

Comparison of Analgesic Effects of Topical Eye Drop of Tetracaine 0.5% with Intravenous Fentanyl and Remifentanyl During Intravitreal Injection of Bevacizumab (Avastin): A Prospective Randomized Controlled Trial

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1. Abstract

1.1. Background: Intravitreal Injection (IVI) of avastin is a very common vitreoretinal procedure, and multiple injections are often required per patient. Patient pain during IVI under topical anesthesia is mild to moderate regardless of anesthetic technique. This study was conducted to evaluate the effectiveness of simultaneous intravenous injection of fentanyl or remifentanyl to topical anesthetic techniques with tetracaine 0.5 % in reducing pain during IVI of avastin.

1.2. Methods: Seventy- five patients were enrolled in this prospective double blind study. Patients with ages between 40 and 80 years old were randomly divided into 3 groups 1:1:1 to receive 0.5% tetracaine drop with IV 0.9%normal saline 2ml (T group, n=25), or with IV fentanyl 1mcg/kg (F group, n=25), or with IV remifentanyl 1 mcg /kg (R group, n=25).Vital signs and ECG of patients were monitored and recorded every 5 minutes. Intensity of pain of patients immediately after IVI injection was evaluated between 0 (no pain) and 10 (worst pain ever felt) by using numerical pain scale. Surgeon satisfaction and akinesia of the eye, during avastin injection was assessed on the operating table.

1.3. Results: Among 75 patients, 48(64%) were women and 27 (36%) were men, and there was no significantly difference between three groups. Also there was no significantly difference between mean average of age and weight of these groups.

Patients in T group was reported more pain (VAS= 2.04 ± 1.54) than F group (VAS= 0.6 ± 1.08) and R group (VAS= 0.28 ± 0.68) and difference was significant (P <0.0001), But there was no difference between F and R groups. Ocular akinesia score during avastin injection was higher in T group than in F or R group and it was statically significant. (p=0.015) But there was no significant difference between F group and R group. (p=0.716). Mean average of surgeon satisfaction was higher in F group (3.84) and R group (3.76) than T group (3.36) and it was statically significant. (p=0.018) But there was no significant difference between F group and R group. (p=0.772).

1.4. Conclusions: Patient pain during IVI under topical anesthesia is mild to moderate. Simultaneous IV injection of fentanyl or remifentanyl with topical eye drop tetracaine 0.5 % reduces pain during IVI of avastin.

2. Introduction

Bevacizumab (avastin) is a human antibody that binds to all VEGF subtypes and has been used successfully in the treatment of tumors [1] Intravitreal injection of avastin can reduce the amount of macular edema secondary to PDR and CNV secondary to Age-Related Macular Degeneration (AMD) and retinal vein occlusion [2] and it has become the standard of care treatment for a variety of ocular conditions, including exudative age-related macular degeneration [3], cystoid macular edema [4], diabetic retinopathy [5], and en-

dophthalmitis [6]. Intravitreal injection of avastin is painful. Needle insertion is associated with pain and anxiety in the patient, and can cause hemodynamic instability and more complain of patient. Most patients need to multiple intravitreal injections of avastin and pain of injection can cause patient discomfort [7]. Patient comfort is especially important for intravitreal anti-VEGF treatments, where the patient is required to return on a regular basis for subsequent injections. If an uncomfortable procedure is experienced, the patient may refrain from this vision-saving treatment [8]. However, to date there is no consensus for the most effective anesthetic technique or agent that should precede the injection, Methods of ocular surface anesthesia include topical drop/gel administration, peribulbar injection, subconjunctival injection, and a pledget soaked in anesthetic [6].

The use of local anesthetics minimizes pain and avoids intraocular complications caused by pain-induced rapid, uncontrolled movements of the eye [7]. Based on recent surveys, most ophthalmologists (65–90%) perform IVI using local anesthetic eye drops. However, their patients complain of short and mild pain during penetrating of sclera by needle [9].

Topical anesthetic drops are delivered painlessly when compared with pledgets or anesthetic injections but may be associated with higher pain levels when the intravitreal injection is actually given [10]. The subconjunctival approach typically provides the best anesthesia

for the actual injection but is muted in overall effectiveness by the discomfort associated with the administration and an increased rate of subconjunctival hemorrhage [7-10]. Ophthalmic formulations of several NSAIDs (such as: ketorolac 0.4% , diclofenac 0.1% and bromfenac 0.9%) and also combination of topical and oral diclofenac have been investigated in reducing IVI-related pain when administered adjunctive to anaesthetic drops [11]. During IVI of bevacizumab in preterm infants with retinopathy of prematurity usually sedation/analgesia is required to optimize safety, as infant movement can increase the risk for iatrogenic cataracts or damage to the sclera [12]. Classical music before and during IVI decreases anxiety in patients without decreasing pain [13]. Preoperative sedation may be used to induce amnesia of the peribulbar injection(s) as well as the surgical procedure to increase overall patient acceptance. The objective of improving patient comfort by inducing amnesia must be balanced with undesirable deep sedation intraoperatively [14]. The aim of this study was to evaluate the effectiveness of simultaneous intravenous injection of fentanyl or remifentanyl to topical anesthetic techniques with tetracaine 0.5 % in reducing pain during IVI of avastin.

3. Material and Methods

This was a single center prospective double blind study. During the study recruitment period of 21 March to 22 August 2019, seventy-five patients attending for scheduled, elective IVI of avastin were identified and given information on the study. Patients who agreed

to participate were recruited as subjects after they had given their informed consent in writing. Inclusion criteria included: patients with age 40 to 80 years and ASA class I, II who were candidates for IVI of avastin. Exclusion criteria was history of previous eye surgery, herpetic eye disease, uncontrolled glaucoma, uveitis, active conjunctivitis, keratitis and bullous keratopathy, patients with thyroid dysfunction, nervous or psychiatric disorders, frequent cough, uncontrolled hypertension and history of drug abuse. Also patients younger than 40 or older than 80 years of age or who were frail, confused, or unfit for surgery were excluded.

Patients approved for the study were randomized to 1 of the 3 treatment groups: group F: 0.5% tetracaine HCL eye drop and fentanyl (50 mcg/ml) 1mcg/kg/ IV bolus+ 0.9% normal saline up to 2 ml, group R: 0.5% tetracaine HCL eye drop and remifentanyl (50mcg/ml) 1 mcg/kg/ IV bolus+0.9% normal saline up to 2 ml, and group T: 0.5% tetracaine HCL eye drop and 0.9% normal saline 2 ml. Before intravitreal injection of avastin, IV access 20-gauge was established. Monitors included an automated blood pressure cuff, electrocardiogram, and pulse oximeter, and vital signs were recorded every 5 minutes. Oxygen was administered at 4 L/min via nasal cannula. All IVI of avastin were conducted with the same technique, under aseptic conditions by the same surgeon to each patient's assignment. Tetracaine HCL 0.5% eye drops (Sinadarou Labs Company, Tehran, Iran) were used as an anesthetic. One drop of tetracaine was instilled 3 times over a 5-minute period before the IVI. Povidone Iodine 5% solution was used to scrub the eyelids and lashes. Then a sterile ophthalmic drape was placed and an eyelid speculum was inserted into the conjunctival fornices to stabilize the lids. Povidone iodine 5% solution and another drop of tetracaine were instilled on the ocular surface. Intravitreal injection of 0.05ml of bevacizumab (avastin) (0.05 mL; Genentech, San Francisco, CA, USA) was performed with a straight injection technique using a 30-gauge needle (insulin syringe) through the pars plana . A mild pressure was applied with a sterile cotton swab over the injection site to reduce subconjunctival hemorrhage and vitreal reflux. All patients received ophthalmic drop chloramphenicol 0.5% (Raha pharmaceutical co, Isfahan, Iran) for prevention of eye infection after the intravitreal injection. The study drug was prepared by an anesthetic nurse who did not participate in the collection of data.

Akinesia of the eye [14], during avastin injection was assessed on the operating table by the surgeon as follows: no movement = 0, mild movement (flicker) = 1, moderate movement = 2, and full movement = 3.

The surgeon was asked to determine his satisfaction based on a NRS from 1 to 4 (1 = bad, 2=average ,3= good, 4= excellent).

Degree of pain was assessed by using a visual analogue scale (VAS). Patients were asked to rate their pain experienced during the IV injection of avastin, between 0 (no pain) and 10 (worst pain ever felt) on VAS just in the recovery room. All complications

such as pain, nausea and vomiting, cardiac and respiratory complications were recorded. In case of nausea and vomiting post-operative (PONV), patients were treated with ondansetron 0.1 mg.kg/ IV. The average of these scores was used for statistical analysis. Bonferroni test was used to compare VAS values and ages between three groups and satisfaction of surgeon and compare patient's eye movements. Gender, PONV, and decrease of SPO2 was compared with the Chi square test. One-way analysis of variance was used to compare hemodynamic parameters. $P < 0.05$ was considered statistically significant.

4. Results

Our study included 75 patients scheduled for intravitreal injection of avastin performed under topical 0.5% tetracaine HCL eye drop with or without IV fentanyl or IV remifentanyl. Among 75 patients, 48(64%) were women and 27 (36%) were men, and in each 3groups there were more women than men, but there was no significantly difference between three groups in terms of gender, and other demographic data (table 1).

Degree of pain after IVI of avastin was lower significantly in fen-

tanyl (1.08 ± 0.6) and remifentanyl (0.68 ± 0.28) groups than tetracaine group (2.04 ± 1.54). ($p < 0.0001$) But there was not statistically significant between F and R group. However, VA pain score was not higher than 5 in none of 3 groups (figure 1).

Ocular akinesia score during avastin injection was higher in T group than in F or R group and it was statically significant. ($p = 0.015$) But there was no significant difference between F group and R group. ($p = 0.716$) (figure 2).

Mean average of surgeon satisfaction was higher in F group (3.84) and R group (3.76) than T group (3.36) and it was statically significant. ($p = 0.018$) But there was no significant difference between F group and R group. ($p = 0.772$) (figure 3).

There was no significant difference about the mean average of heart rate and percent of O2 saturation in three groups. Mean Arterial Pressure (MAP) in T group was higher than F group R group at time of avastin injection. But It was not statistically significant. The mean arterial pressure in the fifth minute after injection was lower in R group than in the other two groups, But It was not statistically significant.

Table 1: demographic data of patients in three groups

Groups	Age (yrs)	Weight (kg)	Male(%)	Female(%)
Fentanyl	66.000±6.325	69.960±7.662	9(36)	16(64)
Remifentanyl	68.550±5.613	69.000±8.515	8(32)	17(68)
Topical anesthesia	68.480±5.959	66.440±9.337	10(40)	15(60)

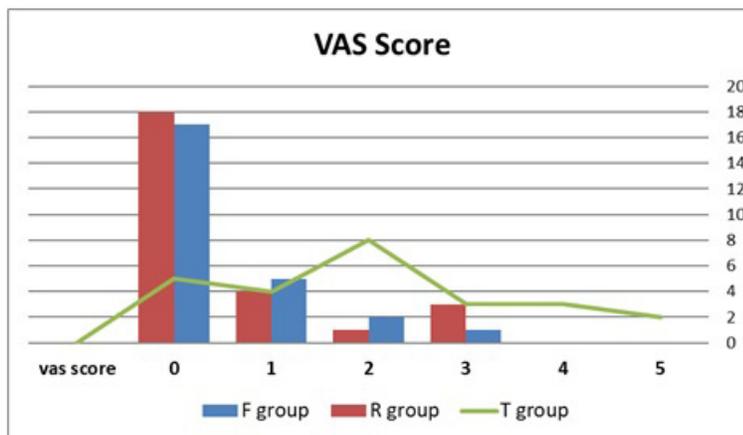


Figure 1: visual analogue scale (VAS) for IVI of avastin in studied groups

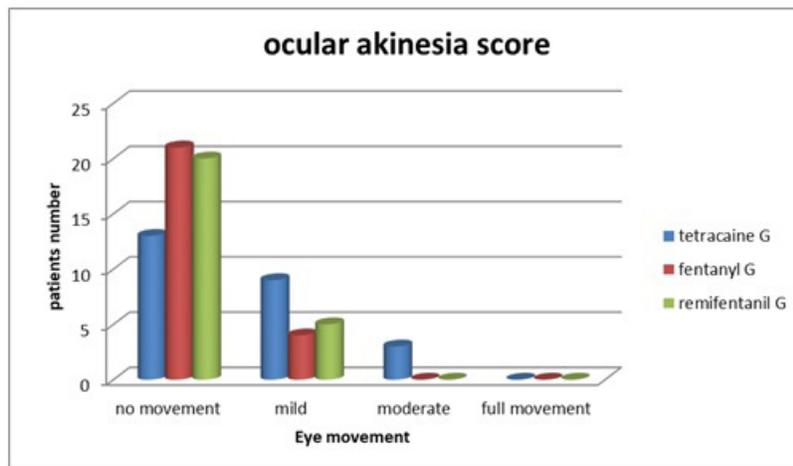


Figure2: ocular akinesia score assessment by surgeon at time of avastin injection

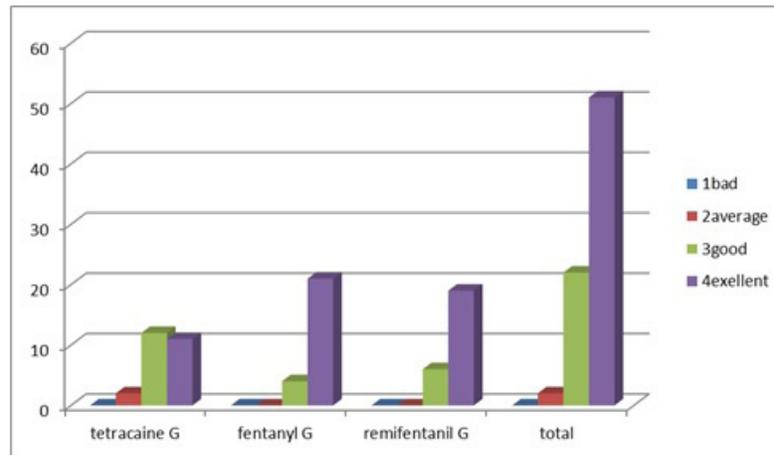


Figure 3: surgeon satisfaction from immobility and corporation of patients during injection

5. Discussion

Treatment with intravitreal injections has become one of the most commonly performed procedures in the everyday practice in ophthalmology. IVIs are often associated with pain resulting in varying levels of patient anxiety. It is, therefore, important to alleviate the IVI related pain in order to provide a well-tolerated treatment to the patients [11]. There are numerous approaches to anesthesia for intravitreal injections [10]. Anesthetic drops which have the fastest and simplest application Most ophthalmologists (65–90%) perform IVI using local anesthetic eye drops [7]. Other techniques include the use of an anesthetic gel, peribulbar block, subconjunctival injection and a pledget soaked in anesthetic [7]. Currently, no method of topical anesthesia prior to intravitreal injection administration has been proven to eliminate pain completely [15]. However, each anesthetic agent has its advantages and disadvantages. Also for immobility of the eye, relieve of patient's anxiety and profound anesthesia during eye surgeries various techniques with or without sedation have been developed [16]. In this study we evaluated and compared the effectiveness of simultaneous intravenous injection of fentanyl or remifentanil to topical anesthetic techniques with tetracaine 0.5 % in reducing pain during IVI of avastin. Maghsoudi and et al [17], observed that intravenous injection of remifentanil produced better analgesia and hemodynamic stability for retrobulbar block. Our study showed that IV sedation with fentanyl and remifentanil before IVI of avastin caused better analgesia than using topical 0.5% tetracaine HCL eye drop alone. The patient's movement during the operation may affect the outcome of the eye surgery, and can be considered as one of the weaknesses of using local anesthetic alone in eye surgeries. In this study, using small dose of IV fentanyl and remifentanil as a sedation caused immobility and decrease of pain of patients during the IVI of avastin. In the study of Boezaart et al 2001 [18] revealed that remifentanil alone can suppress patient's movement without any respiratory depression. In the research of Malik and Eliot [19] revealed that respiratory apnea can occurred with a single dose of remifentanil. But in our study, respiratory apnea did not occur with remifentanil or fentanyl. Only in a limited number of

patients, the respiratory rate decreased following remifentanil injection, which immediately improved the patients' respiratory rate following verbal stimulation. This result showed that respiratory monitoring is indicated during and post IV injection of remifentanil and fentanyl as a sedative and analgesic drugs using during IVI of avastin. The study of Leidinger and et al [20] showed that the use of remifentanil in eye procedures does not cause harmful side effects such as respiratory depression. In this study PONV in R group was more than F group and T group but there was no statistically significant between three groups. ($p > 0.05$) Results of PONV in the study of Leidinger and et al were similar to our study. In the study of Leidinger, incidence rate of PONV in R group was more than placebo but there was not any statistically different between two groups. However, PONV incidence, pain score and surgeon satisfaction were not significantly different between fentanyl and remifentanil group. But because avastin injection is a very short procedure and due to the short effect of remifentanil, and it is rapidly metabolized and its half time is about 3-4 minute, so remifentanil suggests for IVI of avastin.

6. Conclusion

IV injection of fentanyl or remifentanil with topical eye drop tetracaine 0.5 % can reduce pain during Intravitreal injection of avastin.

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