Journal of Clinical & Experimental Ophthalmology

Bilgic et al., J Clin Exp Ophthalmol 2019, 10:6

Case Series Open Access

Polypill Therapy for Recalcitrant Clinically Significant Macular Edema: A Prospective Case Series

Alper Bilgic[1], **Aditya Sudhalkar**[2], **Jay Trivedi**[3], **Tejas Desai**[3], **Usha Vyas**[3], **Bakulesh Khamar**[3]

[1]*Alphavision Augenzentrum Bremerhaven, Germany*

[2]*MS Sudhalkar Medical Research Foundation, Baroda, Gujarat, India*

[3]*NHL Medical College, Ahmedabad, India*

[*]**Corresponding author:** Aditya Sudhalkar, Medical Research Foundation, 22 Pratapgunj, Baroda, Gujarat, India, Tel: +912652793799; E-mail: adityasudhalkar@yahoo.com

Received date: December 11, 2019; **Accepted date:** December 26, 2019; **Published date:** December 31, 2019

Abstract:

Background: To determine the utility of the polycap in treatment of refractory diabetic macular edema.

Methods: Prospective case series. The study included 60 patients (>18 years; 37 males) with well controlled type 2 diabetes mellitus, hypertension and dyslipidemia and diffuse CSME (clinically significant macular edema) refractory to conventional therapy. Patients included had received at least 1). Three intravitreal ranibizumab injections and two sessions of macular laser photocoagulation. A complete ocular and systemic exam was performed along with FFA (fluorescein angiography) and OCT (Optical Coherence Tomography). The polypill was administered orally once daily in the morning after breakfast. Monthly follow-ups were scheduled. Appropriate statistical analysis was done. Outcome measures: Primary-the change in VA from baseline over one year. Secondary-The change in CMT over one year and adverse events.

Results: The median age was 60.4 ± 5.42. Median duration of diabetes: 13.24 ± 4.18 years. 21 patients were on both oral hypoglycemic and insulin therapy. The median duration of CSME was 11.65 ± 3.47 months (5-26 months). Baseline VA improved from 0.72 ± 0.16 logMAR to 0.64 ± 0.09 logMAR (p=0.03) at one year. Median CMT improved from 364.2 ± 31 microns to 297.23 ± 30.11 at one year (p=0.027). Systemic parameters too improved significantly. No adverse events were noted.

Conclusion: The polypill appeared safe and effective in treatment of recalcitrant diabetic macular edema, probably by improved compliance. Trial Registration: N/A.

Keywords: Polypill; Diabetic macular edema; Chronic; Recalcitrant; Compliance systemic control

List of Abbreviations OCT: Optical Coherence Tomography; FFA: Fundus Fluorescein Angiography; CSME: Clinically Significant Macular Edema; CMT: Central Macular Thickness; CDVA: Corrected Distance Visual Acuity; ETDRS chart: Early Treatment Diabetic Retinopathy Study Chart; CFT: Central Foveal Thickness.

Background

Diabetic macular edema [1,2] refractory to treatment with anti-vascular endothelial growth factor injections (anti-VEGF agents), intravitreal/periocular steroids, immunomodulators and laser photocoagulation [3-7] remains one of the most prevalent causes of visual loss in patients with diabetic retinopathy. The visual disability coupled with the cost of treatment (especially for those without medical insurance) can prove to be a tremendous burden for these patients. Additionally, these patients often have co-existent systemic disease, which worsens both the ocular condition and consequently their handicap.

Suggested treatments for such recalcitrant diabetic macular edema include tight systemic control multiple sessions of laser photocoagulation, repeated intravitreal injections, immunomodulators, combination therapy and even vitrectomy with internal limiting membrane removal in select cases [3-7].

The use of a polycap [8-19] has been explored, in patients with and without raised cardiovascular risk to lessen morbidity and mortality. Controversy exists as to its usefulness, with some studies suggesting educed morbidity and mortality [8-10], while other studies [14,15] questioning its benefit and rationale. The role of systemic therapy to alleviate diabetic macular edema has been explored; with numerous publications providing evidence that control of co-morbidities along with tight diabetic control helps improve diabetic macular edema refractory to local therapy [16-23].

We aimed to explore (preliminarily) the utility of the Indian polycap in improving visual acuity and reduction of macular edema in patients with well controlled type 2 diabetes mellitus with co-morbidities (also seemingly well controlled) refractory to conventional therapy. The study also provides preliminary data on the safety of the polycap in these patients.

Methods

This prospective study (a case series) was conducted at the Nagri Eye Hospital and V.S. Municipal Hospital, Ahmedabad, India. The polypill used in this study consists of: Atenolol 50 mg, ramipril 5 mg, hydrochlorothiazide 12.5 mg, simvastatin 20mg and aspirin 100 mg (manufactured by Cadila Pharma Pvt. Ltd.). The study adhered to the tenets of the Declaration of Helsinki. The study was approved by the institutional review board for the Nagri Eye Hospital, Ahmedabad (Nagri Eye Hospital IRB). The approval number was NEH/2011/42. All patients provided written, informed conset for the use of this pill and any alterations in their treatment regime that may arise as a consequence of the introduction of this pill.

Inclusion criteria

Patients included in this study were ≥ 18 years and were required to have:

1). Any NPDR with diffuse clinically significant macular edema refractory (defined subsequently) to conventional treatment with persistence of macular edema in type 2 diabetic patients and a corrected distance visual acuity of 20/40-20/320 Snellen's equivalent on ETDRS testing.

2). Well controlled co-morbidities, if any

3). Intact perifoveal capillary arcade

4). A central foveal thickness of more than 250 microns

5). Clear ocular media

6). Willing patient

7). An HbA1c value of less than 7.0% within the past three months.

8). Co-existent hypertension and dyslipidemia. Should the disease be bilateral, one eye was included in the study.

Patients who had had

1). At least three injections of intravitreal ranibizumab and

2.) Two previous sessions of laser photocoagulation and

3.) The last session of treatment (laser or intravitreal injections) at least three months prior to enrolment and who showed a less than 50 micron change in central foveal thickness from the last scan for two consecutive months were termed to have refractory diabetic macular edema.

Good control of hypertension was defined as a blood pressure consistently recorded to be 140/90 or less, either with pharmacotherapy or lifestyle modification, for at least the past six months, with no change in therapy during that time. Good control of dyslipidemia (either with pharmacotherapy or lifestyle modification) was defined as 1) A serum cholesterol value of 200 mg/dl or less, 2) A serum triglyceride level of 150 mg/dl or less, 3) A serum high density lipoprotein level of 40 mg/dl or more for men and 50 mg/dl or more for women and, 4) A serum low density lipoprotein value of less than 110 mg/dl (all consistently for at least six months) with pharmacotherapy or lifestyle modification, with no change in therapy for the past six months.

Exclusion criteria

Patients with proliferative diabetic retinopathy, a contraindication to any of the components of the pill, with coexistent potentially confounding ocular disease (other than nuclear sclerotic cataract ≤ grade II as per the LOCS III classification) and those unable to maintain regular follow up were excluded from the study.

Examination procedure

A thorough history was obtained from all patients. Details of the current therapy and ocular procedures performed thus far were obtained. The corrected distance visual acuity, particulars of the anterior and posterior segment exam and the special investigations performed were noted. Visual acuity was recorded using the ETDRS chart and intraocular pressure using the Goldman Applanation tonometer. All patients under went fundus fluorescein angiography to rule out neovascular changes, to determine the type of diabetic macular edema (focal or diffuse) as well as to rule out macular ischemia. Angiography was repeated at investigator discretion. Optical coherence tomography (OCT) analysis was performed to determine the central foveal thickness (CFT). This was repeated at each follow up visit.

Once a patient was deemed eligible for the study, polycap therapy was initiated on a once daily basis. The patients were instructed to take the pill in the morning after breakfast.

Follow up visits were scheduled monthly. The CDVA, the retinal findings, the blood glucose levels and the retinal thickness (on OCT scans) were monitored at each visit. Progressive worsening of the diabetic retinopathy lead to exclusion of the patient from the final analysis, as these patients were scheduled for pan retinal laser photocoagulation. Therapy was discontinued if the patients developed any adverse events. Treatment was to be continued for at least three months. If there was evidence of recurrence of diabetic macular edema after stoppage of therapy, the patients had the choice of being reinstated on polycap treatment. The ocular examination and blood pressure measurement was repeated at monthly intervals. The lipid profile and HbA1c levels were monitored at six months. All visual and OCT analyses were performed at three months, six months and at the end of one year. Systemic parameters were assessed at three months and one year.

Follow up

Patients were followed up on days 30, 60, 90, 120, 180, 270 and 365 after initiation of therapy. Patients were instructed to report earlier should they develop any adverse events and/or if their symptoms continued to worsen despite strict adherence to therapy. Further ocular and systemic therapy was permissible if the condition did not improve (judged as mentioned in our inclusion criteria). Therapy was discontinued if patients developed intolerance to the pill.

Statistical analysis

The paired t test was used to assess the change in visual acuity as well as the change in central macular thickness with therapy over time. The paired t-test was also used to analyze the change in blood pressure, serum cholesterol, serum triglyceride levels and serum low density lipoproteins (LDL) levels over time with therapy. The ANOVA test was used to determine if there was a significant change in values over the stated follow up period. Statistical significance was set at $p<0.05$.

Outcome measures

The change in visual acuity over time was the primary outcome measure. Secondary outcome measures included the change in central foveal thickness as documented on serial OCT scans. The proportions of patients who gained and lost 10 or more letters were noted. Adverse events, if any, were documented.

Results

A total of 66 patients with type II diabetes, hypertension and dyslipidemia were deemed eligible for the study of which 4 were lost to follow up prior to the three month visit. Two patients progressed to proliferative diabetic retinopathy on treatment and were excluded from the analysis. The remaining 60 patients were available for the one year follow up and were compliant with therapy.

There were 37 males and 23 females available for analysis at both the three month and one year visit. The median age was 60.4 ± 5.42 years with a range of 52-67 years. The median duration of diabetes mellitus was 13.24 ± 4.18 years with a range of 7-18 years. 21 patients were on both oral hypoglycemic and insulin therapy; the rest were on oral hypoglycemic therapy. All patients were on at least two different oral hypoglycemic agents; six patients were on three. None of the patients were on a thiazolidinedione. The median duration of hypertension in these patients was 13.43 ± 4.53 years. Fourteen patients were on amlodipine and an ACE inhibitor. 20 patients were on atenolol and the rest were on an ACE inhibitor alone. The median duration of dyslipidemia was 9.56 ± 3.86 years. None of the patients with dyslipidemia were on more than one class of drug for dyslipidemia and in all patients the prescribed drug was from the statin group. The introduction of the polycap meant a change in their therapy, and this was in consult with the treating physician. None of the other patients had systemic co-morbidities that required a change in therapy.

The baseline mean visual acuity was 0.72 ± 0.16 logMAR with a range of 0.3- 1 logMAR. The visual acuity at three months was 0.67 ± 0.1 logMAR (p=0.51) and at six months was 0.65 ± 0.09 logMAR (p=0.038 from baseline). The visual acuity at one year was 0.64 ± 0.1 logMAR (p=0.03 from baseline). Eleven patients were pseudophakic. The median duration of CSME was 11.65 ± 3.47 months with a range of 5 to 26 months. The median number of injections was 5.7 ± 1.4 with a range of 3-9 injections. All 60 patients had received two sessions of focal laser. The median central foveal thickness reduced from 364.2 ± 31 microns to 327.12 ± 23.35 microns at three months (p=0.12), 308.42 ± 25.31 at six months (p=0.038 and 297.23 ± 30.11 microns (p=0.027) at one year. 20 patients (33%) gained two or more lines of vision; 26 patients gained one line of vision while 14 patients maintained their vision. None of the patients lost any letters on the ETDRS chart. We noted an inverse correlation between the reduction in CFT and gain in vision(r=-0.64; p=0.015). None of the patients developed any adverse events related to the said therapy. No patient required discontinuation of therapy. None of the patients required any local therapy during the course of follow up. Figure 1 provides an illustrative case.

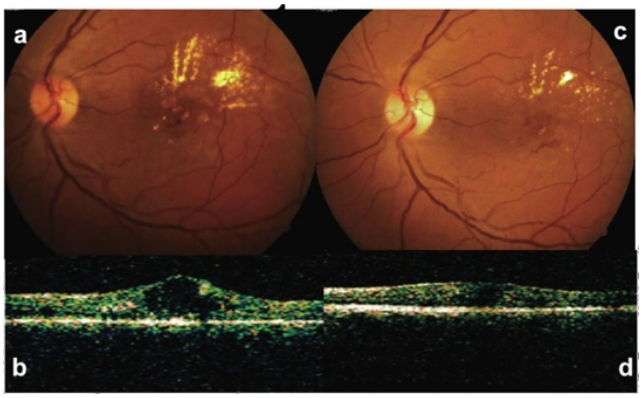

Figure 1: (a) Depicts the fundus photograph of the left eye of a 64 year old female patient who had received five injections of intravitreal ranibizumab and two sessions of laser photocoagulation in an attempt to improve CSME. The exudates and hemorrhage along with retinal thickening are evident, as is the retinal thickening along with intraretinal cystic changes on optical coherence tomography in Figure 1(b). The clinical picture has improved considerably with a reduction in retinal thicknening and exudates and is seen in figure 1(c), while the reduction in CFT is confirmed by OCT in figure 1(d). The CFT improved from 356 microns to 288 microns at one year and the vision from 0.8 logMAR to 0.54 logMAR.

Systemic parameters

The baseline blood pressure was 134.42 ± 13.24 mm Hg and this dropped to 119.43 ± 10.15 mmHg (p=0.044) at the three month visit; the blood pressure was maintained at 116 ± 11.12 (p=0.04) mmHg at the end of one year. The serum cholesterol level fell from 196.4 ± 23.32 md/dl to 165.42 ± 15.42 (p=0.032) mg/dl at the end of three months; this had stabilized to 161.42 ± 14.74 mg/dl (p=0.029) at the end of one year. The serum LDL level dropped from 104.21 ± 13.22 mg/dl to 96.42 ± 7.29 mg/dl at three months (p=0.06) and 87.11 mg/dl ± 9.64 mg/dl at the end of one year (p=0.047). The serum triglyceride level fell from 185 ± 15.32 mg/dl to 167.32 ± 14.26 mg/dl at the end of three months (p=0.057) and 160.42 ± 9.31 mg/dl at the end of one year (p=0.035).

The results appear to suggest that polycap therapy appears to improve visual, anatomic and systemic parameters in patients with refractory diabetic macular edema.

Discussion

Our study clearly shows the potential utility of the polypill in addressing refractory diabetic macular edema. We demonstrate good results in patients with refractory diabetic macular edema. The study is to the best of our knowledge the first of its kind wherein a polypill has been used in an attempt to improve treatment resistant diabetic macular edema. Of note is that all these patients apparently had excellent systemic control for at least six months prior to enrolment and throughout the duration of follow up. They had received multiple attempts at treatment for macular edema without any significant success. However all patients showed some response to therapy with the poly cap right from the first month of treatment and yet they improved with polypill therapy. This suggests that compliance was

probably a matter of concern in this group of patients. Laboratory tests tend to give the treating physician an incomplete picture of the regularity of intake of medications.

Patients often tend to improve compliance, lifestyle modification and dietary regulation when a visit to the physician is imminent; this is probably why the polypill seemed to work in patients with apparently good control. The role of compliance in improving disease is well known [23, 24].

A review of literature reveals that successful attempts have been made in the past to arrest or improve the progression of diabetic retinopathy through the regulation of altered systemic parameters.

THE HOORN STUDY [16] concluded that retinopathy is a multifactorial microvascular complication, which, apart from hyperglycemia, is associated with blood pressure, lipid concentrations, and BMI.

Rehab Benarous et al [17] found that serum lipids are independently associated with the CSME, but not with DR, mild or moderate DME, or macular thickness.

Amod Gupta [18] and Panagiotoglou [19] concluded that Oral atorvastatin therapy in patients with type 2 diabetes with dyslipidemia reduces the severity of hard exudates and subfoveal lipid migration in CSME and could be an important adjunct in the management of clinically significant macular edema.

SM Rassam et al [20] showed that impairment in retinal vascular autoregulation in response to raised systemic blood pressure in diabetic subjects, more so at an elevated blood glucose level, thus providing a mechanism for the detrimental effect of hypertension on diabetic retinopathy and its control can reduce retinopathy as shown by Hans-Henrik Parving [21] and The UK Prospective Diabetes Study (UKPDS) [22].

We speculate that the polypill works by improving compliance and regulating microvascular circulation in diabetics.

The obvious limitations of the study were the small sample size, the lack of a comparative arm and the absence of masking. Despite these limitations, it is important to note that the introduction of the polypill helped improve vision.

Also, only two patients showed progressive worsening of the diabetic retinopathy. While none of the patients had significant non-perfusion as noted on standard fluorescein angiography, the use of the ischemic index and wide field angiography [25] might further improve our understanding of recalcitrant diabetic macular edema. Concurrent therapy might be better.

Conclusion

To conclude, the use of the polycap in the treatment of refractory diabetic macular edema in patients with type 2 DM and coexistent systemic morbidities has shown encouraging results. The purpose of the study was to provide preliminary data on its use in the said condition. The efficacy and safety of this therapy can be confirmed in future randomized controlled trials with multiple arms depending on previous ocular and systemic therapy.

Declaration

Ethics Approval and Consent to Participate: Obtained

Consent for Publication: Obtained.

Availability of Data and Material: Yes. Data will be made available on request

Competing Interests: None

Funding: None

Acknowledgements: None

References

1. Nguyen QD, Brown DM, Marcus DM, Boyer DS, Patel S, et al. (2012) Ranibizumab for diabetic macular edema: results from 2 phase III randomized trials: RISE and RIDE. Ophthalmology 119: 789-801.
2. Nakano S, Yamamoto T, Kirii E, Abe S, Yamashita H (2010) Steroid eye drop treatment (difluprednate ophthalmic emulsion) is effective in reducing refractory diabetic macular edema. Graefes Arch Clin Exp Ophthalmol 248: 805-810.
3. Boyer DS, Yoon YH, Belfort R Jr, Bandello F, Maturi RK, et al. (2014) Three year, randomized, sham-controlled trial of dexamethasone intravitreal implant in patients with diabetic macular edema. Ophthalmology 121: 1904-1914.
4. Kim YT, Kang SW, Kim SJ, Kim SM, Chung SE (2012) Combination of vitrectomy, IVTA, and laser photocoagulation for diabetic macular edema unresponsive to prior treatments; 3-year results. Graefes Arch Clin Exp Ophthalmol 250: 679-684.
5. Dutra Medeiros M, Postorino M, Navarro R, Garcia-Arumí J, Mateo C, et al. (2014) Dexamethasone intravitreal implant for treatment of patients with persistent diabetic macular edema. Ophthalmologica 231: 141-146.
6. Pacella E, Vestri AR, Muscella R, Carbotti MR, Castellucci M, et al. (2013) Preliminary results of an intravitreal dexamethasone implant (Ozurdex®) in patients with persistent diabetic macular edema. Clin Ophthalmol 7: 1423-1428.
7. Sfikakis PP, Grigoropoulos V, Emfietzoglou I, Theodossiadis G, Tentolouris N, et al. (2010) Theodossiadis P Infliximab for diabetic macular edema refractory to laser photocoagulation: A randomized, double-blind, placebo-controlled, crossover, 32-week study. Diabetes Care 33: 1523-1528.
8. The Indian Polycap Study (TIPS) (2009) Effects of a polypill (Polycap) on risk factors in middle-aged individuals without cardiovascular disease (TIPS): A phase II, double-blind, randomised trial. The Lancet 373: 1341-1351.
9. Patel A, Shah T, Shah G, Jha V, Ghosh C, et al. (2010) Preservation of bio availability of ingredients and lack of drug-drug interactions in a novel five-ingredient polypill (polycap): A five-arm phase I crossover trial in healthy volunteers. Am J Cardiovasc Drugs 10: 95-103.
10. Yusuf S, Pais P, Sigamani A, Xavier D, Afzal R, et al. (2012) Comparison of risk factor reduction and tolerability of a full-dose polypill (with potassium) versus low-dose polypill (polycap) in individuals at high risk of cardiovascular diseases: the Second Indian Polycap Study (TIPS-2) investigators. Circ Cardiovasc Qual Outcomes 5: 463-471.
11. Yusuf S (2002) Two decades of progress in preventing vascular disease. The Lancet 360: 2-3.
12. Wald DS, Morris JK, Wald NJ (2012) Randomized Polypill crossover trial in people aged 50 and over. PLoS ONE 7: e41297.
13. Working Group on the Summit on Combination Therapy for CVD, Yusuf S, Attaran A, Bosch J, Joseph P, et al. (2014) Combination pharmacotherapy to prevent cardiovascular disease: Present status and challenges. Eur Heart J 35: 353-364.
14. Spence JD (2014) A single fixed-dose combination for all patients is bad medicine. Can J Cardiol 30: 513-516.
15. Reiner Z (2013) Polypill is not a 'vaccine-like' solution for primary cardiovascular disease prevention in all parts of the world. J Epidemiol Community Health 67: 981-982.

16. Van Leiden HA, M Dekker J, C Moll A, Giel Nijpels, J Heine R, et al. (2002) Blood Pressure, Lipids, and Obesity are associated with retinopathy diabetes care 25: 1320-1325.
17. Benarous R, Sasongko MB, Qureshi S, Feniwick E, Dirani M, et al. (2011) Differential association of serum lipids with diabetic retinopathy and diabetic macular edema. Inv Ophthalmol Vis Sci 52: 7464-7469.
18. Gupta A, Gupta V, Thapar S, Bhansali A (2004) Lipid-lowering drug atorvastatin as an adjunct in the management of diabetic macular edema. Am J Ophthalmol 137: 675-682.
19. Rassam S, Patel V, Kohner E (1995) The effect of experimental hypertension on retinal vascular autoregulation in humans: A mechanism for the progression of diabetic retinopathy. Exp Physiol 80: 53-68.
20. Parving HH (1991) Impact of blood pressure and antihypertensive treatment on incipient and overt nephropathy, retinopathy, and endothelial permeability in diabetes mellitus. Diabetes Care 14: 260-269.
21. United Kingdom Prospective Diabetes Study (UKPDS) 2007.S28 (2002) Diabetes Care 25: s28-s32.
22. Salam A, Stewart F, Singh K, Thom S, Williams HJ, et al. (2013) Interpreting the processes of the UMPIRE trial (INPUT): Protocol for a qualitative process evaluation study of a fixed-dose combination (FDC) strategy to improve adherence to cardiovascular medications. BMJ Open 3: 883-889.
23. Osterberg L, Blaschke T (2005) Adherence to medication. N Engl J Med 353: 487-497.
24. Selak V, Elley CR, Crengle S, Harwood M, Doughty R, et al. (2011) Improving adherence using combination therapy (IMPACT): Design and protocol of a randomised controlled trial in primary care. Contemp Clin Trials 32: 909-915.
25. Patel RD, Messner LV, Teitelbaum B, Michel KA, Hariprasad SM, et al. (2013) Characterization of ischemic index using ultra-widefield fluorescein angiography in patients with focal and diffuse recalcitrant diabetic macular edema. Am J Ophthalmol 155: 1038-1044.