Original Article

Hyperglycemic Effects of a Periocular Dexamethasone Injection in Diabetic Patients after Vitreoretinal Surgery

ZHANG Yong Peng, PENG Xiao Yan[#], LI Zhi Hua, and CHEN Feng Hua

Beijing Ophthalmology and Visual Science Laboratory, Beijing Tongren Eye Center, Beijing Tongren Hospital, Capital Medical University, Beijing 100730, China

Abstract

Objective To examine the hyperglycemic effects of periocular dexamethasone injection in type 2 diabetic patients after vitreoretinal surgery (VRS).

Methods This was a retrospective non-randomized controlled trial. Twenty consecutive hospitalized patients with type 2 diabetes and ocular inflammatory reaction after VRS were enrolled in this study. Ten patients received 2.5 mg dexamethasone and 10 patients received 5 mg dexamethasone. Fourteen consecutive type 2 diabetic patients without ocular inflammatory reaction after VRS were used as control group. We measured fasting blood glucose (FBG) and at 2 h after each meal (post prandial glucose, PBG; 09:00, 13:00, and 19:00 h) after periocular dexamethasone injection. Differences among three groups were determined by *q* tests.

Results The PBG levels in both dexamethasone-treated groups started to increase within 5 h after injection (i.e., PBG at 13:00 h), and were significantly increased at 19:00 h after injection ($P<0.05$). BG levels were almost 2-fold higher than at baseline and compared with the control group. The BG values declined gradually by 24 h to 48 h after injection. There were no differences in BG levels between the two dexamethasone-treated groups ($P>0.05$), except for PBG at 19:00 h on day 2 after injection ($P<0.05$).

Conclusion Periocular dexamethasone injection can cause transient hyperglycemia in diabetic patients after VRS. BG monitoring should be performed following such injection.

Key words: Dexamethasone; Periocular injection; Vitreoretinal surgery; Diabetes mellitus; Blood glucose

Biomed Environ Sci, 2012; 25(3):311-316 doi: 10.3967/0895-3988.2012.03.009 ISSN:0895-3988

www.besjournal.com(full text) CN: 11-2816/Q

INTRODUCTION

Corticosteroids have been used in the treatment of ocular diseases for about 60 years[1-2]. Because systemically administered corticosteroids can cause serious side effects[3-4], local rather than systemic administration of corticosteroids is generally preferred. In this context, subconjunctival, peribulbar, retrobulbar, intravitreal injection and repeated administration of topical eye drops are more commonly used than parenteral administration in diabetic patients because locally administered steroids should maximize the therapeutic effect and minimize the risk of hyperglycemia. However, is this rationale correct? It is well known that systemic application of corticosteroids may lead to hyperglycemia, but there is little research on the influence of locally administered corticosteroids on blood glucose (BG) levels in diabetic patients and there are currently no recommendations for BG monitoring after ocular steroid injection, particularly after ocular surgery.

Recent studies have highlighted the possibility of significant BG elevations after subconjunctival and

[#]Correspondence should be addressed to PENG Xiao Yan. Tel: 86-10-58268285. Fax: 86-10-58268243. E-mail: drpengxy@gmail.com

Biographical note of the first author: ZHANG Yong Peng, male, born in 1975, MD, majoring in ophthalmology.

Received: July 13, 2011; Accepted: September 5, 2011

periocular corticosteroid injection, or after intense, short-term administration of topical corticosteroid eyedrops in diabetic patients[5-8] and in diabetic rats[9]. Furthermore, Weijtens et al.[10-14] demonstrated significant systemic drug diffusion after subconjunctival or peribulbar dexamethasone injection, and concluded that such an injection "is not exclusively a local treatment and may cause systemic side effects when used repeatedly."

Vitreoretinal surgery (VRS) is an important approach to treat proliferative diabetic retinopathy (PDR). However, some diabetic patients develop serious anterior segmental inflammation after VRS, and in this setting periocular dexamethasone injection is routinely used, and is effective at controlling inflammation. The rationale for local steroid administration is to optimize the benefit/risk ratio of therapy by achieving high steroid concentrations in the eye with low serum concentrations. However, a case-by-case evaluation is required to confirm that this approach is appropriate. Yan et al.[15] determined the effect of vitrectomy on BG in diabetic patients. They found that postoperative BG was significantly higher than preoperative BG, reaching a peak at 1-2 h after surgery. Nevertheless, quantitative data are lacking on the influence of different doses of dexamethasone administered periocularly on BG levels in diabetic patients after VRS. Therefore, this is an important issue in ophthalmologic clinical practice. Accordingly, this study was conducted to evaluate the hyperglycemic effect of a single periocular injection of two different doses of dexamethasone after VRS in type 2 diabetic patients, and compared the results with those of other studies.

MATERIALS AND METHODS

Thirty-four consecutively hospitalized patients (15 men and 19 women) with type 2 diabetes who underwent VRS between May 1, 2009 and August 30, 2010 were enrolled in this retrospective, non-randomized, controlled, consecutive-case study. The patients were aged from 34 to 69 years old, with a mean age of 52.71±8.98 years. The duration of diabetes was ranged from 1 to 29 years, with a mean duration of 13.12±7.46 years. Twenty-seven patients had PDR and seven had silicone oil tamponade (Table 1). Patients who received oral, intravenous or periocular corticosteroids within 1 month of enrollment were excluded from the study.

All of the patients were diagnosed and treated by an internist. They were given a standard diabetic diet by the nutritional department at our hospital. Capillary BG at 06:00 h (fasting blood glucose, FBG) and at 2 h after each meal (post-prandial blood glucose, PBG; 09:00, 13:00, and 19:00 h) were measured using the same glucometer (Accu-CHEK® Performa, Roche) throughout the treatment period.

During the 15-month study, 20 diabetic patients developed inflammatory reactions, manifested as a fibrous exudative membrane in the area of pupil, in the anterior chamber after VRS. Ten patients received 2.5 mg dexamethasone disodium phosphate, and another 10 patients received 5.0 mg dexamethasone. Both doses were administered in 0.5 mL of lidocaine sulfate and injected at 08:00 h. Another 14 consecutive diabetic patients who underwent VRS during the same period were randomly selected and served as a control group. All of the injections were conducted by the same person. We reviewed the medical records of all patients. Patient characteristics, diabetes history and serial BG measurements before and after steroid treatment were recorded and analyzed.

All analyses were performed using SPSS software version 11.5. The BG levels at each time in three groups were normally distributed. The variables presented are summarized as mean values±standard deviation (SD). *q* test (or Student Newman Keuls Test, SNK) was used to compare BG levels among both dexamethasone-treated groups and the control group. Differences were considered significant at values of $P<0.05$.

RESULTS

FBG and PBG on the day before surgery, the day of surgery, and for 1-3 days after surgery are shown in Tables 2. Overall, there were no differences in FBG or PBG values among the three groups of patients either before surgery or on the day of surgery ($P>0.05$). Therefore, baseline BG values were similar in all three groups. However, on the day of surgery, PBG at 19:00 h was significantly ($P<0.05$) higher in all three groups compared with the corresponding value on the day before surgery .

On postoperative day 1, there were no differences in baseline FBG among the three groups ($P>0.05$). PBG at 13:00 h was higher in both dexamethasone-treated groups compared with control group, although not significantly ($P>0.05$). PBG at 19:00 h was significantly higher in both dexamet-

Table 1. Patient Characteristics

		Control Group	2.5 mg Dex	5.0 mg Dex
Number		14	10	10
Sex (male/female)		6/8	5/5	4/6
Age (years)		52.07±8.79	54.30±7.33	52.00±11.22
Duration of DM (years)		12.07±7.99	15.10±7.46	12.60±7.06
Classification of Disease	PDR	12	8	7
	Silicone Eye	2	2	3
Antidiabetic Treatments	Diet Alone	0	1	0
	Oral Drugs	3	4	2
	Insulin	7	5	8
	Oral Drugs+ Insulin	4	0	0
Hypertension (yes)		10	4	5

Table 2. Blood Glucose Levels in Each Group

	Control	2.5 mg Dex	5.0 mg Dex	*P1*	*P2*	*P3*
Before Surgery						
FBG (06:00)	5.81±1.27	6.09±1.69	5.91±1.07	0.626	0.866	0.768
PBG (09:00)	9.52±2.58	9.99±2.40	9.07±1.67	0.625	0.638	0.377
PBG (13:00)	10.34±2.81	9.25±3.22	9.04±1.82	0.338	0.255	0.863
PBG (19:00)	8.78±3.03	6.58±2.57	7.88±1.90	0.050	0.412	0.274
Day of Surgery						
FBG (06:00)	7.54±3.87	5.75±1.59	6.36±1.95	0.140	0.326	0.635
PBG (09:00)	9.13±2.88	9.11±2.14	9.90±3.18	0.987	0.508	0.530
PBG (13:00)	9.34±3.21	10.03±2.01	8.58±1.60	0.507	0.471	0.204
PBG (19:00)	13.44±4.20	13.13±2.86	12.62±3.60	0.839	0.593	0.759
Post-operative day 1						
FBG (06:00)	7.01±1.78	7.82±3.88	6.98±1.42	0.439	0.979	0.459
PBG (09:00)	10.42±3.08	11.75±3.73	9.99±3.34	0.356	0.743	0.249
PBG (13:00)	11.14±3.31	12.92±4.12	13.55±2.81	0.221	0.101	0.685
PBG (19:00)	8.71±2.71	17.81±3.08	15.98±5.07	0.000*	0.000*	0.270
Post-operative day 2						
FBG (06:00)	6.25±1.95	11.23±4.05	10.09±4.34	0.001*	0.011*	0.464
PBG (09:00)	11.24±2.82	13.72±4.58	14.94±4.26	0.128	0.026*	0.482
PBG (13:00)	10.86±3.61	12.61±3.08	14.35±4.44	0.266	0.031*	0.306
PBG (19:00)	10.43±3.60	9.73±2.50	14.90±4.13	0.633	0.004*	0.002*
Post-operative day 3						
FBG (06:00)	5.81±0.96	7.30±2.51	8.67±2.75	0.096	0.002*	0.155
PBG (09:00)	9.84±2.36	12.06±3.36	10.40±2.70	0.064	0.632	0.192
PBG (13:00)	10.97±3.10	10.98±3.11	10.78±3.56	0.995	0.888	0.891
PBG (19:00)	9.34±2.79	11.54±3.59	10.66±3.34	0.107	0.328	0.543

Note: *P1*, 2.5 mg dexamethasone versus the control group (*q* test); *P2*, 5.0 mg dexamethasone versus the control group (*q* test); *P3*, 2.5 *vs* 5.0 mg dexamethasone (*q* test). *Significantly different at $P<0.05$.

hasone-treated groups compared with the control group (P<0.05) and the maximum BG value was 24.4 mmol/L in patients treated with 5.0 mg dexamethasone. However, there were no differences in FBG or PBG between the two dexamethasone-treated groups (P>0.05).

On postoperative day 2 (i.e., 1 day after dexamethasone injection), the FBG was higher in both dexamethasone-treated groups compared with the control group (P<0.05). Thereafter, however, the BG levels in patients treated with 2.5 mg dexamethasone stabilized gradually and were not significantly different compared with BG levels in the control group (P>0.05). The BG levels in patients treated with 5 mg dexamethasone remained higher than those in the control group until the morning of postoperative day 3 (i.e. 2 days after dexamethasone injection) (P<0.05). Thereafter, however, the BG levels started to stabilize and was not significantly difference compared with those in the control group (P>0.05).

All systemic treatments were maintained following dexamethasone injection. None of the patients reported severe ocular or systemic discomfort. If the BG level increased significantly (i.e., >20 mmol/L) we measured urinary ketone body concentrations and consulted an internist. However, none of the patients had urinary ketone bodies and no changes in anti-diabetic therapy were necessary. Periocular corticosteroid injections were aimed at reducing ocular inflammation and late sequelae in these diabetic patients, and the results were satisfactory.

DISCUSSION

Corticosteroids have been used by ophthalmologists for more than 50 years[1-2]. Because systemic administration of corticosteroids may cause hyperglycemia, ophthalmologists prefer local ocular injection or repeated administration of topical eye drops rather than oral or intravenous administration in diabetic patients with ocular inflammation. This is because local administration of corticosteroids can achieve higher local bioavailability without systemic side effects. When studying the adverse effects of locally administered corticosteroids in ophthalmologic settings, we tend to focus on glaucoma and cataracts, and seldom consider the systemic side effects. Surprisingly, we found that periocular injection of 2.5 or 5.0 mg dexamethasone in diabetic patients after VRS resulted in very high BG levels, a side effect often unnoticed by ophthalmologists and internists.

An experimental study in rabbits showed that, after subconjunctival steroid injection, 98% of the total dose was absorbed into the systemic circulation[16]. Another study revealed that the intraocular concentrations of a steroid were similar in the injected eye and the contralateral eye[17]. Subconjunctival dexamethasone was also reported to induce significant BG increases in diabetic and non-diabetic rats[9].

A series of clinical studies done by Weijtens et al.[10-14] showed that the majority of the steroid dose administered by subconjunctival or peribulbar injection is absorbed into the systemic circulation because of the rich ocular vasculature.

In one study, diabetic patients received a subconjunctival injection of 1.2 mg dexamethasone during cataract surgery[7]. In that study, the BG level measured 8-10 h after injection on the day of surgery was approximately double that taken at the same time on the days before or after surgery.

A series of studies done by Feldman et al.[6,18-19] have shown that periocular injections of dexamethasone in patients with type 2 diabetes induced a marked hyperglycemic effect, similar to that observed during intravenous pulse methylprednisolone therapy. They assessed the hyperglycemic effect of three consecutive daily periocular dexamethasone injections in patients with diabetes and found that each ocular injection was followed around 6 h later by a near doubling in BG relative to baseline. This was followed by a decrease in the BG level until the next injection, although the level before the next injection was still 13% higher than the baseline level. Using a 14 mmol/L threshold for intervention, the probability of requiring additional hypoglycemic treatment during ocular steroid therapy in patients with HbA1c >7.5% and those with HbA1c ≤ 7.5% was 100% and 60%, respectively. They concluded that the short-term effects of local dexamethasone injections are similar to those of high systemic doses. Thus, the potential immediate advantage of periocular steroid injections compared with the systemic route lies only in the potential ability of achieving higher drug concentrations in the eye. However, these drugs should be used with similar precautions to pulse methylprednisolone therapy. In particular, ophthalmologists performing periocular steroid injections in diabetic patients should consider the need for self-monitoring of BG and modifying hypoglycemic treatment in the event of marked BG

elevations.

Yan et al.[15] reported on the effect of vitrectomy on BG in diabetic patients. They found that postoperative BG levels were significantly higher than those before surgery, reaching a peak 1-2 h postoperatively, The BG levels declined thereafter, and reached near-preoperative levels 5 days postoperatively. There was a positive correlation between BG elevations and the operation time, preoperative BG level and duration of diabetes. Postoperative BG was relative to potentiated anesthesia.

Considering that VRS may actually influence the BG levels in diabetic patients, we also included consecutive diabetic patients who underwent VRS as a control. To our knowledge, no other studies have examined the effects of periocular dexamethasone injections on BG levels in diabetic patients after VRS. We found that, in the control group, the BG level on the night of surgery was significantly higher than that on the day before surgery (P<0.05). Thereafter, however, there were no differences in BG levels in the control group compared with the corresponding BG values on the day before surgery (P>0.05), which differs from the results reported by Yan et al.[15]. The reason for this difference may lie in that we had not have potentiated anesthesia in surgery or maybe something else, such as the difference of patients between the two study.

In our study, the BG levels increased significantly in diabetic patients after periocular dexamethasone injection following VRS. The BG levels in both dexamethasone-treated groups started to increase 5 h after injection (i.e., PBG at 13:00 h) and were significantly higher 11 h after injection (PBG at 19:00 h; P<0.05). The BG level was approximately 2-fold higher compared with the corresponding levels at baseline and in the control group, consistent with the results reported by Feldman et al.[6]. The BG levels in patients treated with 2.5 and 5.0 mg dexamethasone started to decline within 24 and 48 h, respectively, suggesting that larger dexamethasone doses are associated with BG elevations that are sustained for longer. However, there were no differences in BG levels between the two treatment groups (P>0.05) except for PBG at 19:00 h on postoperative day 3 (i.e., 2 days after injection; P<0.05). No patient had the symptom of hyperemia after injection and this should arouse our alarm and attention. The acetome body in urine was all negative in the patients of hyperemia. We continuously monitored the BG levels in these patients after consulting an internist, but BG levels did not increase further. To avoid hypoglycemia after medical interventions, the antidiabetic therapies were unchanged.

Based on the results of this and other studies, we know that BG monitoring is important after local steroid injection in diabetic patients after VRS. The patients should be informed of the possibility of developing hyperglycemia after injection to avoid alarming them in the event of hyperglycemia. For patients with serious hyperglycemia, we suggest that the protocol reported by Feldman et al. should be considered[6]. In this protocol, rapid-acting insulin can be administered according to a sliding scale of glucose values starting at a 14 mmol/L threshold: 4 IU for BG levels of 14-17 mmol/L, 6 IU for BG levels of 17-20 mmol/L and 8 IU for BG levels of 20 and 23 mmol/L.

Understanding the causes of BG variations in diabetic patients after VRS is vital to prevent and control postoperative complications and to avoid causing anxiety among the patients. Our data suggest that periocular steroid injections, partly because of the high doses used and the rich vasculature and resulting systemic circulation, carry a similar risk of short-term complications to systemic routes of administration. However, these side effects are usually ignored by ophthalmologists, internists, nurses and patients. It can be concluded that periocular injection of dexamethasone represents a systemic mode of therapy and should not be considered localized therapy. Therefore, diabetic patients must be given appropriate instructions to monitor and manage their BG levels after periocular steroid injections[5].

The limitation of this study is that it was a retrospective study and we only enrolled 34 patients with type 2 diabetes mellitus. Furthermore, patients only received a single injection, and it is unclear what the effects of multiple injections are. Moreover, the influence of different types, doses, routes and durations of corticosteroid administration is unclear, and requires further investigation.

REFERENCES

1. Ahrendshorst W, Fall H. Role of the adrenal cortex in treatment of ocular diseases with pyrogenic substances. Arch Ophthalmol, 1950; 44(5), 635-42.
2. Woods AC. Clinical and experimental observation on the use of ACTH and cortisone in ocular inflammatory disease. Am J of Ophthalmol, 1950; 33(9), 1325-49.
3. McMahon M, Gerich J, Rizza R. Effects of glucocorticoids on carbohydrate metabolism. Diabetes Metab Rev, 1988; 4(1),

17-30.
4. Boumpas DP, Chrousos GP, Wilder RL, et al. Glucocorticoid therapy for immune-mediated diseases: basic and clinical correlates. Ann Intern Med, 1993; 119(12), 1198-208.
5. Asensio-Sánchez VM, Soto A, Conde S, et al. Retrobulbar triamcinolone injection and glycemic control. Arch Soc Esp ftalmol, 2009; 84 (12), 599-603.
6. Feldman-Billard S, Du Pasquier-Fediaevsky L, Héron E. Hyperglycemia after repeated periocular dexamethasone injections in patients with diabetes. Ophthalmology, 2006; 113(10), 1720-3.
7. Fukushima H, Kato S, Kaiya T, et al. Effect of subconjunctival steroid injection on intraocular inflammation and blood glucose level after cataract surgery in diabetic patients. J Cataract Refract Surg, 2001; 27(9), 1386-91.
8. Kymionis GD, Panagiotoglou T, Tsilimbaris MK. The effect of intense, short-term topical dexamethasone disodium phosphate eyedrops on blood glucose level in diabetic patients. Ophthalmologica, 2007; 221(6), 426-9.
9 Fukushima H, Kato S, Hayashi Y, et al. Influence of subconjunctival steroid injection on blood glucose profile in diabetic rats. Eye, 2001;15(Pt 3),326-8.
10. Weijtens O, van der Sluijs FA, Schoemaker RC, et al. Peribulbar corticosteroid injection: vitreal and serum concentrations after dexamethasone disodium phosphate injection. Am J Ophthalmol, 1997; 123(3), 358-63.
11. Weijtens O, Schoemaker RC, Cohen AF, et al. Dexamethasone concentration in vitreous and serum after oral administration. Am J Ophthalmol, 1998; 125(5), 673-9.
12. Weijtens O, Feron EJ, Schoemaker RC, et al. High concentration of dexamethasone in aqueous and vitreous after subconjunctival injection. Am J Ophthalmol, 1999; 128(2), 192-7.
13. Weijtens O, Schoemaker RC, Lentjes EG, et al. Dexamethasone concentration in the subretinal fluid after a subconjunctival injection, a peribulbar injection, or an oral dose. Ophthalmology, 2000; 107(10), 1932-8.
14. Weijtens O, Schoemaker RC, Romijn FP, et al. Intraocular penetration and systemic absorption after topical application of dexamethasone disodium phosphate. Ophthalmology, 2002; 109(10), 1887-91.
15. Yan H, Han Q, Xu Y, et al. The effect of vitrectomy on blood sugar in diabetic patients. Chinese J of ocular fundus disease, 2000; 16 (3), 157-9. (In Chinese)
16. Tsuji A, Tamai I, Sasaki K. Intraocular penetration kinetics of prednisolone after subconjunctival injection in rabbits. Ophthalmic Res, 1988; 20(1), 31-43.
17. Bodker FS, Ticho BH, Feist RM, et al. Intraocular dexamethasone penetration via subconjunctival or retrobulbar injections in rabbits. Ophthalmic Surg, 1993; 24(7), 453-7.
18. Feldman-Billard S, Lissak B, Benrabah R, et al. Intravenous pulse methylprednisolone therapy in eye disease: Effect on glucose tolerance. Ophthalmology, 2003; 110(12), 2369-71.
19. Feldman-Billard S, Lissak B, Kassaei R et al. Short-term tolerance of pulse methylprednisolone therapy in patients with diabetes mellitus. Ophthalmology, 2005; 112(3), 511-5.