Comparison of the Effects of Povidone-Iodine 5%, Polyhexamethylene Biguanide, and Chlorhexidine as a Preoperative Antiseptic in Endophthalmitis Prophylaxis in Patients Undergoing Phacoemulsification Cataract Surgery

Abstract

Background: This study aims to compare the efficacy and toxicity of povidone-iodine (PI) 5%, polyhexamethylene biguanide (PHMB) 0.02%, and chlorhexidine 0.02% in patients undergoing phacoemulsification cataract surgery. Materials and Methods: This single-center, randomized study was done on 330 patients who referred to Feiz hospital in Isfahan and scheduled for cataract surgery. They were assigned randomly to 1 of 3 groups of 110 eyes who received 1 drop of PI 5% in group 1, 1 drop of PHMB 0.02% in group 2 and 1 drop of chlorhexidine 0.02% in group 3. Pre-operative Cultures samples were obtained without any topical application and it was repeated 5 min after use of antiseptic solutions. Cultures were obtained from the inferior conjunctival fornix, using sterile culture swabs while avoiding contact to the eyelids and lashes. Results: The numbers of colony-forming units (CFUs) did not differ significantly among the three groups (P = 0.149 and P = 0.260, respectively). After the intervention, CFUs numbers in the three groups were decreased with a significant difference in both blood and chocolate agars (P = 0.304 and P = 0.136, respectively). Of the 317 eyes, 108 (34.1%) showed no bacterial growth in the pre-preparation period, which was similar in the three groups. Staphylococcus epidermidis was the most common isolated bacteria. Conjunctival injection was significantly different among studied groups (P = 0.0001), five patients in iodine group had severe conjunctival injection and no one in the other group. SPE was significantly fewer in chlorhexidine group than PHMB and iodine groups (P = 0.0001). Conclusion: Pretreatment with 5% Povidone-Iodine (PVI) for at least 15 min or repeated applications over 10 min is effective in the reduction of conjunctival organisms, and results in less postoperative endophthalmitis.

Keywords: Antiseptic, chlorhexidine, endophthalmitis prophylaxis, phacoemulsification cataract surgery, polyhexamethylene biguanide, povidone-iodine 5%

Introduction

Cataract surgery is one of the most commonly performed surgeries worldwide.[1] Endophthalmitis; a severe inflammation of the anterior or posterior (or both) chambers of the eye that may be sterile or associated with infection, most commonly occurs as a vision-threatening complication of cataract surgery that usually presents within a few days following cataract surgery, and 80% of cases present within 6 weeks.[2] Its incidence is reported to be approximately 0.023%–0.26%, depending on the report[3-5] and Iran reports an overall rate of 0.02%.[4] The insufficient prophylactic protocol is an important factor in the incidence of endophthalmitis following cataract surgery that could be obviated by tailoring the surgical approach.[6,7] Examples of prophylactic measures include preoperative lash-trimming and irrigation of the lacrimal drainage system with antibiotics, antiseptic preparation of the operative site using agents such as povidone-iodine (PI), and preoperative, intraoperative, and postoperative administration of antibiotics.[2] Prophylactic measures for endophthalmitis are targeted against various sources of infection. The reduction of periorbital flora has been associated with a lower incidence of postoperative ocular infections. According to studies, bacterial flora is a potential source of endophthalmitis

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Original Article

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Keywords: Antiseptic, chlorhexidine, endophthalmitis prophylaxis, phacoemulsification cataract surgery, polyhexamethylene biguanide, povidone-iodine 5%

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after cataract surgery.\[8\] Patients’ own bacterial flora, including those residing at the eyelid margin, is the most common source of ocular pathogens.\[9\] Whereas at the end of phacoemulsification, the small incision may not be completely closed by stromal hydration and a potential space may remain between the anterior chamber and cul-de-sac for hours after surgery.\[10\] Thus, the conjunctival flora stays a major source of postoperative endophthalmitis. Various methods have been used to reduce the bacteria load near the surgical field immediately before surgery, such as preparation of the ocular surface with an antiseptic agent before surgery and the use of antibiotics before, during, and after surgery.\[12\] The application of preprocedure antisepsis reduces the ocular surface pathogen load but not alter the bacterial flora. Common ophthalmological practices to prevent postoperative endophthalmitis include topical application of antiseptics, for example, 5%–10% PI or 4% chlorhexidine gluconate and topical antimicrobial agents, for example, chloramphenicol, gentamicin, etc.\[8\] PI is an intermediate level antiseptic with higher microbicidal activity against Gram-negative than Gram-positive bacteria that irritative effects on skin and mucosa are mild; therefore, it is safe, well-tolerated for both preoperative skin and mucosal application. Chlorhexidine gluconate is an effective, safe, commonly used skin antiseptic in surgical procedures with higher microbicidal activity against Gram-positive than Gram-negative bacteria.\[10\] Wu et al. showed that preoperative skin disinfection with 10% PI and conjunctival disinfection with 5% PI significantly reduced the relative risk of postoperative endophthalmitis.\[13\] Currently, the PI 5% is used against postoperative endophthalmitis as the standard and recommended practice in the world.\[10,11,14-21\] There is little evidence about the efficacy of various concentrations of chlorhexidine in eliminating conjunctival pathogens and preventing endophthalmitis after cataract surgery. Some showed that there is no significant difference between the sterilization effectiveness of PI 5% and chlorhexidine 0.02%, while Yokoyama et al., the study showed that PI 10% had a superior disinfectant effect compared to chlorhexidine gluconate 0.05%.\[19\] About polyhexamethylene biguanide (PHMB), Hansmann et al. showed that PHMB was equally effective in achieving relative sterility compared to PI, but potentially longer-lasting effect.\[22\] Efforts continue to minimize the pathogen load in the eyelid and conjunctiva by using preoperative antisepsis. Various types of antiseptics have different efficacies, as well as different profiles of ocular surface toxicity. This study aims to compare the efficacy and toxicity of PI 5%, PHMB 0.02% and chlorhexidine 0.02% in patients undergoing phacoemulsification cataract surgery.

Materials and Methods

This single-center, randomized study was approved by the Institutional Review Board of Isfahan University of Medical Sciences (ethical code: IR. MUI. MED. REC.1397.259), and all participants provided written informed consent. Participants consisted of 330 patients who referred to Feiz hospital in Isfahan and were scheduled for cataract surgery. Inclusion criteria for enrollment included both sex aged over 20 years old with no acute infectious and ocular disease. Furthermore, exclusion criteria were as follows: no allergy to PI, use of antibiotics (ophthalmic or otherwise) within 4 weeks of enrollment, acute conjunctivitis, blepharitis, or dacyrocystitis, previous intraocular surgery, and pregnancy.

All 310 eligible patients were assigned randomly to 1 of 3 studied groups the day before surgery using random allocation software. Group 1 included 110 eyes received 1 drop of PI 5%. Group 2 included 110 eyes received 1 drop of PHMB 0.02%. Moreover, 110 eyes in Group 3 received 1 drop of chlorhexidine 0.02%. Cultures samples were obtained before the surgery without any topical application in all patients. And then, culture samples were repeated 5 min after instillation of studied antiseptic solutions in the inferior fornix of the examined eye. Cultures were obtained from the inferior conjunctival fornix, using sterile culture swabs while avoiding contact with the eyelids and lashes.

The swab was immediately streaked across blood agar for microaerophilic and aerobic bacteria using one side of the swab, then onto chocolate agar media for anaerobic bacteria using the opposite side of the swab. Finally, the swab was placed in thioglycolate broth. To blinding the microbiologist, all specimens were coded before sending it to the microbiology department, and hence, the microbiologist was not aware of specimens groups. Furthermore, the microbiologist was not aware of the before and after specimens.

Collected data in our study were as follows: age (years of old), sex (male, female), side of eyes (left, right), positive rate of conjunctival swabs in three blood agar, chocolate agar and thioglycolate broth, numbers of colony-forming units (CFUs) of aerobic and microaerophilic bacteria (counted on blood agar after 3 days and on chocolate agar after seven days), isolated bacteria and side effects (included conjunctival injection, cornea, and pain score). The positive rate of conjunctival specimens and CFUs were assessed in all obtained samples before and after the intervention. The pain score was measured based on the reported score by the patient using The Eye Sensation Scale (excruciating, severe, moderate, mild, and none). Conjunctival injection was reported using a grading scale ranging from 0 = none to 1 = mild/moderate and 2 = severe. The corneal side effect was determined by the presence or absence of superficial punctate epitheliopathy (SPE). The sample size calculation was based on the difference in positive cultures as reported by Li et al. using the comparison of two proportions formula with power 80% and \(\alpha = 0.05\). SPSS software for Windows (SPSS, Inc., Chicago, IL, USA, version 24) was used for statistical
analyses. Data are reported as mean ± standard deviation or number (%) as appropriate. Chi-square test was used to comparing studied variables among the three groups. The level of significance is considered to be <0.05.

Results
Between April 2018 and March 2019, 356 patients (eyes) were assessed for eligibility, 26 patients were not eligible and did not enter into the study. Three hundred and thirty eligible patients were randomly assigned into three intervention groups. Sampling errors during the collection of the specimens were made in 13 patients that were excluded from the final analysis. Hence, 107 eyes in PI, 104 eyes in PHMB and 106 eyes in chlorhexidine groups were included in the analysis [Figure 1].

The characteristics studied by groups are presented in Table 1. The mean age was similar among studied groups. The number of women in the three groups was a little more than men but was not statistically significant. The ratio of left to right eyes did not differ significantly among the groups. Table 2 shows the results of the comparison of studied groups in regard to the positive rate of conjunctival swabs. Before the intervention, the positive rate of conjunctival swabs was similar among the three groups in two agar plates and thioglycolate broth (P > 0.05). Furthermore, after the intervention, the positive rate of conjunctival swabs did not differ significantly among the three groups (P > 0.05). However, in three blood agar, chocolate agar and thioglycolate broth, the positive rate of conjunctival swabs after intervention among all three studied antiseptic solutions were significantly decreased in comparison to before intervention (P < 0.05).

The numbers of CFUs grown from swabs of eyes before and after intervention on blood and chocolate agars are shown in Tables 3. In both blood and chocolate agars, before the intervention, the numbers of CFUs did not differ significantly among the three groups (P = 0.149 and P = 0.260, respectively). After the intervention, CFUs numbers in the three groups were decreased in comparison to before intervention, but comparing CFUs numbers among groups at this time point revealed no statistically significant difference in both blood and chocolate agars (P = 0.304 and P = 0.136, respectively).

Of the 317 eyes, 108 (34.1%) showed no bacterial growth in prepreparation period, which was similar in the three groups (iodine group 30 [28.0%], PHMB group 40 [38.5%] and chlorhexidine group 38 [35.8%]). Figure 2 shows the bacterial species isolated in pre-preparation specimens. In the three groups, *Staphylococcus epidermidis* was the most common isolated bacteria. In PI group, in 77 prepreparation specimens with bacterial growth, isolated bacteria were *S. epidermidis* (83.1%), *Staphylococcus aureus* (14.3%) and α-hemolytic *Streptococcus* (2.6%). In PHMB group, in 64 pre-preparation specimens with bacterial growth, *S. epidermidis* (53.1%), α-hemolytic *Streptococcus* (20.3%),

### Table 1: Baseline patient characteristics in the three groups (n=317)

| Variables         | PI 5% (n=107) | PHMB 0.02% (n=104) | Chlorhexidine 0.02% (n=106) |
|-------------------|---------------|--------------------|------------------------------|
| Age (year)        | 52.6±13.4     | 55.0±10.7          | 54.4±11.5                    |
| Sex               |               |                    |                              |
| Male              | 64 (59.8)     | 54 (51.9)          | 57 (53.8)                    |
| Female            | 43 (40.2)     | 50 (48.1)          | 49 (46.2)                    |
| Eye               |               |                    |                              |
| Left eye          | 52 (48.6)     | 48 (46.2)          | 64 (60.4)                    |
| Right eye         | 55 (51.4)     | 56 (53.8)          | 42 (39.6)                    |

Data are mean±SD or n (%). PHMB: Polyhexamethylene biguanide, PI: Povidone-iodine, SD: Standard deviation

### Table 2: Comparison of the positive rate of conjunctival swabs in the three groups (n=317)

| Variables         | PI 5% | PHMB 0.02% | Chlorhexidine 0.02% | P    |
|-------------------|-------|------------|---------------------|------|
| Blood agar        |       |            |                     |      |
| n                 | 107   | 104        | 106                 |      |
| Before surgery    | 37 (34.6) | 40 (38.5) | 39 (36.8) | 0.841 |
| Before surgery    | 18 (16.8) | 12 (11.5)  | 19 (17.9) | 0.394 |
| P                 | 0.001 | 0.0001     | 0.0001              |      |
| Chocolate agar    |       |            |                     |      |
| Number            | 107   | 104        | 106                 |      |
| Before intervention | 25 (23.4) | 16 (15.4)  | 19 (18.1) | 0.322 |
| After intervention | 6 (5.6) | 0          | 6 (5.7)  | 0.058 |
| P                 | 0.0001 | 0.0001     | 0.0001              |      |
| Thioglycolate broth|       |            |                     |      |
| n                 | 107   | 104        | 106                 |      |
| Before intervention | 81 (75.7) | 83 (79.8)  | 91 (85.8) | 0.172 |
| After intervention | 63 (58.9) | 65 (62.5)  | 73 (68.9) | 0.310 |
| P                 | 0.007 | 0.0001     | 0.001               |      |

Data are n (%). P values calculated using the Chi-square test. PHMB: Polyhexamethylene biguanide, PI: Povidone-iodine
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Bacillus species (18.8%), Corynebacterium (4.7%), and S. aureus (3.1%) were isolated bacteria. Moreover, in chlorhexidine group, in 68 pre‑preparation specimens with bacterial growth, isolated bacteria included S. epidermidis (57.4%), Bacillus species (30.9%), a‑hemolytic Streptococcus (5.9%), Micrococcus species (2.9%), Corynebacterium (1.5%), and S. aureus (1.5%).

Table 4 lists the comparison of side effects in studied groups. The conjunctival injection was significantly different among studied groups (P = 0.0001), five patients in the Iodine group had severe conjunctival injection, whereas, in other groups, patients did not have severe conjunctival injection. SPE was significantly fewer in chlorhexidine group than PHMB and iodine groups (P = 0.0001). Furthermore, patients in the iodine group significantly reported more pain scores than patients in other groups (P = 0.0001), 17 patients in the iodine group reported severe or excruciating pain, whereas in PHMB and chlorhexidine groups, patients did not report severe or excruciating pain.

Discussion

The primary source of postoperative endophthalmitis, are bacteria present in the eyelids and conjunctiva. Thus eliminating or reducing these microorganisms can decrease the risk of endophthalmitis. In one study comparing PI 5% with chlorhexidine 0.02%, there was no significant difference between the groups. However, in another study, PI 10% had superior effect compared to chlorhexidine 0.05%. In one study conducted in Germany, PHMB was equally effective in achieving relative sterility compared to PI, with.

**Table 3: Comparison of colony‑forming units findings among studied groups (n=317)**

| Variables | Before intervention | After intervention |
|-----------|---------------------|--------------------|
|           | PI 5% | PHMB 0.02% | Chlorhexidine 0.02% | PI 5% | PHMB 0.02% | Chlorhexidine 0.02% |
| Blood agar |       |           |                      |       |           |                      |
| n          | 107   | 104       | 106                  | 107   | 104       | 106                  |
| 0          | 71 (66.4) | 62 (59.6) | 67 (63.2)            | 87 (81.3) | 93 (89.4) | 87 (82.1)            |
| 1‑10       | 31 (29.0) | 28 (26.9) | 24 (22.6)            | 19 (17.8) | 9 (8.7)   | 16 (15.1)            |
| 11‑100     | 5 (4.7)  | 14 (13.5) | 15 (14.2)            | 1 (0.9)  | 2 (1.9)   | 3 (2.8)              |
| Mean±SD    | 1.8±3.6 | 4.8±12.6  | 7.1±20.4             | 0.63±2.0 | 0.53±2.8  | 1.3±4.7              |
| P          | 0.149  |           |                      | 0.304  |           |                      |
| Chocolate agar |       |           |                      |       |           |                      |
| n          | 107   | 104       | 106                  | 107   | 104       | 106                  |
| 0          | 79 (73.8) | 87 (83.7) | 87 (82.1)            | 100 (93.5) | 100 (96.2) | 98 (92.5)            |
| 1‑10       | 20 (18.7) | 11 (10.6) | 16 (15.1)            | 7 (6.5)  | 4 (3.8)   | 5 (4.7)              |
| 11‑100     | 8 (7.5)  | 6 (5.8)   | 3 (2.8)              | 0       | 0         | 3 (2.8)              |
| Mean±SD    | 2.3±7.9 | 2.0±9.9   | 3.5±16.7             | 0.13±0.5 | 0.17±1.1  | 1.3±7.3              |
| P          | 0.260  |           |                      | 0.136  |           |                      |

Data are n (%). P values calculated using the Chi‑square test. PHMB: Polyhexamethylene biguanide, PI: Povidone‑iodine
even longer-lasting effects. According to recent studies, the adverse effect of PI 5% is rare, as well as the 10% concentration. No study, however, has proven the best method to prevent the incidence of endophthalmitis following cataract surgery. Barkana et al. found that PI, ofloxacin, and chlorhexidine had similar effects in that the number of conjunctival bacterial flora reduced. Scoper et al. demonstrated that the most common normal ocular surface bacterial flora is Gram-positive bacteria, such as *S. aureus* and *Streptococcus*, and Gram-negative bacteria seem to be especially common in older individuals.

Some studies have evaluated either the effects of PI solution on the reduction of normal ocular flora for the prevention of endophthalmitis after the surgery or its effects on microbial decontamination of the eyes before transplantation. For example, Beinder et al. (1999) in their study pointed out the importance of the prevention of postoperative endophthalmitis and examined the effects of 1% PI solution on the reduction of colonization with staphylococci in the course of intraocular surgery. The researchers have tested a total of 300 candidates for intrabulbar surgery. For this purpose, samples of conjunctival were prepared and cultured during the three stages. The first sample was prepared immediately before the patient got ready for surgery, the second sample was prepared after instillation of PI solution before opening the conjunctiva, and the third sample was prepared at the end of surgery. The results indicated that *S. aureus* was seen in the conjunctival discharge from 30.3% of patients before the eye disinfection. After eyes were disinfected by PI solution, 7.7% of samples were positive for *S. aureus*, and 3.5% of the samples showed growth for *S. aureus* at the end of the surgery. To evaluate the effect of PI solution on the prevention of the *S. aureus* growth in the course of surgery, they compared the first and second stages’ samples using the McNemar’s test, and the results showed that the use of PI solution could significantly reduce the *S. aureus* growth.

According to the results of this study, it was recommended to use a 1% PI solution in reducing staphylococcal colonization for the prevention of endophthalmitis following cataract surgery. Ta et al. examined the conjunctival flora in 142 patients. The most common bacteria were the central nervous system (CNS) (82%). Antibiotics found to be effective in conjunctival sac bacterial eradication were gentamycin, moxifloxacin, and levofloxacin. Ninety percent of *Streptococcus* sp. was sensitive to fluoroquinolones. Comparison of side effects in this study showed that conjunctival injection was significantly different among studied groups as the five patients in the Iodine group had severe conjunctival injection, but in the other groups, patients did not show severe conjunctival injection. SPE was significantly fewer in the chlorhexidine group than PHMB and iodine groups. In this study, before the intervention, the numbers of CFUs did not differ significantly among the three groups, but after the intervention, CFUs numbers in the three groups was decreased; however, at the mentioned time point, it was revealed no significant difference on both blood and chocolate agars.

In comparing the effectiveness of conjunctival sac irrigation with 5% PVI alone and together with 0.5% moxifloxacin Halachmi-Eyal et al. showed that the additional use of 0.5% moxifloxacin did not increase the effectiveness of the eradication of conjunctival sac organisms. In contrast, Miño de Kaspar et al. determined that the addition of topical levofloxacin to the 1% PVI conjunctival sac wash increased the effectiveness of conjunctival sac decontamination compared to 1% PVI alone. Nentwich et al. compared the instillation into the conjunctival sac of 1% PVI alone to 1% PVI combined with three drops of 10% PVI drops. They showed that the application of 10% PVI resulted in the reduction of CFUs before and after surgery. Stranz et al. compared a single wash of the conjunctival sac with 5% PVI before cataract surgery to a double instillation. A second instillation resulted in a significantly decreased CFU count. Inoue et al. found that the most effective protocol in bacteria elimination was the antibiotic used for 3 days preoperation with an iodine conjunctival sac wash. However, the total disinfection of the conjunctival sac was not attained with any of the strategies. Carrim et al. published that the application of 5% PVI for 3 min for eyelid disinfection and a 3 min conjunctival sac wash before intraocular surgery reduced positive conjunctival sac smears by 57%, especially of CNS. Hosseini et al. in an in vitro study found that longer exposure time and the higher concentration of PVI solutions were more effective in bacterial flora eradication. In contrast, Inoue et al. noted that the use of 5% PVI solution did not result in increasing antimicrobial resistance.
or an adverse change in conjunctival bacterial flora. It is notable that in none of the patients, acute or chronic postoperative bacterial endophthalmitis was observed, the patients who were exposed to PI, tolerated the treatment well without complications and adverse effects such as corneal edema or epithelial defects, and sensitivity to PI. Regarding the no significant differences between the three studied groups, it has been concluded that pretreatment with 5% PVI for at least 15 min or repeated applications over 10 min is effective in the reduction of conjunctival organisms, and this should result in less postoperative endophthalmitis. The additional advantages of using this chemotherapeutics are low cost, rapid onset of action, and no bacterial resistance.

As mentioned, evaluating the conjunctival microbial flora is a surrogate for postoperative endophthalmitis; therefore, this study aimed to compare various types of antiseptics as preoperative prophylaxis in reducing conjunctival pathogens and thus preventing postoperative endophthalmitis. Hence, 107 eyes in PI, 104 eyes in PHMB and 106 eyes in chlorhexidine groups were included in the analysis. The results of this study showed before the intervention, the positive rate of conjunctival swabs was similar among the three groups and after the intervention, it was not significantly different. However, in three blood agar, chocolate agar, and thioglycolate broth, there was a significant reduction after the intervention among all three studied antiseptic solutions in comparison to before the intervention.

The conjunctival injection was significantly different among studied groups; five patients in the iodine group had severe conjunctival injection, whereas, in other groups, patients did not have severe conjunctival injection. SPE was significantly fewer in the chlorhexidine group than PHMB and iodine groups. Furthermore, patients in the iodine group significantly reported more pain scores than patients in other groups, 17 patients in the iodine group reported severe or excruciating pain, whereas in PHMB and chlorhexidine groups, patients did not report severe or excruciating pain.

**Conclusion**

It seems that using 5% Povidone-Iodine (PVI) at least 15 min before treatment or repeated applications over 10 min is effective in reducing conjunctival organisms, and results in less postoperative endophthalmitis.

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**Conflicts of interest**

There are no conflicts of interest.

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