The Pain Relief Effect of Cold Normal Saline Eye Irrigation before Intravitreal Injections: A Double-Blind Randomized Controlled Trial

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Purpose: This study evaluated the effect of cold normal saline eye irrigation on pain sensation during intravitreal injections. We compared the adjunctive method with the standard intravitreal injection procedure.

Methods: We conducted a randomized, single-centre controlled trial. In this study, 64 patients were scheduled for intravitreal anti-vascular endothelial growth factors (Anti-VEGF) injection. Randomized patients ratio was 1:1. Topical anesthesia of 0.5% tetracaine was obtained in all patients. After a standard aseptic procedure, Cold NSS Eye Irrigation was performed. The pain evaluation was tested immediately and 30 minutes after the injection with the Visual Analogue Scale (VAS) and Short-form McGill Pain Questionnaire. 30 minutes after injection, the area of subconjunctival haemorrhage (SCH) has been recorded.

Results: Sixty-four patients were analysed. Baseline patient characteristics were similar except for previous cataract surgery history. Pain score was analysed during immediate injection by VAS. Mean pain score was 0.97 ± 1.06 in the cold NSS Eye Irrigation and 4.53 ± 1.50 in the control group ($p < 0.001$). After 30-minute post-intravitreal injection, the mean pain score in the cold NSS Eye Irrigation was 0.22 ± 0.75 and 3.16 ± 0.99 in the control group. SCH incidence was 40.6% in the Cold NSS Eye Irrigation group and 90.6% in the control group. Mean area of SCH in the Cold NSS Eye Irrigation group was 0.44 ± 0.56 clock-hour and 1.45 ± 0.65 clock-hour in the control group ($p < 0.001$). The differences in pulse rate and oxygen saturation which recorded using pulse oximetry were not statistically significant between both groups.

Conclusions: Cold Normal Saline Eye Irrigation could be an effective pain-relief method during intravitreal injections. This adjunctive method can decrease pain intensity and area of subconjunctival haemorrhage after intravitreal injections.

Keywords: topical anesthesia, intravitreal injections, pain, cold effect, pain score

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Introduction

Intravitreal Injection (IVI) is an effective procedure in the posterior segment of the eye to dispense medicines, for instance, intravitreal anti-vascular endothelial growth factors (anti-

VEGF) for diabetic macular edema antibiotics, endophthalmitis intravitreal antibiotics, and intravitreal macular edema corticosteroids for retinal vascular occlusion. This ophthalmic approach is now commonly used in a growing number of cases every year, because of a comprehensive revolution in the treatment of various retinal disorders in anti-VEGF medication. The intravitreal anti-VEGF injection regimes depend on disease diagnosis and stage. More than one injection was given to most patients. Some patients show pain during and after IV.[1]

Minor complications, which bring unpleasant experiences to the patients, are pain and subconjunctival haemorrhage (SCH).[2] Various methods used today for pre-intravitreal injection anesthesia, including topical drops, 2%-gel sterile lidocaine, subconjunctival injection, pledget soaked in anesthetic and peribulbar injection. Some reports show the efficacy of adjunctive topical medication, including topical apraclonidine and topical nepafenac 0.1% in reducing the patient's discomfort and minor adverse effects. Currently, there is no sufficient data defining the best option for pain reduction before IVIs.[3] Only a few ophthalmic studies demonstrated the benefit of cold temperature as an anesthetic method. One case report from 2014 identified the effect of an anaphylaxis patient or a serious anaphylactoid reaction to lidocaine on the bulbar conjunctiva pre-intravitreal injection of anti-VEGF.[4] After using this technique, the patient reported it as minimal to no discomfort. Moreover, the cold temperature has an analgesic effect in other situations. The use of local ice compresses after scleral buckling has an analgesic effect and reduces swelling on operated eyes.[5] Pain is decreased due to many proposed mechanisms. Nerve conduction is continually slowed down as the temperature falls. Cold also decreases activation threshold of tissue nociceptors.[6] The other obvious result of the cold effect is vasoconstriction, usually lasting about 15 minutes, followed by vasodilation.[7] Cold temperature may minimise these side effects of IVIs and provide patient's comfort.

The aim of this study was, therefore, to define a new, simple adjunctive anaesthetics method and to use the Thai Short-Form McGill Pain Questionnaire (Th-SFMPQ) to compare the pain sensation in cold normal saline irrigation groups to only a topical tetracaine eye drop-group. We also compare the extension of subconjunctival haemorrhage between two groups.

Methods

With regards to intravitreal therapy for patients with intravitreal anti-VEGF injection, we have performed a randomized trial at the Retina Clinic of Thammasat University Hospital from July to August 2019 to determine whether cold normal saline irrigation before injection relieves the sensation of pain and reduces the extension of SCH. The procedure was accepted by the Medical Ethics Committee of Thammasat University. All patients had written informed consent prior to the study.

Eligibility and Randomization

The eligible patients were patients treated by the Retina Clinic of Thammasat University Hospital with intravitreal Bevacizumab, Ranibizumab, or Aflibercept. This study excluded patients who have been using antiplatelet or anticoagulant and who have a bleeding tendency. Other exclusion criteria included an allergic history to the tetracaine eye drop, earlier trauma in the eyes, contagious eye disorders, co-existing intraocular glaucoma, and other ophthalmic procedures obtained on the same day of the intravitreal injection. If an eligible patient was

treated with IVIs for both eyes, the right eye was chosen to join the trial. For allocation, simple randomization has been used. Before intravitreal injection, the odd number received cold normal saline irrigation. The control treatment has been allocated to the even number group. The ophthalmologist who performed the IVIs is the same person throughout the study. The intravitreal injection procedure performed according to standard technique. Other investigators interviewed the patients using the study questionnaire. In this case, the IVI treatment room was created to mask an investigator and patients for the subject's assignment of other patients.

Treatment

All patients were evaluated, including medical and ophthalmic history. Slit-lamp, dilated fundus examination and OCT macula were performed in all patients. Bevacizumab, Ranibizumab and Aflibercept were used for IVI. The intervention and control groups were randomly allocated to patients. The intervention group received cold normal saline solution (NSS) irrigation 20 mL. The control group has a 10 second pause after eyelid speculum was inserted in order to simulate the cold normal saline eye irrigation period. We used this step in bilateral intravitreal injections. Each patient received one drop of 0.5% tetracaine 5 minutes before IVI. Povidone-iodine solution (5%) for the disinfection of periorbital skin and eyelashes was used. A speculum was, then, inserted. We utilized the sterile caliper to measure the distance from the limbus. We administered a tuberculin syringe injection at the supero-temporal quadrant. The 0.05 ml of anti-VEGF was injected via the pars plana. Antibiotic eye drop was instilled at the end of the procedure. We were concerned about the cold stress-related adverse effects.[8] Pulse rate and oxygen saturation were recorded throughout the procedure with oximetry.

Outcomes

A short form of the McGill Pain Questionnaire (SF-MPQ) was employed to assess the patients. The questionnaire was originally published in English, which was relatively difficult to understand and evaluate pain descriptors. Accordingly, the short form of the McGill Pain Questionnaire (SF-MPQ) was translated into the Thai language. The Thai Short-Form McGill Pain Questionnaire (Th-SFMPQ) has strong internal consistency with a high correlation between raters.[9] The SF-MPQ is a multi-dimensional pain assessment questionnaire, which is used in ophthalmology for the assessment of pain after IVIs and refractive surgery. Three sections were included in the questionnaire, including (1) the SF-MPQ's main component; (2) the Visual Analogue Scale (VAS), and (3) the Present Pain Intensity (PPI). The SF-MPQ was mainly comprised of 15 descriptors (11 sensory; 4 affective), which, on an intensity scale, were classified with 0 representing "none", 1 representing "mild", 2 representing "discomforting" (moderate), and 3 representing "distressing" (severe). Patients were asked to mark the point reflecting their pain on the horizontal line for the VAS pain score. The left edge of the line, rated as 0, was "no pain," whereas the right edge was the "worst pain ever experienced", rated as 10. The pain score parameter of VAS is currently the most common method for assessing ocular pain. In this study, the PPI section provided some verbal pain thresholds (0-5, as no pain to excruciating pain).[10] This provided an estimation scale that showed total pain severity.

The primary outcome was pain level measured by the VAS immediately after intravitreal injection. The secondary outcome variables included the area of SCH, MC-SFMPQ,

VAS and PPI at 30-minute post-IVI. SCH was assessed with slit-lamp examination by the second ophthalmologist who was blinded from a patient treatment group assignment. SCH extension was recorded in the clock-hour unit. Pulse rate and oxygen saturation (immediately and 30 min post-IVI) were compared in two groups. Furthermore, gender, age, the IVI for anti-VEGFs indication, eye and anti-VEGF types, and the number of previous IVIs in the study were also recorded.

Statistical Analysis

This study aimed to determine and describe the disparity between pain severity in the two IVI treatment groups using the Thai Short-Form McGill Pain Questionnaire (Th-SFMPQ). At least 54 patients, with a significant level set to 0.05, were calculated as the minimum sample size required for this analysis, and a decreased rate estimated at 20%. Statistical analysis was conducted using the SPSS statistical programme version 23.0. Baseline characteristic of patients identified in descriptive statistics. For pain score, an extension of the subconjunctival haemorrhage, oxygen saturation analysis, pulse rate, independent t-test and a Mann-Whitney U test were used.

Results

Sixty-four patients were analysed. Baseline patient characteristics were similar in the two groups (Table 1). Pain score was analysed during immediate injection by VAS. Mean pain score was 0.97 ± 1.06 in cold NSS Eye Irrigation and 4.53 ± 1.50 in control group ($P < 0.001$) (Table 2). After 30-minute post-intravitreal injection, the mean pain score in the cold NSS Eye Irrigation was 0.22 ± 0.75 and 3.16 ± 0.99 in the control group. The mean pain score immediate and 30-minute post injection were not different in age group correlation analysis. SCH incidence was 40.6% in the Cold NSS Eye Irrigation group and 90.6% in the control group. Mean area of SCH in the Cold NSS Eye Irrigation group was 0.44 ± 0.56 clock-hour and 1.45 ± 0.65 clock-hour in the control group ($P < 0.001$) (Table 4). Cold NSS Eye Irrigation also makes a statistically significant lower score in MC-SFMPQ, VAS and PPI at 30-minute post-injection. The differences of pulse rate and oxygen saturation, which recorded using pulse oximetry were not statistically significant between both groups throughout the procedure till 1-hour after. We found no correlation between sex, age, number of previous injections with VAS.

Discussion

The effect of cold temperature may be related to pain or the patient's discomfort. Our aim was to assess the effectiveness of this new convenient approach to alleviate pain from cold temperature during IVIs and to minimise subconjunctival haemorrhage. Pain reduction from cold temperature application decreased the stimulation signal to motor and sensory nerves and slowed down the rate of nerve conduction velocity as well. Moreover, the use of cold temperature by the local application may inhibit the local metabolic rate resulting in preventing tissue damage from hypoxia and inflammatory processes. There was a case report of presumed anaphylaxis or a severe anaphylactoid reaction to lidocaine using local cold compression as an anaesthetic procedure during IVIs in the previous study. A sterile glove filled with small ice cubes was applied to the lower eyelid of the patient and inferotemporal of bulbar conjunctiva approximately 2 minutes. Another consideration with direct cold compression was frostbite; to avoid this, in this case, the report used the sterile glove as a barrier. We avoided this side effect by using the indirect local cold application. Based on the effectiveness of cold temperature and reduced

Table 1: Baseline Patient characteristics

Characteristics	Total (n = 64)		COLD NSS (n = 32)		CONTROL (n = 32)		P value
	n	%	n	%	n	%	
Gender							1.000
Male	36	56.3%	18	56.3%	18	56.3%	
Female	28	43.8%	14	43.8%	14	43.8%	
Age (y)							0.802
<60	29	45.3%	15	46.9%	14	43.8%	
≥60	35	54.7%	17	53.1%	18	56.3%	
Mean±SD.	59.98	±8.40	59.88	±6.89	60.09	±9.79	0.918 [T]
min-max	36	-80	39	-80	36	-78	
Underlying disease							
DM	49	76.6%	25	78.1%	24	75.0%	0.768
HT	28	43.8%	15	46.9%	13	40.6%	0.614
DLP	8	12.5%	6	18.8%	2	6.3%	0.131
Other	2	3.1%	1	3.1%	1	3.1%	1.000
BCVA							
10/200	3	4.7%	2	6.3%	1	3.1%	
20/100	14	21.9%	8	25.0%	6	18.8%	
20/150	2	3.1%	0	0%	2	6.3%	
20/200	13	20.3%	5	15.6%	8	25.0%	
20/40	2	3.1%	2	6.3%	0	0%	
20/400	3	4.7%	1	3.1%	2	6.3%	
20/50	5	7.8%	3	9.4%	2	6.3%	
20/60	5	7.8%	2	6.3%	3	9.4%	
20/70	12	18.8%	6	18.8%	6	18.8%	
20/80	3	4.7%	3	9.4%	0	0%	
5/200	1	1.6%	0	0%	1	3.1%	
HM	1	1.6%	0	0%	1	3.1%	
SIDE							0.313
OD	36	56.3%	20	62.5%	16	50.0%	
OS	28	43.8%	12	37.5%	16	50.0%	
IOP							
Mean±SD.	12.36	±2.89	12.19	±2.73	12.53	±3.08	0.638 [T]
Indication							0.050 [F]
AMD	10	15.6%	5	15.6%	5	15.6%	
RVO	7	10.9%	1	3.1%	6	18.8%	
DME	39	60.9%	19	59.4%	20	62.5%	
PCV	5	7.8%	5	15.6%	0	0%	

Table 1: Baseline Patient characteristics (cont.)

Characteristics	Total (n = 64)		COLD NSS (n = 32)		CONTROL (n = 32)		P value
	n	%	n	%	n	%	
VH	2	3.1%	1	3.1%	1	3.1%	
NVG	1	1.6%	1	3.1%	0	0%	
Previous injection							
0	5	7.8%	3	9.4%	2	6.3%	
1	15	23.4%	5	15.6%	10	31.3%	
2	21	32.8%	12	37.5%	9	28.1%	
3	8	12.5%	5	15.6%	3	9.4%	
4	3	4.7%	1	3.1%	2	6.3%	
5	4	6.3%	3	9.4%	1	3.1%	
6	2	3.1%	1	3.1%	1	3.1%	
7	2	3.1%	1	3.1%	1	3.1%	
8	2	3.1%	1	3.1%	1	3.1%	
9	1	1.6%	0	0%	1	3.1%	
10	1	1.6%	0	0%	1	3.1%	
Mean±SD.	2.72	±2.27	2.63	±1.95	2.81	±2.58	0.715 M

P value was obtained from Chi-Square test; F = P value from Fisher's Exact Test;
M = P value from Mann-Whitney U Test; and T = P value from Independent t-test.

Table 2: Visual analogue pain score immediately and 30-min post-injection in cold NSS group and control group.

	COLD NSS (n = 32)		CONTROL (n = 32)		P value
	n	%	n	%	
Pain during injection					< 0.001* F
No pain 0	11	34.4%	0	0%	
mild pain: 1-3	20	62.5%	8	25.0%	
moderate pain: 4-6	1	3.1%	21	65.6%	
severe pain: 7-10	0	0%	3	9.4%	
Mean±SD.	0.97	±1.06	4.53	±1.50	< 0.001* M
30-minutes post-injection					< 0.001* C
No pain 0	28	87.5%	0	0%	
mild pain: 1-3	3	9.4%	22	68.8%	
moderate pain: 4-6	1	3.1%	10	31.3%	
Mean±SD.	0.22	±0.75	3.16	±0.99	< 0.001* M

Table 3: Oxygen saturation in cold NSS Eye irrigation group and control group

O2Sat (%)	COLD NSS (n = 32)		CONTROL (n = 32)		P value
	Mean	± S.D.	Mean	± S.D.	
0 minute	98.47	±1.02	98.38	±1.34	0.753
5 minutes	98.41	±1.01	98.38	±1.18	0.910
10 minutes	98.47	±0.98	98.38	±1.36	0.753
20 minutes	98.66	±0.90	98.31	±1.38	0.242
60 minutes	98.69	±1.00	98.50	±1.22	0.503
Total (Average)	**98.54**	**±0.88**	**98.39**	**±1.14**	**0.557**
Difference	**0.22**	**±0.83**	**0.13**	**±0.91**	**0.668**

P value was obtained from Independent t-test.

Table 4: Average Pulse rate (bpm) in cold NSS Eye irrigation group and control group.

Pulse rate (bpm)	COLD NSS (n = 32)		CONTROL (n = 32)		P value
	Mean	± S.D.	Mean	± S.D.	
0 minute	71.59	±8.32	82.22	±11.36	<0.001*
5 minutes	71.66	±8.15	83.00	±10.63	<0.001*
10 minutes	72.13	±8.14	81.94	±9.62	<0.001*
20 minutes	72.38	±7.75	83.28	±10.54	<0.001*
60 minutes	72.41	±8.31	83.41	±10.26	<0.001*
Total (Average)	**72.03**	**±8.04**	**82.77**	**±10.06**	**<0.001***
Difference	**0.81**	**±2.51**	**1.19**	**±5.11**	**0.711**

P value was obtained from Independent t-test (significance at the 0.05 level).

Table 5: Size of SCH (Subconjunctival haemorrhage, SCH) in cold NSS Eye irrigation and control group

	COLD NSS (n = 32)		CONTROL (n = 32)		P value
	n	%	n	%	
SCH					<0.001* C
Yes	13	40.6%	29	90.6%	
No	19	59.4%	3	9.4%	
SCH (wClock hour)					<0.001* F
0	19	59.4%	3	9.4%	
1	12	37.5%	9	28.1%	
1.5	0	0%	6	18.8%	
2	1	3.1%	13	40.6%	
2.5	0	0%	1	3.1%	
SCH (Clock hour)					<0.001* C
0	19	59.4%	3	9.4%	
1 - 1.5	12	37.5%	15	46.9%	
2 - 2.5	1	3.1%	14	43.8%	
Mean±SD.	**0.44**	**±0.56**	**1.45**	**±0.65**	**<0.001* M**

C was the P value from Chi-Square test; M = P value from Mann-Whitney U Test;
F = P value from Fisher's Exact Test (significance at the 0.05 level).

Table 6: Scores of the main component of TH-SFMPQ and present pain intensity 30 minutes post-injection.

Pain descriptor	COLD NSS (n = 32)		CONTROL (n = 32)		P value
	Mean	± S.D.	Mean	± S.D.	
Sensory					
Throbbing	0.00	±0.00	0.16	±0.37	0.021*
Shooting	0.38	±0.49	0.84	±0.51	0.001*
Stabbing	0.16	±0.37	0.53	±0.51	0.002*
Sharp	0.06	±0.25	0.34	±0.65	0.035*
Cramping	0.00	±0.00	0.09	±0.30	0.078
Gnawing	0.00	±0.00	0.09	±0.30	0.078
Hot-burning	0.00	±0.00	0.38	±0.66	0.001*
Aching	0.00	±0.00	0.13	±0.34	0.040*
Heavy	0.00	±0.00	0.09	±0.30	0.078
Tender	0.00	±0.00	0.22	±0.42	0.005*
Splitting	0.00	±0.00	0.09	±0.30	0.078
Total	0.59	±0.61	2.97	±3.43	<0.001*
Affective					
Tiring-exhausting	0.00	±0.00	0.22	±0.42	0.005*
Fearful	0.25	±0.51	0.66	±0.79	0.017*
Sickening	0.19	±0.40	0.25	±0.44	0.549
Punishing-cruel	0.00	±0.00	0.13	±0.34	0.040*
Total	0.44	±0.56	1.25	±1.50	0.019*
PPI	0.44	±0.80	2.41	±0.80	<0.001*

Table 7: Visual analogue pain score immediately and after 30-min post injection correlation analysis

	Age < 60 (n = 29)		Age ≥ 60 (n = 35)		P value
	Mean	± S.D.	Mean	± S.D.	
VAS immediately	2.76	±2.39	2.74	±2.09	0.907
VAS 30 min post injection	1.72	±1.85	1.66	±1.63	0.989

P value from Mann-Whitney U Test

pain intensity, we designed this convenient and economical anesthetic method.

Another concerning side effect of IVIs is SCH. SCH is caused by direct injury to tiny conjunctival blood vessels. This condition resolves spontaneously by itself without any consequence. Although this is a minor side effect, this problem often causes the patients to come back with their concern. Lagstein, et al. (2017) evaluated the effect of installation of topical apraclonidine 30 minutes before IVIs. Apraclonidine was α-1 and α-1-adrenergic agonists. α-1 adrenergic agonist had a vasoconstrictive effect. The study showed a decrease in size of SCH in the specific group of populations (phakic patients, non-hypertensive patients, and non-AMD-CNV patients)[11]. Currently, there is no study to evaluate the cold effect on this side effect during IVIs.

The causes of these side effects led to our new anesthetic method. Cold temperature via Cold NSS Eye irrigation is expected to have both analgesic and vasoconstrictive effects. According to our study, pain intensity and extension of subconjunctival haemorrhage were significantly decreased in the cold normal saline irrigation group. In this study, the VAS pain score determined a clinically important difference in pain perception as we used a minimum difference of 0.9-1.3.[12, 13] In this study, the difference in VAS pain score exceeded the upper limit of this range both immediately and 30 minutes after IVI, indicating the anesthetic effect of Cold NSS Eye irrigation. There is no cold stress side effect from this method, as shown in the results. Due to the many steps of assessment, we have an effort to minimise the observer's bias. We had two teams of ophthalmologists. After IVI was done by the first ophthalmologist, the patient was sent to the second ophthalmologist to evaluate pain intensity and subconjunctival haemorrhage. In other words, Cold NSS Eye irrigation has both anesthetic and vasoconstrictive effects during IVIs.

Conclusion

At present, IVIs are commonly used in retina practice. Pain and other side effects of the treatment may affect the compliance of patients. Reducing these side effects brings the patient's comfort. Cold normal saline eye irrigation during IVIs alleviated the pain intensity and extension of subconjunctival haemorrhage.

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