsuitable as a participant for reasons such as not abiding

by doctors' instructions regarding consultation and dosage, the patient was excluded from the study. All participating patients also did not receive any NSAIDs, including bromfenac ophthalmic solutions, within 1 month prior to starting the study.

Nineteen eyes of 19 patients, naive for intravitreal injections of anti-VEGF or steroids, who fulfilled the selection criteria were randomized and administered BF (Bronuck[®]; Senju Pharmaceutical, Osaka, Japan; 10 eyes) or BM (Rinderon[®]; Shionogi & Co., Osaka, Japan; 9 eyes). Instillation was performed twice a day in the BF group and four times a day in the BM group for a total of 12 weeks. To ensure that the drops were properly administered, medication adherence was checked at each follow-up visit.

Sex, age, type of diabetic retinopathy, presence or absence of cataract, HbA1c level, CST, best-corrected visual acuity (BCVA), and IOP were collected for patient background. Ophthalmic evaluations included CST, BCVA, IOP, and corneal examinations. CST was measured using OCT (Cirrus HD-OCT4000, Carl Zeiss, Jena, Germany), BCVA was evaluated using a Snellen chart, IOP with a Goldman tonometer (Haag-Streit AG, Bern, Switzerland), and corneal findings, including fluorescein staining, were examined using a slit lamp microscope (Haag-Streit Original Slit Lamp 900[®] BQ/900[®] BQ LED, Bern, Switzerland). All examination parameters were observed before instillation (baseline) and at 4, 8, and 12 weeks after the start of instillation. The medical personnel in charge of patient background collection and examinations were not informed of the administration status of the test drugs.

The primary endpoint was an intergroup comparison of changes in CST values from baseline to 12 weeks after drug administration. The secondary endpoints included intergroup and intragroup comparisons of CST, BCVA, and IOP values at 4, 8, and 12 weeks. CST and BCVA values were subanalyzed according to the HbA1c level.

For CST, BCVA, and IOP, Student's t-test was used for comparisons between drug groups, while the paired t-test was used for intragroup comparisons. Statistical significance was set at $p \leq .05$. SAS statistical software (version 9.4, SAS Institute Inc.) was used for the statistical analyses.

Results

The baseline characteristics were balanced, and there was no significant difference between the two groups in terms of patient background (Table 1).

Table 1. Patient background.

	BF group (N = 10)	BM group (N = 9)	p Value
Men: women	9:1	8:1	.937*
Age	65.9 \pm 8.2	67.4 \pm 12.4	.750 [#]
Stages of DR (NPDR:PDR)	8:2	7:2	.906*
HbA1c (%)	7.5 \pm 0.7	7.5 \pm 0.9	.878 [#]
CST (μm)	302.8 \pm 34.5	340.9 \pm 66.1	.128 [#]
Visual acuity (number of characters)	76.5 \pm 8.3	68.1 \pm 9.4	.054 [#]
Intraocular pressure (mmHg)	14.6 \pm 3.2	14.2 \pm 1.2	.744 [#]

HbA1c: glycosylated hemoglobin; CST: central subfield thickness; BF: bromfenac; BM: betamethasone.

*Chi-square test.

[#]Student's t-test.

The change in values of CST from baseline to 12 weeks after administration was $-5.6 \pm 25.4 \mu\text{m}$ in the BF group and $-0.3 \pm 26.8 \mu\text{m}$ in the BM group, with no significant difference between the groups. CST was $302.8 \pm 34.5 \mu\text{m}$ at baseline, $313.5 \pm 57.4 \mu\text{m}$ at 4 weeks, $298.0 \pm 37.0 \mu\text{m}$ at 8 weeks, and $293.2 \pm 48.0 \mu\text{m}$ at 12 weeks in the BF group, while $340.9 \pm 66.1 \mu\text{m}$ at baseline, $335.6 \pm 50.0 \mu\text{m}$ at 4 weeks, $346.5 \pm 74.8 \mu\text{m}$ at 8 weeks, and $344.6 \pm 76.4 \mu\text{m}$ at 12 weeks in the BM group. Compared to baseline, there were no significant changes after administration in either group, and no significant intergroup differences were observed at any time point of observation (Figure 1).

BCVA was 76.5 ± 8.3 characters at baseline, 77.2 ± 7.8 characters at 4 weeks, 78.3 ± 5.8 characters at 8 weeks, and

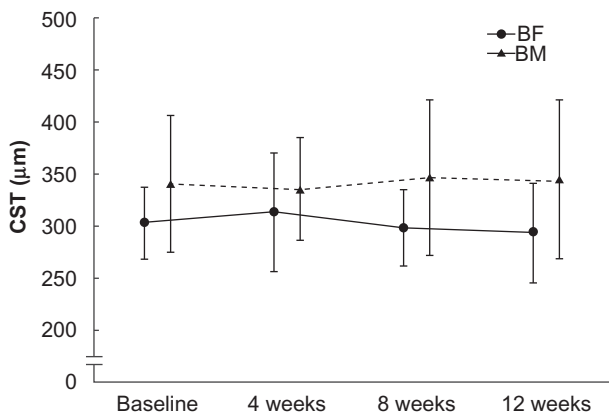


Figure 1. Measurement of central subfield thickness (CST) at baseline and 4, 8, and 12 weeks of administration of either bromfenac (BF) or betamethasone (BM) in patients with diabetic macular edema.

Table 2. Best-corrected visual acuity (BCVA) of all patients.

	BF group (n = 10)		BM group (n = 9)		
	Upper row: BCVA (characters)	<i>p</i> Value*	Upper row: BCVA (characters)	<i>p</i> Value*	<i>p</i> Value**
Baseline	76.5 ± 8.3	–	68.1 ± 9.4	–	.054
4 weeks	77.2 ± 7.8	.524	70.0 ± 6.3	.306	.043
8 weeks	0.7 ± 3.3	.258	1.9 ± 5.2	.393	.556
	78.3 ± 5.8		68.0 ± 2.6		<.001
12 weeks	1.8 ± 4.7	.649	2.0 ± 6.2	.601	.939
	74.4 ± 15.5		67.1 ± 4.1		.218
	–2.1 ± 14.1		1.1 ± 5.8		.554

BF: bromfenac; BM: betamethasone.

*Paired t-test (vs. baseline).

**Student's t-test (BF group vs. BM group).

Table 3. CST of patients with HbA1c levels of less than 8%.

	BF group (n = 7)		BM group (n = 6)	
	Upper row: CST (μm)	<i>p</i> Value*	Upper row: CST (μm)	<i>p</i> Value*
Baseline	300.1 ± 30.9	–	362.0 ± 67.9	–
4 weeks	295.1 ± 32.9	.349	351.2 ± 53.1	.423
8 weeks	–5.0 ± 13.0	.025	–10.8 ± 30.4	.800
	287.9 ± 28.8		366.3 ± 71.6	
12 weeks	–12.3 ± 10.9	.043	4.3 ± 39.7	.881
	276.3 ± 27.2		364.0 ± 76.0	
	–17.3 ± 15.8		2.0 ± 31.1	

HbA1c: glycosylated hemoglobin; CST: central subfield thickness; BF: bromfenac; BM: betamethasone.

*Paired t-test (vs. baseline).

74.4 ± 15.5 characters at 12 weeks in the BF group, while 68.1 ± 9.4 characters at baseline, 70.0 ± 6.3 characters at 4 weeks, 68.0 ± 2.6 characters at 8 weeks, and 67.1 ± 4.1 characters at 12 weeks in the BM group. Compared to the baseline, no significant improvement was observed in either group. Significant differences were observed between the two groups at 4 and 8 weeks (Table 2).

IOP was 14.6 ± 3.2 mmHg at baseline, 14.9 ± 2.3 mmHg at 4 weeks, 14.9 ± 2.3 mmHg at 8 weeks, and 14.7 ± 2.0 mmHg at 12 weeks in the BF group, while 14.2 ± 1.2 mmHg at baseline, 15.7 ± 3.7 mmHg at 4 weeks, 16.1 ± 2.0 mmHg at 8 weeks, and 17.0 ± 3.3 mmHg at 12 weeks in the BM group. There was no significant difference between the BF and BM groups at all time points of observation; however, in the BM group, a significant increase in IOP was observed at 8 and 12 weeks compared to baseline (Supplementary Table S1).

CST and BCVA were analyzed in a subgroup of patients with an HbA1c level of less than 8%, which is considered a good glycemic control. The values of CST in this subset of patients were $300.1 \pm 30.9 \mu\text{m}$ at baseline, $295.1 \pm 32.9 \mu\text{m}$ at 4 weeks, $287.9 \pm 28.8 \mu\text{m}$ at 8 weeks, and $276.3 \pm 27.2 \mu\text{m}$ at 12 weeks in the BF group, while $362.0 \pm 67.9 \mu\text{m}$ at baseline, $351.2 \pm 53.1 \mu\text{m}$ at 4 weeks, $366.3 \pm 71.6 \mu\text{m}$ at 8 weeks, and $364.0 \pm 76.0 \mu\text{m}$ at 12 weeks in the BM group. Among these patients in the BF group, CST significantly decreased at 8 and 12 weeks compared to baseline (Table 3). Examination of BCVA in patients with an HbA1c level of less than 8%, we observed values of 75.9 ± 9.2 characters at baseline, 76.4 ± 8.4 characters at 4 weeks, 77.3 ± 6.6 characters at 8 weeks, and 72.0 ± 18.2 characters at 12 weeks in the BF group, while 66.5 ± 7.6 characters at baseline, 67.5 ± 4.7

characters at 4 weeks, 67.3 ± 2.7 characters at 8 weeks, and 66.8 ± 4.8 characters at 12 weeks in the BM group. Compared to baseline, no significant changes were observed in either the BF or BM groups (Supplementary Table S2).

Supplementary Figure S1 shows the representative OCT data of the patients in the BF group at baseline and 12 weeks, with an HbA1c level of 6.7%, indicating good glycemic control. The CST improved from $309 \mu\text{m}$ to $289 \mu\text{m}$, which was the average value of the CST change in the glycemic control group within the BF group. BCVA was 80 and 83 characters at baseline and 12 weeks, respectively.

Adverse events of subretinal fluid (one case, BF group), vitreous hemorrhage (one case, BF group), and elevated IOP (one case, BM group) were observed; all were non-serious events and disappeared/recovered or improved after discontinuation of drug administration.

Discussion

In this study, after analyzing all the patients, we observed no significant improvement in CST and BCVA values with the administration of BF and BM. In patients with good glycemic control with an HbA1c level of less than 8%, CST improved in the BF group; however, the effect on BCVA could not be confirmed. Additionally, compared to baseline, IOP significantly increased at 8 and 12 weeks after administration in the BM group. We have previously reported that compared to betamethasone ophthalmic solution, BF significantly suppressed retinal thickness and intraocular flare value in CME after cataract surgery,¹³ and the results of the present study were in line with those of the previous report.

Chronic inflammation of retinal microvessels causes an increase in inflammatory mediators, including PGs and VEGFs, weakening the blood-retinal barrier and resulting in macular edema.^{14,15} Corticosteroids can reduce macular edema through several mechanisms. One mechanism involves inhibition of the COX-1 and COX-2 inflammatory pathways. NSAIDs act mainly through potent inhibition of prostaglandin E2 (PGE2) synthesis by suppression of arachidonic acid transformation catalyzed by COX-1 and COX-2. Topical NSAIDs do not appreciably reach the posterior segment, whereas intravitreal injection allows greater bioavailability and efficacy of the drug. However, it has been reported that sodium bromfenac reaches the retina sufficiently with topical administration.¹¹ A study using rabbits has confirmed that the instillation of BF twice a day can maintain an IC₅₀ for COX in choroid tissues;¹¹ it has been shown that the instillation of NSAIDs reduced the concentration of PGE2 in the vitreous body.¹⁶ It is believed that BF demonstrated sufficient migration even in ophthalmic solution treatment, and exhibited anti-inflammatory action via PGE2 inhibition in the vitreous body, improving diabetic macular edema. Furthermore, the effects of bromfenac on nuclear factor erythroid 2-related factor 2 (Nrf2), a transcription factor,¹⁷ and VEGF,¹⁸ apart from COX-2, have been reported. Bromfenac exerts an anti-inflammatory effect on substances other than PGE2 similar to sodium diclofenac, which, in addition to inhibition of cyclooxygenase,

regulates leukotriene production by inflammatory cells via a mechanism mediated in part through the redistribution of arachidonic acid in lipid pools.¹⁹ In DME, in addition to increased vascular permeability, retinal inflammation is also an important factor, and these anti-inflammatory actions may be associated with and involved in the improvement of DME.

HbA1c level reflects glycemic control 1–2 months before measurement. The Japanese Clinical Practice Guideline for Diabetes 2019²⁰ showed the target level of glycemic control and indicated a target level of less than 8.0% when treatment strengthening was difficult. Hence, patients with HbA1c levels < 8.0% were subanalyzed as the group with good glycemic control. Many studies have shown that high blood glucose levels are a risk factor for DME.^{21–24} Additionally, in a study with a VEGF inhibitor, bevacizumab, and triamcinolone, compared to the group in which bevacizumab was effective and that in which bevacizumab was ineffective while triamcinolone administration in the vitreous body was effective, the HbA1c level was higher in the group in which both were ineffective.²⁵ Thus, it is thought that drug treatment for DME is affected by glycemic control, and the effect is even greater in ophthalmic solution treatment. Since it was easier to achieve treatment effects via BF in the group with good glycemic control, the improvement in CST by BF might have been observed only in the group with glycemic control. Furthermore, the selection of patients with good glycemic control excluded patients with large fluctuations in the measured values, resulting in a smaller standard deviation of the measured values in the BF group. This may be one reason why a statistically significant difference was observed. Future studies with a larger number of cases are required.

Although previous studies with topical nepafenac ophthalmic solutions showed no effect on DME, it is possible that the patients in their study had milder DME than the patients in our study and the effect of the drug was difficult to ascertain.²⁶ In another paper on the effect of nepafenac ophthalmic solutions, the baseline retinal thickness was $417 \mu\text{m}$ and the retinal thickness after ophthalmic solution administration was significantly reduced by $267 \mu\text{m}$.²⁷ Although the small number of patients in this study remains an issue for future research, the fact that the effect of bromfenac was observed especially in patients with good glycemic control is worthy of special mention and will be of great significance for future research.

As VEGF inhibitors are the first choice for DME treatment, patients who refused vitreous injection and wished to participate in the study were included, with the option of treatment with anti-VEGF. In the present study, the effect on BCVA could not be confirmed in patients who showed an improvement in CST values. This could be because baseline visual acuity was relatively good at 75.9 characters, and DME persisted and was not completely remitted even at 12 weeks. Meanwhile, Browning et al. reported a poor correlation between OCT-measured retinal thickness and visual acuity in DME and indicated that the long-term prognosis of visual acuity cannot be estimated by short-term OCT

results.²⁸ In a study where nepafenac was instilled to DME patients for 210 days, retinal thickness decreased, and visual acuity improved.²⁷ Hence, the effect of bromfenac ophthalmic solution on visual acuity may require a longer period. Therefore, it is necessary to perform studies for a longer period in the future.

Administration of ophthalmic steroids presents risks such as elevated IOP, delayed wound healing, corneal infection, and cataract progression. Meanwhile, the side effects of BF were observed in 1.87%, including corneal erosion (0.42%), conjunctivitis (0.29%), blepharitis (0.23%), irritation (0.21%), eye pain (0.21%), superficial punctate keratitis (0.16%), itchiness (0.16%), corneal epithelial detachment (0.03%), and heat sensation (0.03%).²⁹ Therapy using 0.05% difluprednate ophthalmic emulsion is a useful and effective treatment, and there are also side effects such as increased IOP with topical administration of steroids.³⁰ In the present study, compared to baseline, the level of IOP increased significantly at 8 and 12 weeks in the BM group, with no significant change in IOP in the BF group even after 12 weeks. Moreover, in addition to the absence of complication risks compared to ophthalmic steroids, BF also demonstrated improvements with instillation twice daily. Hence, it is believed that, compared to BM, which requires instillation four times daily, it is easier to continue the administration of BF due to safety and patient adherence to long-term instillation. A few critical side effects have been reported with BF, and this study showed that the effect of BF on macular edema was different from that of BM.

The number of patients in each group of our study was not determined by case design. Although it would be desirable to study more patients, bromfenac ophthalmic solutions and steroid ophthalmic solutions for DME are off-label, and it was ethically difficult to obtain consent in many patients. This is an issue for future research, and we believe it is of great significance as an exploratory study to be conducted next on a larger scale.

In the present study, in patients with good glycemic control, Bronuck Eye Drops (bromfenac) did not affect IOP and demonstrated the effect of significantly improving CST in DME, compared to Rinderon Ophthalmic Solution (betamethasone). The first-line treatment for DME is the administration of anti-VEGF drugs in the vitreous body; however, for patients with mild DME and with few treatment choices due to systemic medical history, treatment with Bronuck Eye Drops may be considered, as it allows treatment via instillation.

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No potential conflict of interest was reported by the author(s).

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Data availability statement

The datasets generated and analyzed during the current study are not publicly available, but are available from the corresponding author upon reasonable request.

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