



# Comparative Effect of Local Anesthesia with Lidocaine 2% Versus Topical Anesthesia on Cognitive Function in Ophthalmic Surgery

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Received 2019 August 13; Revised 2019 October 18; Accepted 2019 October 25.

## Abstract

**Background:** Multiple clinical trials targeted the assessment of cognitive function following local versus general anesthesia in patients undergoing ophthalmic surgery, but no previous clinical trials have focused on the effect of topical anesthesia on cognitive function.

**Objectives:** This study aimed to compare the effect of local anesthesia with lidocaine 2% versus topical anesthesia with Oxybuprocaine (benoxinate hydrochloride 0.4%) on cognitive function in patients undergoing elective cataract surgery.

**Methods:** This is a prospective randomized clinical trial carried out on 60 patients undergoing elective cataract surgery by phacoemulsification. Thirty patients received local anesthesia with lidocaine 2% and thirty patients received topical anesthesia with Oxybuprocaine (benoxinate hydrochloride 0.4%). Patients' satisfaction was assessed postoperatively using the Iowa satisfaction with anesthesia scale (ISAS). Cognitive assessment for all patients was done preoperatively and 1 week postoperatively using paired-associate learning test (PALT) and category verbal fluency (VF) test (animal category).

**Results:** There was no statistically significant difference between local and topical anesthesia groups in the mean of responses to the 11 statements of ISAS ( $P = 0.071$ ). Regarding cognitive assessment, there was a statistically significant postoperative decline in the local anesthesia group in both PALT scores ( $P = 0.005$ ) and VF scores ( $P = 0.01$ ). In the topical anesthesia group, there was no statistically significant difference between pre- and postoperative PALT scores ( $P = 0.326$ ) or VF scores ( $P = 0.199$ ).

**Conclusions:** Postoperative cognitive dysfunction following elective cataract surgeries under local anesthesia can be attributed to the effect of local anesthesia rather than the effect of surgery.

**Keywords:** Cognitive Function, ISAS, Lidocaine, Oxybuprocaine (Benoxinate), PALT, VF

## 1. Background

Peribulbar anesthesia was considered the most popular technique of anesthesia for cataract surgery over the last years. Advances in cataract surgery, including the use of smaller and self-sealing incisions, have shortened the duration of surgery; thus anesthesiologists became able to use short-acting anesthetics (1). Surprisingly, in the United Kingdom, in 2007, 21% of cataract surgeries were performed using topical anesthesia and 3.5% using peribulbar anesthesia (2). It has been reported that the incidence of intraoperative complications in cataract surgeries is less in topical anesthesia (3), but the pain is better controlled with peribulbar anesthesia compared to topical anesthesia (4).

Great interest was directed towards studying the ef-

fects of anesthetic drugs on cognitive function (5). Multiple clinical trials revealed that both general and regional anesthesia are incriminated in causing postoperative cognitive dysfunction (POCD) (6-10). Recently, local anesthesia was also found to cause postoperative impairment in cognitive function (11). The POCD was thought to be a reversible condition. However, POCD was found to be positively correlated with long-term cognitive dysfunction (12). Also, POCD may manifest as impairment in concentration, immediate and delayed memory, or executive dysfunctions. Sometimes, these deficits can be mild and only diagnosed by psychometric tests (13).

The reported neurotoxic side effects of Lidocaine can be considered one of the possible pathophysiological mechanisms for POCD following local anesthesia. The neurotoxicity of lidocaine is known to be dose-dependent.

Clinically relevant concentrations of lidocaine were found to induce apoptosis, while higher concentrations may induce necrosis and unspecific cell death (14, 15).

While multiple clinical trials were conducted to compare the effect of general versus regional anesthesia on cognitive function (7-10, 16), but no previous clinical trials have focused on the effect of local versus topical anesthesia on cognitive function.

## 2. Objectives

The aim of this work was to study the effect of local anesthesia with lidocaine 2% versus topical anesthesia with Oxybuprocaine (benoxinate hydrochloride 0.4%) on cognitive function in patients undergoing elective cataract surgery.

## 3. Methods

### 3.1. Study Design and Population

This is a prospective randomized controlled trial that was carried out on 60 patients undergoing elective cataract surgery by phacoemulsification with intraocular lens implantation. The patients assessed for eligibility were 100 patients. Forty patients were excluded (18 patients did not meet the inclusion criteria, 12 patients declined to participate, and 10 patients were excluded for other reasons). Sixty patients were randomly assigned into one of two groups; the first group received local anesthesia with lidocaine 2% (30 participants) (local anesthesia group), and the second group received topical anesthesia with Oxybuprocaine (30 participants) (topical anesthesia group). The patients, the neurologist, and the surgeons were blinded to the method of anesthesia. Randomization was done using a closed opaque envelope technique. In such a technique, the anesthetist selected a sealed envelope that contained a paper carrying the name of the group to which the patient was scheduled. No patients were lost to follow up or excluded from the analysis. The patients were recruited in the period from December 2016 to January 2018 from the Ophthalmology Outpatient Clinic of Beni-Suef University Hospital. Written informed consent was obtained from all participants on the day of surgery. The study was approved by the Local Ethics Committee in the Faculty of Medicine, Beni-Suef University (FWA00015574 in 8th of March 2018). The study was conducted in accordance with the Declaration of Helsinki. The study was registered in the Pan African Clinical Trial Registry (PACTR201903779653918).

### 3.2. Inclusion and Exclusion Criteria

Patients were included if they were between 40 years to 70 years old with immature cataracts.

The following patients were excluded from the study: patients with mature cataract, a history of previous ocular trauma or surgery, ocular co-morbidities such as exfoliation syndrome, posterior synechia, uveitis, phacodonesis, strabismus or poor fixation due to nystagmus, marked auditory dysfunction affecting their ability to complete testing, pre-existing cognitive disorder, allergy to either local or topical anesthetics, and inability to understand the instructions concerning the study or if the patient refused the local or topical anesthesia techniques.

The included patients were subjected to the following:

- Cognitive Assessment:

It was done for all patients preoperatively and one week postoperatively by a neurologist who was blinded to anesthesia technique. Verbal memory was assessed using paired-associate learning test (PALT). In such a test, the examiner would say ten pairs of words in front of the participant. These pairs contain four semantically unrelated pairs and six semantically related pairs. After two minutes, the first word of the pairs is mentioned to the participant and he/she is asked to recall the second one. The test is repeated three times. A score 1 was given for each correct incompatible pair while a score 0.5 was given for each correct compatible pair. The total score for the test ranges from 0 to 21 (17). Attention and executive function were assessed using category verbal fluency test. In this test, the participant is asked to name as many animals as he can within 1 minute. Each animal he/she names, takes a score 1 (18).

- Assessment of Patients' Satisfaction:

Patients' satisfaction was assessed by a neurologist who was blinded to the anesthesia technique using the Iowa satisfaction with anesthesia scale (ISAS). This questionnaire measures patient's satisfaction with their monitored anesthesia care (MAC). Patients have to respond to 11 statements by placing a mark along a single response out of six options for responses. The responses are: -3 = disagree very much, -2 = disagree moderately, -1 = disagree slightly, 1 = agree slightly, 2 = agree moderately, and 3 = agree very much. A totally satisfied patient was given a score +3, and a totally dissatisfied patient was given a score -3. The mean score of their responses to all the statements ranged from -3 to +3. Patients were given the questionnaire immediately after the operation. The time required to fill in the questionnaire was not limited. None of the anesthesiologist or the operator was in contact with the patient during this time (19).

- Anesthetic Technique:

Anesthesia for cataract surgery was done for all included patients by the same anesthesiologist. The included 60 patients in the study were randomly assigned to one of the two groups; the first group received local anesthesia with lidocaine 2% (total volume 6 mL) with hyaluronidase 30 IU (30 participants) (local anesthesia group), and the second group received topical anesthesia with Oxybuprocaine (benoxinate hydrochloride 0.4%) every 1 minute 3 times before the surgery (30 participants) (topical anesthesia group). All included patients were transferred to the preparation room. The anesthesia technique and the operation procedure were explained to the patients, no premedication was given, only psychological reassurance. Venous line was inserted under antiseptic technique. Standard monitoring was done for all included patients (oxygen saturation, electrocardiogram, and blood pressure measurement). In the local anesthesia group, peribulbar injection technique was done with a 25 G needle under complete antiseptic technique. The patients should look straight ahead, then injection of a volume 4 mL of the local anesthetic inferolaterally was done after negative aspiration followed by injection of 2 mL through the medial canthus. Digital pressure was applied after each injection for 5 seconds every 20 seconds over a period of 3 minutes. The patients were then transferred to the operation room, nasal mask with oxygen supply 3 - 4 L/min was applied and standard monitoring was done.

- Surgical Technique:

Cataract surgery was done for all participants by the same surgeon using the same surgical technique. In all patients, a 2.4 mm sized incision in the clear cornea was created at the most curved axis. A sutureless incision was made then phacoemulsification was performed with implantation of a foldable single piece lens into the capsular bag. In both groups, the surgical time was 15 - 20 minutes, the operation room stay was one hour, and the hospital stay 8 hours. The patients wear eye patches after surgery for 3 days.

### 3.3. Statistical Methods

Calculation of sample size was done using G\*Power version 3.1.9.2 Software based on our pretrial pilot study. The power ( $1 - \beta$ ) was 80% and the probability of type I error ( $\alpha$ ) was 5%. A total of 60 participants with 1:1 ratio of the two arms in our study were required for the two-sided significance of 95%. The data were coded and entered using: the statistical package for social science version 18 (SPSS V. 18) (Chicago, USA). For quantitative variable, student *t*-test was used for comparison between mean of responses of ISAS between local and topical anaesthesia groups, and Paired-sample *t*-test was used for comparison between means of

preoperative and postoperative cognitive tests in local and topical anesthesia groups. For qualitative variables, number and percent were calculated and chi-square test was used for comparison between local and topical anesthesia groups. The significance value  $P < 0.05$  is considered statistically significant.

## 4. Results

The mean age of the patients in the local anesthesia group ( $n = 30$ ) was  $52.67 \pm 10.97$  years, while the mean age of the patients in the topical anesthesia group ( $n = 30$ ) was  $55.93 \pm 9.78$  years. Regarding sex, 46.7% ( $n = 14$ ) of the patients in the local anesthesia group were males and 53.3% ( $n = 16$ ) were females. In the topical anesthesia group, 36.7% ( $n = 11$ ) were males and 63.3% ( $n = 19$ ) were females. There was no statistically significant difference between both groups in either age groups ( $P = 0.228$ ) or sex ( $P = 0.432$ ) (Table 1).

Regarding ISAS, the mean responses to the 11 statements for the patients in the local anesthesia group were ( $-0.273 \pm 0.39$ ) and for the patients in the topical anesthesia group was ( $-0.094 \pm 0.36$ ). There was no statistically significant difference between both groups ( $P = 0.071$ ) (Table 2).

Regarding PALT in the patients in the local anesthesia group, postoperative total score of PALT ( $10.45 \pm 5.38$ ) was significantly lower than preoperative PALT ( $11.3 \pm 4.56$ ) ( $P = 0.005$ ). In the topical anesthesia group, there was no statistically significant difference between the mean value of preoperative PALT ( $10.33 \pm 5.05$ ) and postoperative PALT ( $10.1 \pm 4.97$ ) ( $P = 0.326$ ) (Table 3).

Regarding VF in the patients in the local anesthesia group, postoperative total score of VF ( $8.7 \pm 1.535$ ) was significantly lower than preoperative VF ( $9.3 \pm 2.003$ ) ( $P = 0.01$ ). In the topical anesthesia group, there was no statistically significant difference between the mean value of preoperative VF ( $8.83 \pm 2.56$ ) and postoperative VF ( $8.63 \pm 2.06$ ) ( $P = 0.199$ ) (Table 4).

**Table 1.** Demographic Characteristics of the Patients in Both Local and Topical Anesthesia Groups<sup>a</sup>

|        | Local Anesthesia Group (N = 30) | Topical Anesthesia Group (N = 30) | P Value <sup>b</sup> |
|--------|---------------------------------|-----------------------------------|----------------------|
| Age, y | 52.67 ± 10.97                   | 55.93 ± 9.78                      | 0.228                |
| Sex    |                                 |                                   | 0.432                |
| Male   | 14 (46.7)                       | 11 (36.7)                         |                      |
| Female | 16 (53.3)                       | 19 (63.3)                         |                      |

<sup>a</sup>Values are expressed as No. (%) or mean ± SD.

<sup>b</sup>P value  $\geq 0.05$  (non-significant).

**Table 2.** Iowa Satisfaction with Anesthesia Scale in Both Local and Topical Anesthesia Groups

| ISAS   | Local Anesthesia Group (N = 30) | Topical Anesthesia Group (N = 30) | P Value              |
|--|---------------------------------|-----------------------------------|----------------------|
| 1. I was too cold or hot                           | 0.3 (1.44)                      | 1.37 (1.38)                       | 0.005 <sup>a</sup>   |
| 2. I would want to have the same anaesthetic again | 0.43 (1.28)                     | -1 (1.46)                         | < 0.001 <sup>a</sup> |
| 3. I itched  | -1.2 (1.47)                     | -1.07 (1.48)                      | 0.728                |
| 4. I felt relaxed                                  | 1.1 (0.99)                      | -1.5 (1.46)                       | < 0.001 <sup>a</sup> |
| 5. I felt pain                                     | -2.6 (0.56)                     | 1.5 (0.94)                        | < 0.001 <sup>a</sup> |
| 6. I felt safe                                     | 0.73 (1.53)                     | -0.8 (1.32)                       | < 0.001 <sup>a</sup> |
| 7. I threw up or felt like throwing up             | -1.33 (1.09)                    | -1.57 (1.14)                      | 0.421                |
| 8. I was satisfied with my anesthetic care         | 2 (0.79)                        | 0.07 (1.64)                       | < 0.001 <sup>a</sup> |
| 9. I felt pain during surgery                      | -2.73 (0.78)                    | 1.8 (0.89)                        | < 0.001 <sup>a</sup> |
| 10. I felt good                                    | 1.23 (1.17)                     | -0.8 (1.32)                       | < 0.001 <sup>a</sup> |
| 11. I hurt   | -0.93 (1.2)                     | 0.97 (1.16)                       | < 0.001 <sup>a</sup> |
| Mean of responses to the 11 statements             | -0.273 (0.39)                   | -0.094 (0.36)                     | 0.071                |

Abbreviation: ISAS, Iowa satisfaction with anesthesia scale.

<sup>a</sup>P value < 0.05 (significant).

**Table 3.** Pre- and Postoperative PALT Scores in Both Local Versus Topical Anesthesia Groups

| PALT                              | Preoperative Assessment | Postoperative Assessment | P Value            |
|-----------------------------------|-------------------------|--------------------------|--------------------|
| Local anesthesia group (n = 30)   | 11.3 (4.56)             | 10.45 (5.38)             | 0.005 <sup>a</sup> |
| Topical anesthesia group (n = 30) | 10.33 (5.05)            | 10.1 (4.97)              | 0.326              |

Abbreviation: PALT, paired-associate learning test.

<sup>a</sup>P value < 0.05 (significant).

**Table 4.** Pre- and Postoperative VF Scores in Both Local Versus Topical Anesthesia Groups<sup>a</sup>

| VF                                | Preoperative Assessment | Postoperative Assessment | P Value <sup>b</sup> |
|-----------------------------------|-------------------------|--------------------------|----------------------|
| Local anesthesia group (n = 30)   | 9.3 ± 2.003             | 8.7 ± 1.535              | 0.01*                |
| Topical anesthesia group (n = 30) | 8.83 ± 2.56             | 8.63 ± 2.06              | 0.199                |

Abbreviation: VF, verbal fluency.

<sup>a</sup>Values are expressed as mean ± SD.

<sup>b</sup>P value < 0.05 (significant).

## 5. Discussion

Among the many postoperative complications, postoperative cognitive dysfunction gained great attention in the last years (20). The incidence of POCD ranges between 8.9% and 46.1% (21, 22). It may return to baseline within months, but sometimes recovery may be delayed or incomplete. In more severe cases, POCD may progress to a catastrophic deterioration of cognition with subsequent increased mortality (13).

The effect of general versus regional anesthesia on cognitive function was thoroughly investigated by many researchers. In a systematic review (included 16 studies) done by Davis et al., 2014, the investigators found that only three studies showed an increased incidence of POCD fol-

lowing general anesthesia compared to regional anesthesia, while the remaining thirteen studies showed that both general and regional anesthesia cause POCD with no significant differences between them (10). Even local anesthesia with either lidocaine or bupivacaine was recently found to cause significant postoperative impairment in verbal memory, attention and executive function (11).

The aim of this work was to compare the effect of local anesthesia with lidocaine 2% versus topical anesthesia with Oxybuprocaine on cognitive function in patients undergoing elective cataract surgery. Specific cognitive tests were used to detect even subclinical postoperative cognitive impairment. The results revealed that in the local anesthesia group, there was a significant postoperative decline in verbal memory, attention and executive function, but in

the topical anesthesia group, there was no statistically significant difference between pre- and postoperative cognitive function. So, we conclude that local anesthesia with lidocaine can be involved in POCD.

There were no previous studies that compared the effect of local versus topical anesthesia on cognitive function in patients undergoing ophthalmic surgery. However, multiple clinical trials targeted the assessment of postoperative cognitive function following local versus general anesthesia in patients undergoing ophthalmic surgery. In 1993, Krier et al. studied geriatric patients undergoing ophthalmic surgery to differentiate the effect of local versus general anesthesia on cognitive function. Their results revealed that both general and local anesthesia cause POCD with no significant differences between them (23).

Additionally, Karhunen et al. in 1982, compared the effect of general versus local anesthesia on cognitive function in patients undergoing cataract surgery. They found that there was no significant difference in most cognitive tests between both groups, but in the general anesthesia group, there was a more significant decline in memory function (8).

Different findings were obtained by Campbell et al. in 1993 who conducted a study on a group of patients (aged 65 - 98 years) randomized to receive either general or local anesthesia for cataract surgery. Cognitive assessment was done preoperatively, as well as at 24 hours, 2 weeks, and 3 months postoperatively. The investigators found no evidence of long-term POCD in either general or local anesthesia groups (24).

In contrary to these findings, Hall et al. in 2005 found a significant improvement in cognitive function at 1-year follow-up visit after cataract surgery (25). Similar findings were obtained by Tamura et al. in 2004 who found that cognitive function was markedly improved after cataract surgery in elderly Japanese patients (26). Such a long-term improvement was explained by the improvement of visual function that resulted in subsequent improvement in cognitive function.

The variability of the results among studies can be attributed to several factors such as differences in the studied population, the absence of a standard POCD definition, different follow-up periods, and heterogeneity of the psychometric tests used to assess cognitive function. Additionally, the impact of some potential confounders can make it difficult to isolate the effect of anesthesia (27, 28).

The reported cognitive impairment following local anesthesia can be attributed to the larger amount of anesthetic drugs absorbed into systemic circulation in comparison to topical anesthesia. The cellular and subcellular mechanisms that can explain the occurrence of cog-

nitive dysfunction following local anesthesia are evolving rapidly. Several pathways are implicated in the neurotoxicity of local anesthesia. Lidocaine is known to trigger various biochemical cascades, including apoptosis through mitochondrial pathway independently of death receptor signaling. It can lead to DNA fragmentation and disruption of the mitochondria membrane. This results in the uncoupling of the oxidative phosphorylation, with subsequent release of cytochrome c and initiation of the caspase pathway causing apoptosis (14, 15).

### 5.1. Conclusions

Local anesthesia in ophthalmic surgeries may cause a significant postoperative decline in verbal memory, attention, and executive function compared to topical anesthesia. So, the reported postoperative cognitive dysfunction in patients undergoing elective cataract surgery under local anesthesia may be attributed to the effect of local anesthesia rather than the surgery per se.

### Footnotes

**Authors' Contribution:** Wael Fathy participated in study conception and design, sequence alignment and helped to draft manuscript. Mona Hussein and Hossam Khalil participated in collection and analysis of data and helped to draft manuscript. All authors read and approved the final manuscript with agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

**Clinical Trial Registration Code:** PACTR201903779653918.

**Conflict of Interests:** Authors have no conflict of interest.

**Ethical Approval:** The study was approved by Local Ethical Committee in Faculty of Medicine, Beni-Suef University (FWA00015574 in 8th of March 2018).

**Funding/Support:** Authors did not receive any funding for this work.

**Patient Consent:** A written informed consent was obtained from each participant in this study.

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