

A double-blinded randomized clinical trial for pain perception: The efficacy and safety of topical cold saline solution anesthesia in phacoemulsification

Mehmet Demir, Cetin Akpolat, Murat Karapapak¹, Selam Yekta Sendul, Dilek Guven

Purpose: To compare the efficacy and safety of cold saline solution (0.9% NaCl) with topical ophthalmic proparacaine for maintaining topical anesthesia of patients undergoing phacoemulsification surgery.

Methods: The prospective, double-blinded, and randomized clinical study was randomly assigned to two groups that underwent phacoemulsification surgery due to cataracts. The cold saline group included 86 eyes of 86 patients with topical anesthesia of cold saline solution alone. The proparacaine group included 84 eyes of 84 patients with topical ophthalmic proparacaine (room temperature) anesthesia alone. The patients were scored according to a pain survey questionnaire of Visual Analog Scale (VAS) ranked between 0 and 10. The surgeon scored surgical experience by a Surgeon Questionnaire Scale (SQS) in three parameters, each of which was ranked from 1 to 3 based on questions regarding ease and comfort during the surgery.

Results: The mean VAS scores were 1.29 ± 0.65 and 1.22 ± 0.66 for the cold saline and proparacaine groups, respectively ($P = 0.182$). The mean scores of SQS (lower values represented favorable results) were 4.11 ± 0.76 and 3.97 ± 0.74 in the cold saline and proparacaine groups, respectively ($P = 0.163$). Ten patients in the proparacaine group experienced corneal epitheliopathy in the postoperative period. **Conclusion:** As an easily accessible and cost-effective method, cold saline solution alone might be an alternative to topical ophthalmic proparacaine alone with comparable safe and effective results. The absence of allergic or toxic effects also provided a significant advantage in the cold saline application.

Key words: Cold saline solution, phacoemulsification, proparacaine, topical anesthesia

Cold temperature application can provide local anesthesia, which is defined as cryoanalgesia, and there are various areas for the application of cold temperature to control pain, including the musculoskeletal system, dental, dermatologic, and ophthalmic procedures.^[1] Topical ophthalmic anesthesia including various kinds of agents has been widely used for ophthalmic examinations and procedures due to its rapid onset, efficacy, easy application, and low risk of side effects. Cold saline solution is a part of cold temperature application and may have the potential to provide topical ophthalmic anesthesia by blocking the pain sensation of the cornea in ophthalmic procedures, especially cataract surgery.^[1]

In phacoemulsification under cryoanalgesia, the constant stimulation of the corneal receptors utilizing cold and the anterior chamber (AC) pressure can induce saturation of the nervous transmission through mechanical and thermal stimuli, which decreases the transmission of pain sensations with the same intensity.^[2] Easy accessibility, cost-effectivity, and the absence of allergic or toxic effects of the cold saline solution are its advantages; more irrigation fluid usage, cold intolerance, and irritation are the disadvantages of the cold saline solution when compared to the actual classic proparacaine alone.

Department of Ophthalmology, Sisli Hamidiye Training and Research Hospital, Istanbul, ¹Department of Ophthalmology, Basaksehir Cam and Sakura City Hospital, Turkey

Correspondence to: Dr. Cetin Akpolat, Sisli Hamidiye Etfal Training and Research Hospital, Department of Ophthalmology, Istanbul, Turkey. E-mail: akpolatcetin@yahoo.com

Received: 25-Apr-2021

Revision: 07-Jul-2021

Accepted: 21-Jul-2021

Published: 23-Dec-2021

Access this article online

Website:

www.ijo.in

DOI:

10.4103/ijo.IJO_876_21

Quick Response Code:



A cataract is the leading cause of reversible vision loss worldwide.^[3] The advances in cataract surgery techniques have been updated to the modern method of phacoemulsification surgery mostly under local anesthesia, including topical anesthesia.^[4-6] Agarwal *et al.*^[7] performed the first cataract surgery with non-pharmacological anesthesia in 1998, and in 2005, Gutiérrez-Carmona *et al.*^[8] performed phacoemulsification using the cryoanalgesia method, which was previously described by Toczolowski *et al.*^[9] There are some scales to measure pain scores during phacoemulsification, including the Visual Analog Scale (VAS), Likert scale, numerical rating scale, and 10-point verbal pain score.^[10]

We aimed to conduct this clinical study to assess the efficacy and safety of topical cold saline solution alone versus topical proparacaine alone in patients who underwent phacoemulsification surgery.

Methods

The randomized and double-blinded clinically-controlled study (clinical registration number: 2939, The clinical

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

For reprints contact: WKHLRPMedknow_reprints@wolterskluwer.com

Cite this article as: Demir M, Akpolat C, Karapapak M, Sendul SY, Guven D.

A double-blinded randomized clinical trial for pain perception: The efficacy and safety of topical cold saline solution anesthesia in phacoemulsification. Indian J Ophthalmol 2022;70:124-30.

registration number was incorrectly specified, it has been corrected. 2021.01.80) was prospectively conducted according to the principles of the Declaration of Helsinki. The institutional review board approved the study protocol. Informed consent was signed by all patients before the phacoemulsification procedure. The sample size was calculated by using a confidence level of 95%, a confidence interval of 10, and a population size as 1,800 (the total number of cataract surgeries at the hospital). This gave us a sample size of 82.

Patients

Patients with visual impairment due to cataracts, according to the lens opacities classification system III (LOCS) scoring were eligible for the study.^[11] Among these, patients without any communication problems, including hearing and speech disabilities, and patients tolerant to local anesthesia were enrolled in the study. The exclusion criteria for this study were uncontrolled systemic diseases, psychological problems, intensive head tremor, age (<18 years), a history of analgesic and non-steroid anti-inflammatory drug (NSAID) use within 3 months, traumatic cataract, lens dislocation, axial length >26.00 mm, and <18.00 mm, uncontrolled or neovascular glaucoma, active inflammatory ocular disease (uveitis), central corneal opacities, zonule defects (iridodonesis and phacodonesis), vitreous hemorrhage and complicated surgeries. Using a computerized random number generator, the selected patients were randomly allocated to the two groups using permuted block randomization of size 4 to undergo local anesthesia with cold saline solution and proparacaine %0.5 (5 mg) at room temperature. The patients who had phacoemulsification surgery under topical anesthesia of cold saline solution alone served as the 'cold saline group' and the patients who had phacoemulsification surgery under topical anesthesia of proparacaine alone comprised the 'proparacaine group' (Fig. 1: CONSORT Flow Diagram). Since proparacaine is mostly used in our clinic and is one of the commonly used topical agents for topical anesthesia in phacoemulsification surgeries, we specifically selected proparacaine as the topical agent in the comparison of cold saline solution. The demographic and clinical features of the patients and the follow-up duration were recorded for statistical analysis. In addition to pain assessment, the patients had detailed preoperative and postoperative ophthalmic examinations, including best-corrected visual acuity (BCVA, in decimal), intraocular pressure (IOP, mmHg), biomicroscopic anterior, and posterior segment findings.

Topical anesthesia and surgical procedure

The type of topical anesthesia was performed randomly by an independent researcher. Preoperative proparacaine was not instilled prior to draping the patient in both groups. The ocular surface was gently washed with a bolus infusion of 20 mL of cold saline solution (0.9% NaCl, kept between +1°C and +4°C in the refrigerator) for 30 s in the cold saline group and topical ophthalmic proparacaine at room temperature (proparacaine hydrochloride 0.5%) required 10 s in the proparacaine group to provide the topical anesthesia. Later on, the cornea was washed periodically with small amounts of chilled saline solution (for the cold saline group) and saline solution at room temperature (for the proparacaine group) to prevent corneal dryness during the surgery. Following the topical anesthesia

with cold saline solution or ophthalmic proparacaine, phacoemulsification was performed by the same experienced surgeon. Supplemental intracameral (lidocaine 2%) or sub-Tenon's (lidocaine 2% with bupivacaine 0.75%) anesthesia were added as rescue analgesia in case of requirement. All the patients were prescribed topical ophthalmic steroids and antibiotics postoperatively. The patients had slit-lamp evaluations at postoperative day 1, week 1, months 1 and 3. Any peri- or postoperative complications, especially regarding the topical anesthesia, were recorded.

Pain assessment

The patients were instructed to verbally inform the surgical team in case of any discomfort and disturbing tolerable or intolerable pain during the surgery. The notifications of the pain and the requirement for supplemental rescue analgesia were noted by another independent researcher regarding the surgical step. The VAS was used for subjective pain evaluation as a pain survey questionnaire. The VAS, a derivation of the standard reported in the past, is a modified unidimensional scale, which is 10 cm in length (equivalent to 10°) and is visible with its numbers (degrees) only on the side of the examiner.^[12] The 0-point represented no pain and that the 10-point represented the most intense pain.^[3,13,14] The VAS was applied by a different practitioner (unaware of the anesthetic technique) other than the surgeon 15 min after the end of the surgery and the second pain measurement was taken 5 m after the first measurement, and the mean value of the two measurements was recorded as the final value. The surgeon scored his experience of each patient's surgery using four subscales according to the Surgeon Questionnaire Scale (SQS). Three of the subscales included patient cooperation, ocular movement, and AC stability, which were ranked on a scale of 1 (representing good patient cooperation, no ocular movement, and stable anterior chamber, respectively) to 3 (representing poor patient cooperation, uncontrollable ocular movement, and unstable anterior chamber, respectively) for each parameter, with a cumulative range between 3 and 9 points for each patient. The lower values represented favorable results. The fourth parameter described the intraoperative complications in any step of the surgery.

Statistical analysis

Statistical analysis of the patient data was performed using SPSS for Windows, version 21.0 (IBM Corp., Armonk, NY, USA). The continuous variables were presented as the mean \pm standard deviation. The VAS score was analyzed using a two-sample proportion test (Stata version 12.1, Stata Corp) to compare the degree of pain during the surgery among the study population. The Kolmogorov-Smirnov test was used for data normality distribution. The Chi-square test, paired and independent samples t-tests were also used for statistical analysis. A *P* value <0.05 was considered statistically significant within the 95% confidence interval.

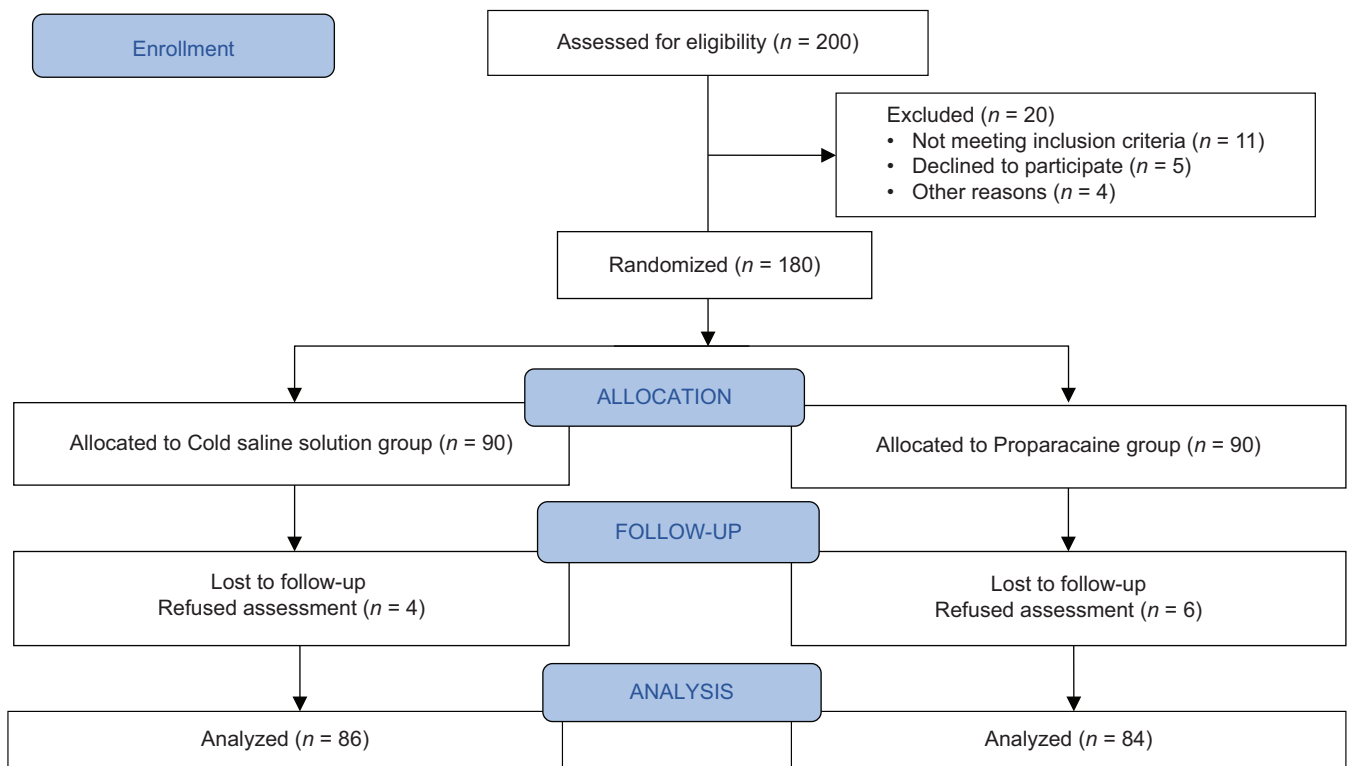
Results

A total of 86 eyes of 86 patients in the cold saline group and a total of 84 eyes of 84 patients in the proparacaine group were included in the present study based on the exclusion and inclusion criteria. The demographic characteristics of the patients, follow-up durations, preoperative ophthalmic examination findings or measurements, comorbidities,

Table 1: Demographic properties of the patients, follow-up durations, preoperative examination features, comorbidities, and intraoperative interventions

Characteristics	Values of Cold Saline Group	Values of Proparacaine Group	P
Number of patients (M/F)	38/48	38/46	0.348/0.412
Age (mean±SD/range, years)	69.38±9.88/38-87	71.66±8.42/42-82	0.288
Axl (mean±SD/range, mm)	22.52±1.29/18.56-26.00	23.16±1.40/19.04-25.58	0.304
Follow-up duration (mean±SD/range, days)	97.92±14.42/90-137	102.45±14.86/90-156	0.107
Surgery duration (mean±SD/range, min)	21.58±3.46 (13-27)	22.06±3.32 (12-29)	0.273
Cataract Type			
Nuclear (mean density±SD/G2-G3-G4)	3.19±0.68/12-42-29	3.25±0.74/9-41-29	0.081
Mature	2	5	
PSC	1	0	
Complicated cataract conditions			
PSX	6	4	
Small pupil (<4 mm)	2	1	
Comorbidities (DM/HT/DM + HT)	6/12/6	8/10/4	
Retinopathy (DME/SMD)	7/10	5/12	
Previous anti-VEGF injection	6	5	

M: Male, F: Female, SD: Standard deviation, Axl: Axial length, G: Grade, PSC: Posterior subcapsular cataract, PSX: Pseudoexfoliation, DM: Diabetes mellitus, HT: Hypertension, DME: Diabetic macular edema, SMD: Senile macular degeneration, VEGF: Vascular endothelial growth factor

**Figure 1: CONSORT Flow Diagram**

and previous interventions were represented in Table 1. A significant correlation was observed between the nuclear density and age in both the groups ($r = +0.522$, $P = 0.018$ for the cold saline group; $r = +0.604$, $P = 0.010$ for the proparacaine group). All the patients in the proparacaine group required 10 s for the time duration of topical anesthesia, whereas all cases in the cold saline group required 30 s for the time duration of topical anesthesia. However, this difference in the time duration

of topical anesthesia did not result in a difference in the average time duration of the surgery between the groups.

We did not observe any allergy and corneal toxicity, or haze induced by topical cold saline solution in the perioperative and postoperative periods. However, 10 patients in the proparacaine group had corneal epitheliopathy in the postoperative period; 9 patients experienced mild central and paracentral punctate corneal epithelial erosions up to

1 postoperative day, 1 patient experienced moderate-severe central corneal epithelial defect up to 1 postoperative week. Twelve patients felt a burning sensation after topical proparacaine instillation, 4 of them were among the patients who experienced corneal epitheliopathy. No allergic reactions were reported due to proparacaine applications. We also compared intra- and intergroup preoperative and postoperative results of the endothelial cell count and corneal thickness. However, we did not find any intra- or intergroup preoperative or postoperative differences.

Preoperative BCVA significantly improved at month 3 of the postoperative period compared to baseline ($P = 0.001$ for both groups), and an insignificant IOP reduction was observed in the postoperative 3rd month compared to baseline in both groups [Table 2]. Three and 2 patients with preoperative IOP measurements of 22 mmHg expressed reductions under 20 mmHg in the postoperative 3rd month in the cold saline and proparacaine groups, respectively.

We used the VAS to assess and compare the mean score of the pain experienced by the patients. The pain survey questionnaires of VAS were scored with a nonsignificant difference ($P = 0.182$). We did not also note any significant difference in the mean pain scores between the male and female patients in both the inter- and intragroup analyses [Table 3].

In the cold saline group [Table 4]: 15.12% of the patients experienced moderate or severe pain with scores greater than 3 on the 10-scaled VAS, which was described as representing the level of moderate pain (7, 8). The remaining 73 patients (84.88%) experienced mild pain or no pain. In the proparacaine group [Table 4]: 11.90% of the patients experienced moderate or severe pain (greater than 3/10). The remaining 74 patients (88.10%) experienced mild pain or no pain.

Thirty-three and 34 tolerable pain reports were scored 3 or less in the cold saline and proparacaine groups, respectively [Tables 4 and 5]. The remaining tolerable pain reports (10 eyes in the cold saline group and 9 eyes in the proparacaine group) were scored higher than 3 on VAS [Tables 4 and 5]. All intolerable reports in both the groups were scored higher than 3 on VAS. We noted that the patients mostly experienced tolerable or intolerable pain perception during the distention of AC regardless of the stage of phacoemulsification in both groups. We noted that patients had tolerable pain during the injection of viscoelastic before capsulorhexis (5 eyes in the cold saline group and 4 eyes in the proparacaine group), during the entrance of phacoemulsification probe into the AC when the irrigation is on (11 eyes in both groups), during the nucleus fragmentation (10 eyes in the cold saline group and 9 eyes in the proparacaine group), during the I/A procedure (8 eyes in the cold saline group and 10 eyes in the proparacaine group), and during the implantation of intraocular lens (9 eyes in both groups). Three patients (2 patients with grade 3 cataract and 1 patient with grade 2 cataract) who experienced intolerable pain in the cold saline group had supplemental intracameral anesthesia. One patient (with grade 2 cataract) who experienced intolerable pain in the proparacaine group had supplemental sub-Tenon’s anesthesia. All intolerable reports in both groups were noted during nuclear fragmentation.

The frequency score or SQS obtained from the physician who performed the surgery revealed that both the groups had a favorable experience in terms of the comfort and ease of the surgical procedure and the complications during the intervention. The mean SQS subscale and composite scores were similar in the cold saline and proparacaine groups ($P > 0.05$ for all) [Table 6].

Table 2: Intra- and intergroup preoperative and postoperative alterations and comparisons of BCVA and IOP values

Parameters	Baseline	Postop 3 rd Month	P**
BCVA (decimal)			
Mean±SD (range) ‘Cold Saline Group’	0.23±0.16 (0.01-0.5)	0.79±0.24 (0.15-1.00)	0.001†
Mean±SD (range) ‘Proparacaine Group’	0.20±0.14 (0.01-0.4)	0.78±0.26 (0.10-1.00)	0.001†
P*	0.556	0.652	
IOP (mmHg)			
Mean±SD (range) ‘Cold Saline Group’	15.41±2.92	14.83±2.49	0.092
Mean±SD (range) ‘Proparacaine Group’	16.96±2.80	16.62±2.72	0.174
P*	0.072	0.068	

BCVA: Best-corrected visual acuity, IOP: Intraocular pressure, *Analyzed with independent samples t-test, **Analyzed with paired samples t-test, SD: Standard deviation, †Statistically significant

Table 3: Intra- and intergroup assessments of VAS scores for pain perception during phacoemulsification

	VAS Score for Cold Saline Group	VAS Score for Proparacaine Group	P*
Total patients (number of patients, score range)	1.29±0.65 (n=86, 0-7)	1.22±0.66 (n=76, 0-7)	0.182
Male (number of patients, score range)	1.27±0.56 (n=38, 0-7)	1.21±0.60 (n=33, 0-7)	0.161
Female (number of patients, score range)	1.33±0.74 (n=48, 0-7)	1.24±0.76 (n=43, 0-7)	0.140
P**	0.176	0.252	

VAS: Visual Analog Score, *Intergroup analysis with independent samples t-test, ** Intragroup analysis with independent samples t-test representing the male and female comparison

Discussion

In the present study, we demonstrated that topical cold saline solution alone compared to a topical ophthalmic agent (proparacaine) alone is an effective and safe local anesthetic method for phacoemulsification with acceptable patient pain perception and favorable experience for the surgeon without any peri- or postoperative complications, including corneal toxicity or haziness and allergic reactions.

Phacoemulsification is usually performed under local anesthesia, including topical, sub-Tenon, subconjunctival,

intracameral, peribulbar, and retrobulbar anesthesia.^[15] However, phacoemulsification under local anesthesia is not a completely pain-free surgery, with possible pain at various levels of severity and in various stages of the procedure, especially when the AC is unstable.^[16-19] Similarly, we noted pain perception in some patients during manipulation causing distention of the AC. Supporting our results, an experimental animal study reported that a single drop of topical proparacaine might damage the corneal epithelium by the disruption of the intercellular spaces, reduction in the microvilli and micro-plicae, and prominence of the cell nucleus.^[20] Topical ophthalmic anesthetic agents may also cause side effects, including endothelial cell damage and retinal toxicity, corneal haziness, ocular inflammation with possible hypopyon, stromal edema, Descemet membrane folding, allergic reactions with results of conjunctival hyperemia, periorbital erythema, edema, and dermatitis.^[21,22] Our results demonstrated that topical ophthalmic anesthesia with cold saline solution did not cause these adverse effects, possibly as the saline salutation is preserve-free.

The peripheral axons of trigeminal neurons innervating the cornea and conjunctiva transmit the pain.^[23] The major nerve bundles lose their myelin sheaths as soon as reaching the cornea following the limbus and become transparent afterward, thus providing protective reflexes against mechanical, pain, cold, and chemical stimuli, induction of tear secretion, and trophic support for epithelial and stromal cells without the prevention of light transmission.^[24] They form a subepithelial nerve plexus in the stroma whose ascending branches penetrate Bowman's layer and ramify extensively to terminate within the surface epithelium layers. Functionally, the corneal sensory neurons can be classified as polymodal nociceptors, specific mechano-nociceptors, or cold thermoreceptor neurons. Polymodal nociceptors are normally silent and respond to chemical, mechanical, and thermal stimuli. They become sensitized by the inflammatory mediators released by ocular surface injury. The transient receptor potential (TRP) cation channel subfamily V member 1 (TRPV1) channels are important for sensory transduction and sensitization of polymodal nociceptors.^[23] Most cold thermoreceptors discharge continuously at the normal eye surface temperature with an

Table 4: Assessment of mean pain scores regarding VAS levels in the cold saline and proparacaine groups

VAS Level	Cold Saline Group	Proparacaine Group
Number of eyes with VAS 0 (no pain)	40	40
Number of eyes with VAS 1 (mild pain)	18	19
Number of eyes with VAS 2 (mild pain)	8	9
Number of eyes with VAS 3 (mild pain)	7	6
Number of eyes with VAS >3 (moderate to severe pain)	13	10

VAS: Visual analog scale

Table 5: Comparison of the patients with tolerable and intolerable pain in the cold saline and proparacaine groups

	Cold Saline Group	Proparacaine Group	P
Total	86	84	0.656
Patients with no pain	40 (46.51%)	40 (47.62%)	0.818
Patients with pain	46 (53.49%)	44 (52.38%)	0.705
Tolerable pain	43	43	0.798
Intolerable pain	3	1	0.342

Table 6: The number of patients in the SQS subscales and mean values for the SQS subscale and composite scores representing the surgical experience of the surgeon during phacoemulsification

	1. Patient Cooperation Subscale (n=86* and 84**)	2. Ocular Movement Subscale (n=86* and 84**)	3. AC Stability Subscale (n=86* and 84**)	4. Complication
1-point (Favorable score)				
Cold Saline Group (n)	68	58	62	-
Proparacaine Group (n)	69	58	65	-
2-points				
Cold Saline Group (n)	10	19	18	-
Proparacaine Group (n)	8	19	17	-
3-points (Poor score)				
Cold Saline Group (n)	8	7	4	-
Proparacaine Group (n)	7	17	2	-
Subscale: Mean SQS [‡]	1.32±0.26 (1-3)	1.46±0.22 (1-3)	1.33±0.28 (1-3)	Composite: Mean SQS [‡]
Cold Saline Group (n=86)	1.26±0.24 (1-3)	1.39±0.26 (1-3)	1.32±0.24 (1-3)	4.11±0.76 (3-9)
Proparacaine Group (n=84)	0.102	0.118	0.389	3.97±0.74 (3-9)
P				0.163

[‡]Surgeon Questionnaire Scale, AC: Anterior chamber, *for Cold Saline Group, **for Proparacaine Group n: number of the patients

increase or decrease in the firing frequency upon cooling or warming, respectively. TRP cation channel subfamily M member 8 (TRPM8) is the main transduction channel for cooling or cold.^[23]

Cold temperatures have direct effects on nerve conduction and can decrease the activity in the polymodal neurons, diminish painful mechanical stimuli transmission, and reduce the nerve conduction velocity with a rapid onset.^[25,26] A previous study conducted in cats showed that mechanical sensory and thermal fibers can alter the quality of pain sensation by affecting polymodal nociceptors.^[2] Cryoanalgesia can reduce the proportion of corneal polymodal nociceptors.^[27] Cryoanalgesia can also affect separate sensory nociceptor TRP ion channels that exist for the transmission to the central nervous system of the modality and the spatial-temporal characteristics of peripheral non-noxious and noxious stimuli.^[28] The cold application can also provide local anesthesia and decrease ocular discomfort (burning and stinging) via vasoconstriction promotion, which decreases the release of inflammatory mediators (leukotrienes and prostaglandins) similar to the mechanism of NSAIDs.^[1,25,29]

Gupta *et al.* found a VAS pain score of 0.70 ± 0.97 (range, 0–5) under topical anesthesia with intracameral lignocaine.^[3] Jacobi *et al.*^[30] compared the VAS pain scores with peribulbar anesthesia (VAS = 0.73 ± 1.5 ; range, 0–5) and with 2% lignocaine drops (VAS = 0.84 ± 1.30 ; range, 0–7) for phacoemulsification. Similar VAS pain score outcomes have been demonstrated for phacoemulsification under topical anesthesia with lignocaine 2% jelly.^[31,32] We noted similar comparable VAS pain score results with these studies. Sansanayudh *et al.*^[25] suggested that cold topical tetracaine could suppress ocular discomfort during application and observed that lowering the temperature of ophthalmic tetracaine resulted in a weaker burning sensation, especially in patients who experienced worse burning sensations.

A study conducted by Alvarez-Marín *et al.*^[33] in 2002 showed satisfactory pain control during phacoemulsification under local anesthesia of an intracameral irrigation solution at 4°C. Gutiérrez-Carmona and Alvarez-Marín^[15] conducted a randomized clinical trial to compare cryoanalgesia with topical anesthesia. Suggesting our study, their study demonstrated the safety of cryoanalgesia with an acceptable level of VAS pain score in patients who underwent phacoemulsification surgery that was similar to the results with topical anesthesia. Moreover, they reported that some patients preferred cryoanalgesia to topical anesthesia. Similar to our study, both studies used cold anesthesia alone.^[15,17] However, we instilled the topical cold saline solution, which differed from the method of Gutiérrez-Carmona and Alvarez-Marín,^[15] who applied an eye mask of cold gel placed over the eye, and Alvarez-Marín *et al.*^[33] who used intracameral cold anesthesia. The results of another study conducted in patients who underwent phacoemulsification demonstrated that the combination of topical anesthesia and intraocular cold irrigation solution yielded a more satisfactory outcome of VAS pain score than topical anesthesia alone.^[34] In contrast to this study, a previous study reported no difference in the perception of pain between topical anesthesia alone and topical anesthesia plus cold intraocular irrigation solution for phacoemulsification.^[1]

The study has some limitations including relatively small sample size, the short time duration of surgery

type (phacoemulsification), cryoanalgesia in less variety of cataracts and other situations, and the selection of only one topical agent (proparacaine). Further studies with larger sample sizes, long-time duration surgery type, and selection of more than one topical agent are warranted to investigate the efficacy and safety of cold saline solution as a topical anesthetic. Since our cases required a short time duration for phacoemulsification, reuse of chilled saline solution several times may also be experienced for long-duration surgeries in further studies. We might propose a recommendation for the indication of cold saline anesthesia in case of an allergic reaction to proparacaine, inappropriate conditions for the sterility of proparacaine, and economic insufficiency for proparacaine purchase. We might add limits to the cold saline during one phacoemulsification surgery in case of cold intolerance and irritation.

Conclusion

In conclusion, our study revealed that sole cold saline solution anesthesia might be the alternative to sole topical medical anesthesia in providing effective and safe topical anesthesia during phacoemulsification. The absence of potentially toxic or allergic reactions is also the superiority of chilled saline solution. The results of the study suggested a feasible, more accessible, and economical topical anesthetic method for use in routine ophthalmic surgeries.

Ethics approval

The institutional review board approved the study protocol.

Consent to participate

Informed consent was signed by all participants.

Consent for publication

Informed consent for publication was signed by all participants.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Korpan NN. A history of cryosurgery: Its development and future. *J Am Coll Surg* 2007;204:314-24.
2. Acosta MC, Belmonte C, Gallar J. Sensory experiences in humans and single-unit activity in cats evoked by polymodal stimulation of the cornea. *J Physiol* 2001;534:511-25.
3. Gupta SK, Kumar A, Kumar D, Agarwal S. Manual small incision cataract surgery under topical anesthesia with intracameral lignocaine: Study on pain evaluation and surgical outcome. *Indian J Ophthalmol* 2009;57:3-7.
4. Akpolat Ç, Kurt MM, Evliyaoğlu F, Cinhüseynoğlu MN, Elçioğlu MN. Outcomes of phacoemulsification surgery in high myopic patients with cataract. *Turkiye Klinikleri J Ophthalmol* 2016;25:219-24.
5. Chang DF. Tackling the greatest challenge in cataract surgery. *Br J Ophthalmol* 2005;89:1073-7.
6. Coelho RP, Biaggi RH, Jorge R, Rodrigues Mde L, Messias A. Clinical study of pain sensation during phacoemulsification with and without cryoanalgesia. *J Cataract Refract Surg* 2015;41:719-23.
7. Agarwal A, Agarwal S, Sachdev MS. No anesthesia cataract surgery with karate chop. In: *Phacoemulsification, Laser Cataract Surgery,*

- and Foldable IOLs. New Delhi: Jaypee Brothers; 1998. p. 144–54.
8. Gutiérrez-Carmona FJ. Phacoemulsification with cryo-analgesia: A new approach for cataract surgery. In: Phacoemulsification, Laser Cataract Surgery, and Foldable IOLs. 2nd ed. New Delhi: Jaypee Brothers; 2000. p. 226-9.
 9. Toczolowski J. [Thirty years of cryo-ophthalmology. Work dedicated to the memory of Dr. Tadeusz Krwawicz]. *Klin Oczna [Polish]* 1994;96:129-31.
 10. Heard JA, Zacarias AAG, Lawrence AT, Stoicea N, Palettas M, Fiorda-Diaz J, *et al.* A prospective observational cohort study to evaluate patients' experience during sequential cataract surgery under monitored anesthesia care and topical anesthesia. *Medicine (Baltimore)* 2020;99:e21834.
 11. Grewal DS, Brar GS, Grewal SPS. Correlation of nuclear cataract lens density using Scheimpflug images with lens opacities classification system III and visual function. *Ophthalmology* 2009;116:1436-43.
 12. Singer AJ, Thode HC Jr. Determination of the minimal clinically significant difference on a patient visual analog satisfaction scale. *Acad Emerg Med* 1998;5:1007-11.
 13. Collins SL, Moore RA, McQuay HJ. The visual analog pain intensity scale: What is moderate pain in millimeters? *Pain* 1997;72:95-7.
 14. Lee J, Stiell I, Hobden E, Wells G. Clinically meaningful values of the visual analog scale of pain severity. *Acad Emerg Med* 2000;7:550.
 15. Gutiérrez-Carmona FJ, Alvarez-Marín J. Randomized comparative clinical study of cryoanalgesia versus topical anesthesia in clear corneal phacoemulsification. *J Cataract Refract Surg* 2005;31:1187-93.
 16. Hou C-H, Lee J-S, Chen K-J, Lin K-K. The sources of pain during phacoemulsification using topical anesthesia. *Eye* 2012;26:749-50.
 17. Dadacı Z, Borazan M, Acır NÖ. Pain perception in phacoemulsification with topical anesthesia and evaluation of factors related with pain. *Turk J Ophthalmol* 2016;46:151-5.
 18. Naik MP, Sethi HS, Yadav A. Topical vs peribulbar anesthesia: Comparison of anterior chamber depth and the resultant visual outcome after phacoemulsification. *Clin Ophthalmol* 2020;14:3775-80.
 19. Shi C, Yuan J, Zee B. Pain perception of the first eye versus the second eye during phacoemulsification under local anesthesia for patients going through cataract surgery: A systematic review and meta-analysis. *J Ophthalmol* 2019;2019:4106893.
 20. Brewitt H, Bonatz E, Honegger H. Morphological changes of the corneal epithelium after application of topical anaesthetic ointments. *Ophthalmologica* 1980;180:198-206.
 21. Wen Q, Fan T, Bai S, Sui Y. Cytotoxicity of proparacaine to human corneal endothelial cells *in vitro*. *J Toxicol Sci* 2015;40:427-36.
 22. Yagci A, Bozkurt B, Egrilmez S, Palamar M, Ozturk BT, Pekel H. Topical anesthetic abuse keratopathy: A commonly overlooked health care problem. *Cornea* 2011;30:571-5.
 23. Kovács I, Luna C, Quirce S, Mizerska K, Callejo G, Riestra A, *et al.* Abnormal activity of corneal cold thermoreceptors underlies the unpleasant sensations in dry eye disease. *Pain* 2016;157:399-417.
 24. Shetabi H, Hashemi SJ, Haghi F, Moradi Farsani D. Safety and efficacy of fentanyl versus pethidine in cataract surgery under propofol-based sedation: A double-blind randomized controlled clinical trial. *J Res Med Sci* 2020;25:81.
 25. Sansanayudh W, Phansucharitthai T, Sansanayudh N. The effect of cold tetracaine on the severity of burning sensation upon instillation. *Clin Ophthalmol* 2018;12:2377-82.
 26. Algafly AA, George KP. The effect of cryotherapy on nerve conduction velocity, pain threshold, and pain tolerance. *Br J Sports Med* 2007;41:365-9.
 27. Mannan R, Pruthi A, Khanduja S. Comparison of surgeon comfort assessment during phacoemulsification using bilateral topical anesthesia versus ipsilateral topical anesthesia: A randomized controlled study. *Int Ophthalmol* 2018;38:1235-42.
 28. Scuderi G, Scuderi L, Calafiore S, Fenicia V, Abdolrahimzadeh S. Deep topical anesthesia with ropivacaine-soaked sponge for phacoemulsification. *Int Ophthalmol* 2019;39:2851-6.
 29. Bleakley CM, McDonough SM, MacAuley DC, Bjordal J. Cryotherapy for acute ankle sprains: A randomized controlled study of two different icing protocols. *Br J Sports Med* 2006;40:700-5.
 30. Jacobi PC, Dietlein TS, Jacobi FK. A comparative study of topical vs. Retrobulbar anesthesia in complicated cataract surgery. *Arch Ophthalmol* 2000;118:1037-43.
 31. Bardocci A, Lofoco G, Perdicaro S, Ciucci F, Manna L. Lidocaine 2% gel versus lidocaine 4% unpreserved drops for topical anesthesia in cataract surgery: A randomized controlled trial. *Ophthalmology* 2003;110:144-9.
 32. Soliman MM, Macky TA, Samir MK. Comparative clinical trial of topical anesthetic agents in cataract surgery: Lidocaine 2% gel, bupivacaine 0.5% drops, and benoxinate 0.4% drops. *J Cataract Refract Surg* 2004;30:1716-20.
 33. Alvarez-Marín J, Montesinos Ventura BM, Gutierrez Carmona FJ. Facoemulsificacionbajocrioanestesia: Nuestra experiencia [Phacoemulsification under cryoanalgesia: Our experience]. *Arch Soc Canar Oftalmol* 2002;77:33-40.
 34. Torres-Moreno AJ. Anestesiaticas con soluciones frias en facoemulsificacion [Topical anesthesia with cold solutions in phacoemulsification]. *Rev Mex Oftalmol* 2009;83:197-200.