ORIGINAL ARTICLE

Comparison of different doses of subconjunctival sunitinib with bevacizumab in the treatment of corneal neovascularization in experimental rats

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Background: To compare the efficacy of subconjunctival administration of bevacizumab and different doses of sunitinib malate in reducing corneal neovascularization (CNV). **Materials and Methods:** In this experimental study, central corneal cauterization was created in the right eye of fifty male Sprague–Dawley rats. On day 1 (1 week after cauterization), rats were randomly assigned into five treatment groups. Group control (n = 10) received subconjunctival injection of 0.02 ml of base saline solution. Group 1 (n = 10) received 0.02 ml of bevacizumab (25 mg/ml). Group 2, 3, and 4 (n = 10 for each group) were treated with 0.02 ml of sunitinib malate (10, 20, and 50 μg/ml, respectively). On days 1, 7, and 14, digital photographs of the cornea were taken, and the area of CNV was measured. **Results:** During the 2-week follow-up, CNV area in treatment groups was less than in control group ($P < 0.05$). On day 7, corneal avascular area was highest in Group 3 at 63%. On day 14, the area of CNV in Groups 2 and 3 was less than in Group 1 ($P = 0.031$ and 0.011, respectively), but the difference between Groups 2 and 3 was not statistically significant ($P = 0.552$). The decreased CNV area on day 14 in Group 4 was significant in comparison to bevacizumab, but it was not significant on day 7 ($P = 0.25$ on day 7 and 0.002 on day 14). **Conclusion:** Subconjunctival sunitinib malate is more effective than bevacizumab in regressing CNV. This effect is more prominent on day 14.

Key words: Bevacizumab, corneal neovascularization, rat, subconjunctival, sunitinib

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INTRODUCTION

Corneal angiogenesis is directed by several different mediating factors.[1,2] Vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF) are in consensus to leave the most impressions in corneal neovascularization (CNV). Within the VEGF family, VEGF-A is considered to be the major factor involved in hemangiogenesis.[3] VEGF-A, together with its tyrosine kinase receptors, VEGFR1, and VEGFR2, promote many aspects of the angiogenic process.[1] Furthermore, PDGF induces the necessary pericyte recruitment that supports the vascular maturation. The mural cells surrounding capillaries express PDGF receptor type B (PDGFRB).[4]

Bevacizumab is a recombinant humanized monoclonal antibody directed against all isoforms of VEGF-A.[5,6] It has been used in the off-label treatment of ocular pathologies such as wet-type age-related macular degeneration and proliferative diabetic retinopathy.[7,8] However, all experimental and clinical studies have failed to show complete regression of CNV with the administration of bevacizumab.[9-14]

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Sunitinib is a small molecule tyrosine kinase receptor inhibitor with antiangiogenic activity. It selectively inhibits VEGFR2 and PDGFRB phosphorylation.[15,16] Thus, sunitinib that blocks both mainstream mediators of angiogenesis (i.e., VEGF and PDGF pathways) seems to be more effective in inhibiting and/or treating CNV than bevacizumab which blocks only the VEGF cascade. It has been shown that orally administered sunitinib could reduce choroidal neovascularization in mice.[17] In one study, topical administration of sunitinib reduced VEGFR2 levels and inhibited CNV.[15] Another study showed the superior activity of topical sunitinib over topical bevacizumab in prevention of experimentally induced CNV.[18] Ko *et al*. in a study[19] comparing the inhibition of CNV by subconjunctival and topical bevacizumab and sunitinib in a rabbit model suggested that sunitinib was more effective than bevacizumab for inhibition of CNV.

This study was designed to assess the efficacy of subconjunctival administration of bevacizumab and sunitinib malate in their respective attempts to treat the induced CNV in a rat experimental model.

MATERIALS AND METHODS

Fifty male Sprague–Dawley rats weighting 200–250 g were randomized into five treatment groups ($n = 10$ in each group). Right eye of each was considered for the investigation. All experimental interventions were in accordance with the guidelines of the Association for Research in Vision and Ophthalmology Statement for the Use of Animals in Ophthalmic and Vision Research. The Institutional Animal Care and Use Committee of Tehran University of Medical Sciences also approved our study protocol.

Induction of corneal neovascularization

Rats were anesthetized by intraperitoneal injections of ketamine hydrochloride (25 mg/kg) and xylazine hydrochloride (5 mg/kg). We used tetracaine hydrochloride as a topical anesthetic agent to further remove corneal reflex. To prevent synechia of iris with the inflamed cornea, we administered a drop of tropicamide to induce mydriasis before cauterization of the cornea. Afterward, CNV was induced by pressing an applicator stick (with a diameter of 1 mm) coated with 75% silver nitrate/25% potassium nitrate (Arzol, Keene, N.H., USA) to the central cornea for 3 s. Finally, the eye was rinsed with 5 ml of balanced salt solution and blotted with tissue paper to remove excess silver nitrate. Topical chloramphenicol was instilled before, and then 1 and 5 min after the cauterization for prophylaxis of bacterial keratitis in the injured eye. One investigator cauterized all animals.

Study groups

Rats were randomly assigned into five treatment groups. Immediately after the procedure of corneal cauterization, Groups 1–5 were injected subconjunctivally by 0.02 ml of either normal saline (control group), bevacizumab (Avastin; Genentech Inc., San Francisco, CA, USA) 25 mg/ml (Group 1), and 10, 20, and 50 μg/ml (Groups 2, 3, and 4) of sunitinib malate (Sunitinib malate Sigma-Aldrich, USA), respectively. One investigator who was blind to treatment groups performed all injections.

Evaluation of corneal neovascularization

All eyes were photographed using a Canon 10 Megapixel Digital Camera attached to a slit lamp biomicroscope (Haag-Streit, Koeniz, Switzerland) with ×25. Photographs were obtained before drug administration (day 1) and on day 7 and 14 after treating CNV.

Before injection, evaluation of the corneal burn was performed using a slit lamp biomicroscope. Poor extension of corneal burn area, corneal perforation, or infection was considered as exclusionary criteria. The extent of the chemical burn area, percentage of the corneal surface that was scarred, and CNV area in terms of percentage of total corneal area that was vascularized were measured by a masked investigator to treatment groups. Photographs were analyzed by the software ImageJ 1.31v (Wayne Rasband at the Research Services Branch, National Institute of Mental Health, Bethesda, MD, USA). The efficacy of the treatment was considered as the amount of reduction in the percent of CNV from the treatment day to the two successive evaluation time points.

Statistical analysis

Analysis used SPSS version 17 (SPSS, Inc., Chicago, Illinois, USA). Differences were considered statistically significant when $P < 0.05$. The one-sample Kolmogorov–Smirnov test was used to check normality of the distribution of the data.

As the data fitted the normality curve, parametric tests were used. Treatment groups were compared in terms of corneal avascular area and scar tissue at specific time points, using the analysis of variance test. Equality of the variances was compared using Levene statistic. Once the variances were equal or unequal, pairwise multiple comparisons were performed using the Tukey's or Tamhane tests, respectively.

RESULTS

Forty-six had acceptable CNV and scar area on the treatment day [Figure 1]. Percentage of vascularized and scar area for each group is illustrated in Table 1. Four eyes were excluded from follow-up; one from control group and one from Group 3 due to perforation. Two eyes were excluded from Group 2 because of infection.

There was no statistically significant difference ($P > 0.05$) regarding CNV area among the study groups on day 1. In the

control group, mean neovascularized area was 61% on day 1 that increased to 66% and 68.4% on day 7 and 14, respectively. All treatment groups had significantly less CNV area compared to the control group on day 7 and 14 ($P < 0.001$).

In Group 1, CNV area decreased about 28.7% and 30.2% by the day 7 and 14 after cauterization, respectively. The decrease in neovascularized area from day 7 to day 14 was not statistically significant in this group ($P = 0.154$). Although CNV area in Group 2 was significantly reduced, it was not significant in comparison to bevacizumab throughout the follow-up period ($P = 0.81$ on day 7 and 0.08 on day 14). In Group 3, CNV area was reduced significantly ($P = 0.007$) between the two consecutive measurements on day 7 and 14. In this group, CNV was significantly less than Group 1 on day 14, but it did not differ significantly on day 7 ($P = 0.41$ on day 7 and = 0.04 on day 14). The decreased CNV area on day 14 in Group 4 was significant in comparison to bevacizumab, but it was not significant on day 7 ($P = 0.25$ on day 7 and $P = 0.002$ on day 14). The neovascularization area did not differ significantly between Group 3 and 4 during the follow-up period ($P = 0.133$) [Figures 2 and 3].

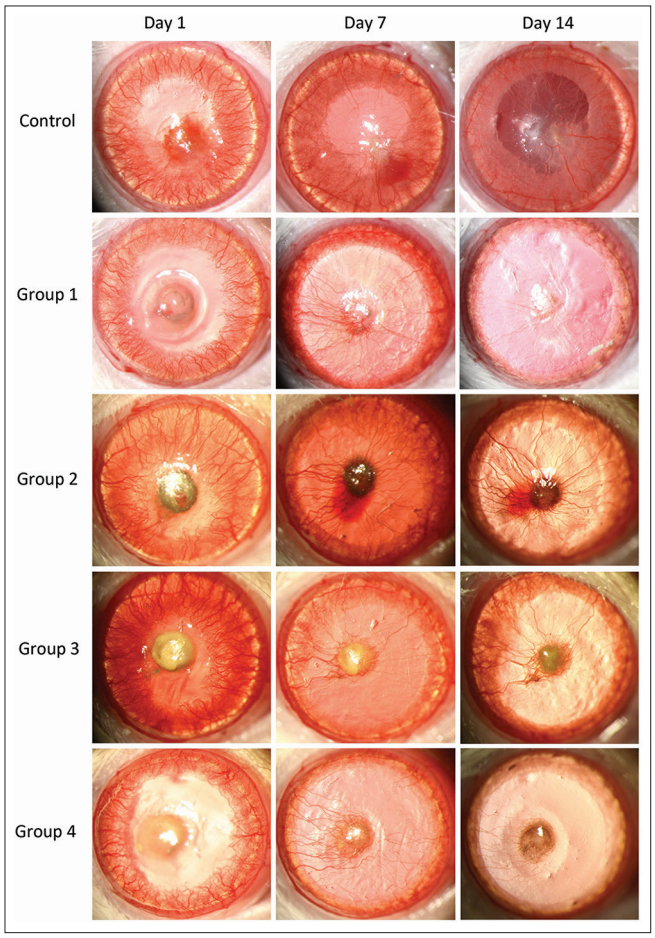

Figure 1: Representative photographs of the treatment groups demonstrating neovascularization extension on the treatment day (day 1), day 7, and day 14. Eyes in group control were treated with balanced salt solution and showed increasing corneal neovascularization during 14 days of follow-up. Group 1 received a single subconjunctival injection of bevacizumab. Group 2, 3, and 4 were treated with subconjunctival injection of sunitinib malate (10, 20, and 50 μg/ml, respectively)

Comparison between the antiangiogenic efficacies of these two revealed a 1.12-fold greater potency for bevacizumab, in comparison to sunitinib malate after 1 week of follow-up. Although the difference between the inhibitory effect of sunitinib malate 10 μg/ml and bevacizumab remained insignificant after 14 days, the trend shifted drastically in favor of sunitinib malate, with a 1.25-fold greater efficacy for sunitinib malate 10 μg/ml for the resolution of the remnants of CNV during the aforementioned period. In the groups with higher doses of sunitinib malate treatment, there was a greater efficacy for sunitinib malate in comparison to bevacizumab although this greater efficacy was not statistically different on day 7 and was only significant on day 14 in Groups 3 and 4 (20 and 50 μg/ml). Accordingly, the inhibition of CNV achieved with sunitinib 20 μg/ml was 1.32-fold and 1.47-fold greater than that achieved with bevacizumab after 1 and 2 weeks of follow-up, respectively. After the same treatment intervals, these ratios were 1.32-fold and 1.56-fold greater in Group 4 (50 μg/ml) in comparison to bevacizumab group.

Table 1: Corneal neovascularization by slit-lamp biomicroscope during the various stages of follow-up

Groups	Day 1		Day 7		Day14	
	CNV±SD	Scar±SD	CNV±SD	*P**	CNV±SD	*P**
Control	61.6±14.3	4.66±1.1	66.0±18.9	0.192	68.4±19.8	0.075
Group 1	60.3±7.6	3.75±0.5	31.6±9.5	0.002	30.1±11.52	0.002
Group 2	58.4±14.8	6.37±0.7	32.8±15.1	0.017	20.7±10.6	0.012
Group 3	66.7±12.0	6.0±0.4	28.8±5.9	<0.001	22.2±5.4	<0.001
Group 4	63.7±12.4	5.36±0.61	25.8±13.7	<0.001	16.5±6.1	<0.001

CNV = Corneal neovascularization; SD = Standard deviation. *Wilcoxon test was used; *P* values represent comparison of mean percent of corneal neovascularization area at Day 7 and Day 14 with Day 1.

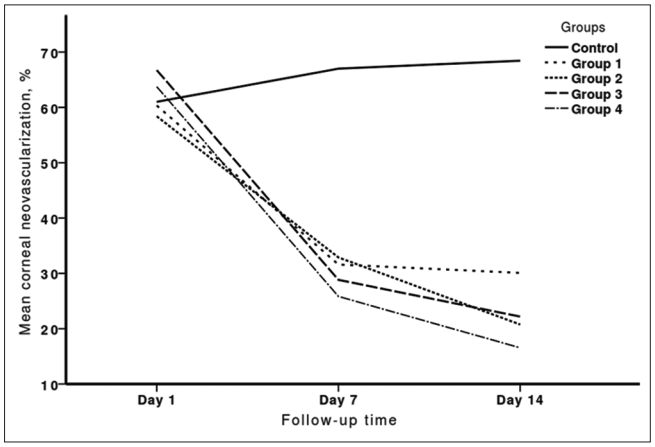

Figure 2: mean corneal neovascularization area during follow-up time in control and treatment groups

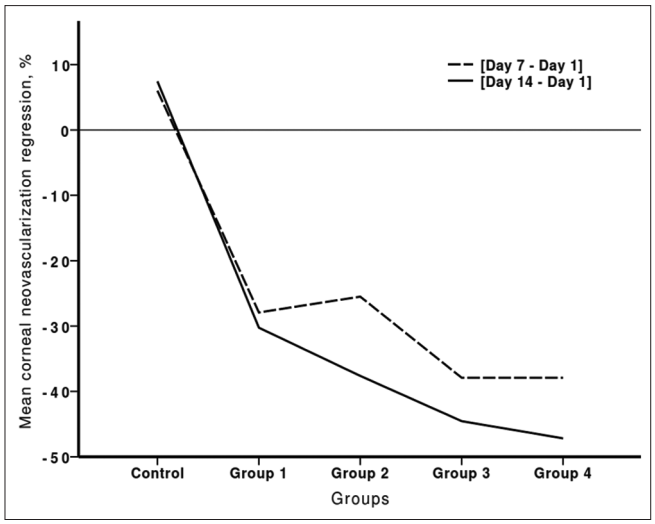

Figure 3: mean corneal neovascularization area regression during follow-up time (day 7 to day 1 and day 14 to day 1) in control and different treatment groups

DISCUSSION

Similar to findings of the earlier studies,[10,12,18-20] we observed that CNV regressed significantly following bevacizumab treatment. However, this reduction should not be interpreted as a complete resolution of the condition, an issue that emphatically suggests the presence of other regulators of angiogenesis that may act irrespective of or in conjunction with the VEGF pathway. Jo *et al*. in their study reported an enhancement of the VEGF pathway in formation of new vessels through the PDGF-B signaling pathway.[4] This enhancement is further highlighted, considering the notion that newly formed vessels, i.e., CNV would regress spontaneously unless encapsulated by the pericytes around the capillaries and smooth muscle cells (aka mural cells) around the larger vessels. The recruitment of mural cells to the endothelial layer is mainly dependent on levels of PDGF-B in the adjacent areas, as secreted by endothelial cells.[21,22]

Sunitinib malate is a multi-targeted tyrosine kinase receptor inhibitor that unlike the conventional anti-VEGFs inhibit the tyrosine kinase receptor complex of VEGFR1, VEGFR2, and PDGFRB phosphorylation in a time- and dose-dependent manner.[16] Previous reports have demonstrated that simultaneous inhibition of both VEGFR2 and PDGFRB may not only prevent angiogenesis through inhibition of endothelial proliferation by VEGFR2 but also induce regression of neovascularization, possibly through destabilization of pericyte-endothelial cell interaction by PGDFR. These reports suggest that inhibition of PDGFR may only augment the therapeutic effects of this drug on CNV. Our results confirm that inhibition of CNV achieved with sunitinib malate 10 μg/ml has not had a significant difference compared to that achieved with bevacizumab [Table 1].

Our observations could be due to a number of reasons

The inhibitory effect of bevacizumab is generally seen in newly forming vessels rather than the established ones. Therefore, there could be a possibility that the initial advantage of bevacizumab over sunitinib malate 10 μg/ml is temporary and will disappear over the course of treatment; analysis of data during the 2nd week of treatment between the same categorical groups confirms this explanation. In addition, the percentage of CNV regression in bevacizumab-treated group, unlike the rest of the categories, does not suggest a significant change between weeks 1 and 2 of treatment.

We evaluated the inhibitory effect only in terms of the mean percentages of neovascularized corneal area, which does not allow for the exact area of CNV. Furthermore, we did not analyze the diameter or the number of newly formed vessels in the cornea. Such information may prove vital to detect the delicate differences between bevacizumab and lower doses of sunitinib malate treatment. This may be another reason for the lack of significant difference between the strength of bevacizumab and sunitinib malate 10 to successfully regress the CNV area, particularly in the 1st week of treatment.

The initial lower dose of sunitinib malate 10 μg/ml may well be below par, the minimum dosage of sunitinib malate to exert its superior effects on CNV inhibition in comparison to bevacizumab. We believe this may be a more realistic scenario for this observation, as we were able to detect significant differences between the higher doses of sunitinib malate (20, 50) and bevacizumab in the other groups.

Another interesting observation is the same therapeutic potency of sunitinib malate 20 μg/ml and 50 μg/ml; both showing 1.32-fold greater efficacy over bevacizumab after 7 days. We believe this could be explained by a variety of factors; first, sunitinib malate; unlike bevacizumab that targets only the VEGF system, is a multi-targeted receptor inhibitor. This inhibition of VEGFR1, VEGFR2, and PDGFRB prevents the activation of a wider intracellular pathways (including Mek-Erk and PI-3 Kinase-Akt) involved in the angiogenesis associated with CNV, whereas bevacizumab is only effective in the inhibition of pathways correlated with the VEGF system. This means that a lower dose of sunitinib malate could potentially induce a comparable result to a higher dose of bevacizumab in terms of their therapeutic effects; second, sunitinib malate is a receptor inhibitor, whereas bevacizumab is a monoclonal antibody of VEGF-A and more accurately, is a ligand inhibitor. During an interaction between a ligand and the related receptor, a minimal dose of ligand proves enough to exert a satisfactory effect on its respective receptor. This is largely owing to the activation of a cascade of intracellular pathways that are capable of enhancing the initial response

to the ligand by triggering a complex of secondary messengers. This results in a logarithmic increase in the therapeutic response with increase in the initial dose of ligand (geometric progression). While bevacizumab is arguably a potent inhibitor of angiogenesis with disabling the central mediator of this process in VEGF-A, it is of the extreme importance to recall that every day, considerable amounts of VEGF are produced in the body, especially in the pathological states, providing every opportunity for the inevitable progression of CNV. This, in our opinion, makes the task of ligand-targeted drugs including bevacizumab a difficult one, considering the fact that even a very minor portion of the daily produced VEGF, if not neutralized by bevacizumab, is more than capable of inducing a considerable angiogenic effect. In other words, the initial dosage of bevacizumab needed to provoke a significant clinical response is set at a comparatively higher level as opposed to drugs that target the receptor, instead of ligand, like sunitinib malate. Hence, the clinical response of ligand-targeted bevacizumab with the increase in the primary dosage increases in a more linear manner; third, the insignificant difference between the antiangiogenic effects of sunitinib malate 20 μg/ml and 50 μg/ml in this period might indicate the saturation of receptor sites, it suggests the efficacy of lower doses of sunitinib malate applied in our study, compared to the previous works.

In 2006, a report by Takahashi *et al*. demonstrated that orally administered sunitinib malate was able to significantly reduce the volume of experimental choroidal neovascularization membranes in mice.[17] The effect of time-dependent therapy has previously been cited in earlier studies. In an experimental rabbit model, topical sunitinib malate significantly inhibited CNV; this effect was 2.6-fold and 2.9-fold more effective than bevacizumab, after 7 and 14 days of treatment, respectively.[18] However, the dose-dependent effect has never been acknowledged in the preceding reports, and to the best of our knowledge, this is the first study to address this issue in an experimental murine model.

In our previous study, we showed that both topical and subconjunctival bevacizumab is useful, but the subconjunctival route is more effective than the topical one.[23] The lower dose of the subconjunctival injection has comparable effectiveness with higher doses of topical administration. Similarly, the decision to apply the same therapeutic form of sunitinib malate was dependent on a number of reasons. Subconjunctival route of administration is widely used with relatively few side effects. It has less epithelial toxicity in the long term.[24] It would be suitable for noncompliant patients as well as those with preexisting epitheliopathy.

Despite our concern about direct conjunctival irritation of sunitinib, we did not observe any conjunctival necrosis or infection in any of the groups. Seven days after cauterization, small areas of intrastromal pigmented scarring in the paracentral cornea were seen in two eyes. They remained stable in size after treatment, one eye within sunitinib 20 μg/ml and one within sunitinib 50 μg/ml. Furthermore, we did not observe any subconjunctival yellow deposit or iris staining in our study. This meets our expectation that such deposits are mostly indicative of the topical administration of sunitinib malate as they might show that sunitinib malate is able to reach the intraocular space through this method of application.[18,19] Moreover, another explanation could easily stem from the lower doses of sunitinib malate applied in our study, as opposed to the earlier reports with much higher doses of sunitinib malate.

The limitations of our study, however, include the short follow-up period and lack of information about the biocompatibility of sunitinib malate. Further trials with longer periods of follow-up will be necessary to address this point. In our study, doses of sunitinib malate were drastically decreased from the previous reports, mainly to minimize the ocular toxicity associated with sunitinib malate[25] and also to establish an objective comparison between the angioinhibitory effects of the bevacizumab versus the corrected values of sunitinib malate. The controversy in sunitinib malate dosage for the optimal CNV treatment is not ignorable and mandates further studies to elucidate the optimal dosage. There remains the need to determine the proper treatment intervals duration; larger studies with further follow-up periods are missed at the moment.

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Conflicts of interest

There are no conflicts of interest.

AUTHORS' CONTRIBUTIONS

- MNH contributed in the conception of the work, conducting the study, revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work.
- MSS contributed in the conception and design of the work, conducting the study, approval of the final version of the manuscript, and agreed for all aspects of the work. (It was her residential thesis)
- MM contributed in drafting and revising the draft, approval of the final version of the manuscript.

- HZM contributed in the conception of the work, conducting the study, analysis of the data.
- YSh contributed in the design of the work, and agreed for all aspects of the work
- FRM, AZ,MFT,BBS contributed in the conception of the work, and agreed for all aspects of the work
- MA contributed revising the draft.
- MAA and SHA contributed in the conception of the work, and agreed for all aspects of the work.

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