Comparison between two intravitreal injection techniques with respect to fluid reflux, intraocular pressure, and therapeutic effect

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Abstract:

CONTEXT: Effect of fluid reflux on intraocular pressure (IOP) and therapeutic benefits.
AIMS: The aim of this study is to compare two intravitreal injection techniques in terms of fluid reflux, short-term IOP changes, and therapeutic effect.
SETTINGS AND DESIGN: A prospective, double-blinded, randomized interventional study.
SUBJECTS AND METHODS: Sixty eyes were randomly allocated to two groups (direct intravitreal injection technique and oblique intravitreal injection technique). IOP was measured before and immediately after the injection of 0.1 ml comprising of bevacizumab (1.25 mg/0.05 ml) and dexamethasone (0.2 mg/0.05 ml) and then at 30 min after the injection. Occurrence and amount of vitreous reflux were recorded. Best-corrected visual acuity (BCVA) and central macular thickness (CMT) were assessed preinjection and 6 weeks postinjection.
RESULTS: IOP (mmHg ± standard deviation) increased significantly immediately after injection to 24.30 ± 3.02 (direct intravitreal injection) and 31.50 ± 3.49 (oblique intravitreal injection). These pressure rise differed significantly between both groups (mean difference: 7.2, \( P < 0.0001 \)). Thirty minutes after injection, there was no significant difference in IOP increase between the groups. Occurrence and amount of fluid reflux were significantly higher with direct intravitreal injection. There was no significant difference in BCVA and CMT outcome between both groups.
CONCLUSIONS: Direct intravitreal injection technique has lower rise in IOP and higher incidence of fluid reflux than the oblique intravitreal technique. Fluid reflux does not cause a therapeutic compromise in terms of BCVA or CMT changes, so the reflux fluid must be the vitreous not the drug. Thus, direct injection technique seems to be the preferred technique.
Keywords:
Anti-vascular endothelial growth factor, fluid reflux, intraocular pressure, intravitreal injection technique, intraocular pressure, macular edema, optical coherence tomography macula

Introduction

Intravitreal injections are one of the most commonly performed procedures in ophthalmology. Their use has increased enormously in the recent past as the mode of delivery of steroids and anti-vascular endothelial growth factor, antibiotics, and chemotherapeutic drugs for the management of various posterior segment disorders. These intravitreal injections are considered a safe procedure with few complications. One of the concerns related to intravitreal injection is bleb formation at the site of injection due to reflux of fluid after injection. This may be undesirable because...
it may result in unpredictable change in postinjection intraocular pressure (IOP), loss of injected drugs, and a free-communicating port which may increase the risk of endophthalmitis.

This fluctuation of IOP with fluid reflux has been published by many of the well-designed studies concluding that patients who developed vitreous reflux had either no change in IOP or a small drop in IOP that rapidly normalized, contrary to those without vitreous reflux at the site of injection who had a significant initial elevation of IOP that rapidly normalized.[9,8-10]

It has been found that there is a significant variation in fluid reflux and IOP with respect to injection technique.[8-11] The incidence of fluid reflux after intravitreal injection can be reduced by doing a simple modification in the needle angle. The tunnelled intravitreal injection technique causes lesser vitreous reflux and more rise in IOP than a straight injection technique.[9,11] Therefore, by changing the injection technique fluid reflux is reduced.

Loss of a drug in fluid reflux may result in lower intravitreal dosage. However, it is unclear whether the refluxed fluid is drug or vitreous.[12,13] On literature search, we found none of the studies have evaluated whether there is any therapeutic compromise due to fluid reflux.

In our study, we have compared direct intravitreal injection technique with oblique intravitreal injection technique in terms of fluid reflux, short-term IOP changes, and therapeutic effect of 0.1 ml intravitreal injection (0.05 ml dexamethasone + 0.05 ml bevacizumab). The primary objectives were to study the fluid reflux and IOP changes. The secondary objectives were to study therapeutic benefits in terms of best-corrected visual acuity (BCVA) and change in macular thickness.

**Subjects and Methods**

A prospective, double-blinded randomized interventional study was conducted at the tertiary care center in North India. Approval from the Institutional Ethical Committee was obtained before recruiting the participants and the tenets of the Helsinki declaration were followed during the study. Written informed consent was obtained from each subject including detailed explanations of all procedures before participation in the study. The study has been registered in the Clinical Trials Registry-India. The time period of the study was 1 year (from September 1, 2018 to August 31, 2019). Sample size of 60 patients was calculated by https://www.surveysystem.com/sscalc.htm. (Population size: 155, confidence level: 95%, confidence interval: 10%).

Subjects (n = 100) presenting with macular edema in retina clinic and outpatient departments were assessed and screened for inclusion and exclusion criteria presented in Table 1. Finally, 60 eyes (n = 60) of sixty patients were enrolled in the study. By a random number table method, eligible patients (n = 60) were randomized into direct injection technique (Group 1, n = 30) and oblique injection technique (Group 2, n = 30) in ratio of 1:1 [Figure 1]. All these patients were assigned for 0.1 ml of intravitreal injection comprising of bevacizumab (1.25 mg/0.05 ml) and dexamethasone (0.2 mg/0.05 ml) using either of the injection techniques as per the randomization. Visual acuity was recorded as per the logarithm minimum angle of resolution visual acuity chart. Macular edema was measured in terms of central subfield thickness (CST, in µm), cube volume (in mm³), and central average thickness (in µm) on optical coherence tomography (OCT) macula (Carl Zeiss Cirrus TM HD-OCT 4000).

All injections were performed by the same surgeon. After instillation of 0.05% proparacaine hydrochloride eye drops topically three times every 5 min for anesthesia, the periorcular skin was cleaned, and the eye was draped under aseptic precautions and lid speculum was inserted. After mobilization of the conjunctiva, the drug was injected into the vitreous cavity at pars plana (3 mm, 3.5 mm, 4 mm posterior to the limbus in aphakic, pseudophakic, and phakic patients respectively) in superotemporal quadrant at an angle of 90° for direct injection technique [Figure 2a][10] or 15°–30° for oblique injection technique [Figure 2b][10] via a 30G needle on 1 mL insulin syringe (DISPOVAN®). The needle was withdrawn along the same angle as the injection technique. A cotton tip applicator was placed over the injection site for 10s immediately after needle removal. Subsequently, the injection site was observed for reflux under operative microscope. If any subconjunctival bleb was observed, the injection was determined as reflux positive. Bleb diameter was measured after wait of 1 min by using a sterile Castroviejo’s caliper. Antibiotic eye drops were prescribed for a week after the injection starting immediately after the injection.

**Table 1: Inclusion and exclusion criteria are tabulated**

| Inclusion criteria | Exclusion criteria |
|--------------------|-------------------|
| Patients above the age of 18 years who have unilateral or bilateral macular edema secondary to various pathologies (diabetes mellitus, postcataract surgery, ARMD, uveitis, and RVOs) | Not willing to give consent |
| History of glaucoma and intraocular hypertension | History of any intravitreal injection within 3 months |
| Previous history of vitreoretinal surgery | Known allergy to bevacizumab and dexamethasone |

ARMD: Age-related macular degeneration, RVO: Retinal vein occlusion
IOP was be measured by rebound tonometer (iCare TA01i) in the sitting position preoperatively, immediately and at 30 min after the injection for each patient. Visual acuity was recorded at 1 week and 6 weeks after the injection. Macular thickness assessed in all patients at 6 weeks after injection.

Statistical analysis
Med Calc statistical software version 14.8.1 (Med Calc software Ltd, Acacialaan 22, 8400 Ostend, Belgium) was used for the statistical analysis. ANOVA test or paired sample $t$-test were used to compare before and after intra-group observations. Independent sample $t$-test was used to test for the difference between unpaired groups. The Chi-square test was used to compare the categorical variables. Pearson correlation coefficient was used to test the association between two continuous variables. $P < 0.05$ was considered statistically significant.

Results
Sixty eyes of the 60 patients were enrolled in our study that fulfilled the eligibility criteria. Out of which, two patients were lost to follow-up in the oblique group [Figure 1]. The mean age of the participants was $57.33 \pm 14.04$ years (range: 22–76 years; 43 males and 17 females). Demographic and clinical data of the patients are summarized in Table 2. In our study, mean pre- and post-injection IOP was $15.40 \pm 1.92$, $27.90 \pm 4.86$ mmHg, respectively. There was a significant rise in IOP in all patients immediately after the injection with a mean difference of $12.50 \pm 4.29$ mmHg, $P < 0.0001$. In Group 1 (direct technique), pre- and post-injection IOP was $14.96 \pm 1.90$ mmHg and $24.30 \pm 3.02$ mmHg, respectively. There was significant rise in IOP immediately after injection with
Figure 3: Showing inverse correlation between fluid reflux and immediate postinjection intraocular pressure

Table 2: Baseline characteristics of the participants are presented

| Diagnosis                  | Direct group | Oblique group | Total |
|----------------------------|--------------|---------------|-------|
| Mean age (years)           | 58.26±13.12  | 56.40±15.07   |       |
| Male                       | 20 (33.3)    | 23 (38.3%)    | 43 (71.7%) |
| Female                     | 10 (16.7)    | 7 (11.7%)     | 17 (28.3%) |
| Diagnosis                  |              |               |       |
| Coat’s disease             | 0 (0)        | 1 (1.7)       | 1 (1.7) |
| DME                        | 14 (23.3)    | 16 (26.7%)    | 30 (50.0) |
| Intermediate uveitis       | 2 (3.3)      | 1 (1.7)       | 3 (5.0) |
| Irving gas syndrome       | 0 (0)        | 1 (1.7)       | 1 (1.7) |
| Methyl alcohol poisoning   | 0 (0)        | 1 (1.7)       | 1 (1.7) |
| Posttraumatic              | 0 (0)        | 1 (1.7)       | 1 (1.7) |
| RVO                        | 12 (20.0)    | 6 (10.0)      | 18 (30.0) |
| Wet ARMD                   | 2 (3.3)      | 3 (5.0)       | 5 (8.3) |
| Total                      | 30 (50.0)    | 30 (50.0)     | 60 (100) |

RVO: Retinal vein occlusion, DME: Diabetic macular edema, ARMD: Age-related macular degeneration

a mean difference of $9.33 \pm 2.60$ mmHg, $P < 0.0001$. Similarly, in Group 2 (oblique technique), preinjection and postinjection IOP were $15.83 \pm 1.88$ mmHg and $31.50 \pm 3.49$ mmHg, respectively, and significant rise in IOP was noted immediately after injection with a mean difference of $15.67 \pm 3.15$ mmHg, $P < 0.0001$. On comparing both the groups rise in postinjection, IOP was more significant in Group 2 with a mean difference of $7.2$ mmHg, $P < 0.0001$. The mean IOP post-30 min of injection in Group 1 was $16.53 \pm 1.77$ mmHg and in Group 2 was $17.96 \pm 1.65$ mmHg ($P = 0.002$), which was within normative range of IOP.

Out of 60 patients, 27 of them had fluid reflux (bleb formation) at the site of injection where 25 patients belonged to Groups 1 and 2 were from Group 2. There was a statistically significant difference in the incidence of fluid reflux in both the groups, $P < 0.0001$. A significant inverse correlation was noted between fluid reflux and immediate postinjection IOP (Pearson correlation coefficient: $0.718, P < 0.0001$), as depicted in Figure 3.

Mean BCVA of all patients was $1.03 \pm 0.41, 0.69 \pm 0.42$ preinjection and 6 weeks postinjection, respectively. There was a significant improvement in BCVA at the end of 6 weeks with mean difference of $0.34 \pm 0.26, P < 0.0001$.

Mean change in BCVA at 6 weeks postinjection is tabulated in Table 3. When we compared both the groups, there was statistically insignificant difference in BCVA outcome at 6 weeks postinjection mean difference $0.1269, P = 0.2543$. Correlation between fluid reflux and BCVA at 6 weeks postinjection which was statistically insignificant (correlation coefficient: $0.046, P = 0.733$).

Mean change in central macular thickness (CMT) at 6 weeks postinjection has been shown in Table 3. On comparing both the groups, there was no significant difference at 6 weeks postinjection with a mean difference $3.74, P = 0.91; 0.60, P = 0.16; 14.15, P = 0.20$. There was an insignificant correlation between fluid reflux and CST at 6 weeks postinjection (correlation coefficient: $0.127, P = 0.344$), whereas a modest correlation was noted between BCVA and CST at 6 weeks postinjection which was statistically insignificant (correlation coefficient: $0.162, P = 0.226$).

Discussion

In our study, we found a significant rise in IOP after intravitreal injection in all the participants, but the rise in IOP was more in the oblique group compared to a direct group. Other studies have also shown that there is a significant rise in IOP after an intravitreal injection and studies have also stated that oblique intravitreal technique causes a higher rise in postinjection IOP compared to a straight injection technique.

At the same time, the oblique injection technique had a higher incidence of fluid reflux compared to the direct technique. In addition, the participants who had reflux had relatively lower rise in IOP when compared to the participants with no reflux (regardless of the injection technique) and this was statistically significant. Similar results have been shown by the other published studies. However, this rise in IOP in both the groups was transient which got normalized within 30 min of injection.

Another concern related to the fluid reflux is the possibility that the injected drug is lost in the refluxed fluid which may result in subtherapeutic effect. It was shown in a previous study that fluid reflux is a liquefied vitreous in the majority of the cases. Similarly, Brodie et al. studied the volume and composition reflux following intravitreal injection and concluded that very small amount of drug
is lost in reflux.\[^{19,20}\] To our best knowledge, none of the previously published studies have attempted to establish the correlation between the fluid reflux and therapeutic compromise. We found that there was no significant difference in therapeutic outcome in terms of BCVA and macular thickness on OCT at 6-week postinjection in subjects with or without the reflux. There was statistically insignificant correlation between fluid reflux and BCVA or CMT suggesting that refluxed fluid must be the liquefied vitreous and not the drug.

In our study, no serious complications such as endophthalmitis, vitreous hemorrhage, cataract, severe uveitis, or retinal detachment were detected related to injection as well as injection technique. Only self-limiting complications such as subconjunctival hemorrhages were observed.

### Conclusions

Direct intravitreal injection technique has lower rise in IOP than the oblique intravitreal technique and direct injection technique has a higher incidence of fluid reflux, suggesting an inverse correlation between IOP and fluid reflux. Fluid reflux does not cause a therapeutic compromise in terms of BCVA or CMT changes, so the reflux fluid must be the vitreous not the drug. Thus, keeping in mind, the above-mentioned observations, direct injection technique seems to be the preferred technique due to lower IOP rise and similar therapeutic benefits when compared to oblique injection technique.

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### Conflicts of interest

There are no conflicts of interest.

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