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Study *in vitro* and *in vivo* on the synergy between iodophor-impregnated incision drapes and antisepsis with 2% chlorhexidine-70% isopropanol or 10% iodine povidone

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Abstract

Background: If the previous antisepsis is done with povidone iodine (PVP-I), iodophore-impregnated incision drapes (Ioban2) will not diminish surgical site infection (SSI). Could they do so if antisepsis were done with chlorhexidine 2% in isopropanol 70% (ClxIPA) instead?

Methods: 1) *In vitro*: Assessment of the synergistic effect of ClxIPA-Ioban2 by antiseptogram of eich microorganisms. On other dishes, PVP-I (or sterile distilled water as a control) were used, instead of ClxIPA. 2) *In vivo*: The cutaneous microbiota from the back of the second phalange of the 2nd -5th fingers of both hands of volunteers were studied. Then antisepsis was carried out on both hands with ClxIPA and, on the non-dominant hand, a band of Ioban2 was wrapped around the sampling surface. Two hours later, the microbiota was collected from both hands into a solution with culture medium and an antiseptic inhibitor. The $\log_{10}$-reduction of the before-after microbiota for each volunteer, was compared with him/herself. A similar process was done with PVP-I or distilled water (control).

Results *In vitro*, a significant increase in inhibition halos were obtained when using Ioban2 together these two antiseptics. In vivo, Ioban2 helped both antiseptics to reduce microbial colonization 2 hours after antisepsis. Moreover, the antimicrobial efficacy, in both experiments, was significantly higher with ClxIPA than with PVP-I (with or without Ioban2).

Conclusion:-Ioban2 increases significantly the antimicrobial efficacy of ClxIPA, *in vitro* and *in vivo*. Presurgical antisepsis with ClxIPA + Ioban2 could decrease the SSI, but it must be verified by controlled studies.

Keywords: Synergy; Ioban2; Chlorhexidine-Isopropanol; Iodine-Povidone

1. Background

Surgical site infection (SSI) is currently the hospital care-associated infection ~~with~~ with the highest prevalence [1], and in theory, it is also the one that can best be prevented [2].

The Spanish National Health System has launched a "zero" program (IQZ) coordinated by the Sociedad Española de Medicina Preventiva, Salud Publica e Higiene (SEMPSPH), with several measures of proven efficacy [3].

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One is the antisepsis of the skin in the area of the intervention using a solution of 2% chlorhexidine in 70% isopropanol (ClxIPA), since current practice [4-7] prefers it to 10% povidone iodine (PVP-I), due to its direct and residual efficacy. For some time after application it can control recontamination of the skin with the microbiota from the skin itself (sweat glands, hair follicles) or with another origin (digestive or respiratory mucosa of the same patient, or from health personnel).

Another measure that could improve this antisepsis is to place surgical antimicrobial incision drapes, which will slowly release iodine (Ioban2) during the intervention, thus counteracting the natural loss of the product´s antiseptic efficacy when applied before surgery.

However, Cochrane´s reviews [8] insist that plastic incision drapes (mixing those with iodine with those without) increase the risk of SSI; they did a subanalysis of incision drapes that carry iodine coming to the conclusion that they have the same SSI rate when plastic drapes were not used. Therefore, they are not indicated as another prevention measure for SSI. However, the Cochrane subanalysis only includes two old studies (1987 and 2002). In them, skin antisepsis was done with PVP-I, which was less effective than ClxIPA, so, if we apply this antisepsis at present, we would achieve a less microbial contamination on the patient's skin during the intervention.

This decrease in the microbiota amount could be important for the iodophore-impregnated incision drapes, because they contain a small amount of the metal that can greatly influence the "inoculum effect", obtaining different results depending on the number of microorganisms on the skin. Given this proviso, will the iodophor-impregnated incision drapes, placed after antisepsis with ClxIPA, be sufficiently effective so as to significantly reduce SSI?

Before checking this point, we first must ask if the iodine can alter the residual power of ClxIPA applied to the skin, since this would be a contraindication for its use. Several authors used double antisepsis with Chlorhexidine or PVP-I and report that the two antiseptics not only did not antagonize each other´s effects but that they reinforced each other[9-11], although it is possible that the stronger antiseptic effect may have been due only to the mechanical effect of a double application. But, regardless of this, at least, we can accept that iodine will not significantly decrease the effectiveness of chlorhexidine applied to the skin.

However, in the absence of studies describing ClxIPA and the subsequent application of iodophor-impregnated incision drapes (which carry molecular iodine instead of povidone iodine), we have carried out two experiments, one in vitro on several microorganisms, and another in vivo, in 40 volunteers, using this disinfection method alone or in concert with a subsequent use of Ioban2.

In addition, we have improved the collection power of skin colonization compared to what is usually done, with a swab applied to the skin [12] since, as we have seen, a swab only collects about 1% of the colony forming units (c.f.u.) of the existing microbiota from a specific surface [13]. Here, we rub the back of the second phalange of the 2^{nd} -5^{th} fingers of both hands of volunteers against the botton of the culture dish. With this improvement in the skin colonization counting, we hope to be able to determine if Ioban2 improves, or not, the antisepsis carried out on the skin with Chlorhexidine 2% in isopropanol 70% (ClxIPA) or povidone iodine 10% (PVP-I), because we will use the latter antiseptic as antisepsis-control

2. Methods

2.1. Volunteers

40 Adults of both sexes, who expressed consent, after being informed of how the experiment would be carried out, and possible risks or inconveniences during its implementation.

2.2. Material

- ClxIPA: Chlorhexidine 2% (Lab Guinama, La Pobla de Valbona, Spain) in isopropanol 70% (Lab Panreac, Castellar del Valles, Spain), the mix was elaborated in our laboratory before the experiments.
- PVP-I, povidone iodine 10% (Lab Meda-Pharma, Bordeaux, France).
- Blood agar dishes, Saboureaud-dextrose and Müeller-Hinton dishes (Lab BD. Tullstrasse. Heildelderg. Germany) and empty sterile dishes.
- Nutrient-Broth (Lab BD).
- Antiseptics inhibitor [13-15]: Nutrient Broth (Lab BD) + 6% Tween80 (Lab Panreac) + 0.5% sodium bisulfite (Lab Panreac) + 0.5% sodium thiosulfate (Lab Panreac. Castellar del Valles. Barcelona. Spain).

- Iodophor-impregnated antimicrobial field, Ioban2 (3M Health Care. St Paul MN. USA)
- ATCC microorganisms: *S. aureus, S. epidermidis, S. hominis, E. faecium, C. albicans, T. glabrata, P. aeruginosa* and *E. coli.*

2.3. Methods

2.3.1. In vitro study

The microorganisms described above were cultured in Nutrient-Broth for 24 h (bacteria) or 48 h (yeast). Each of the cultures was diluted 100 times and with this dilution the surfaces of the Müeller-Hinton´s dishes (for bacteria) or Saboureaud-dextrose´s dishes (for yeasts) were contaminated. The dishes were allowed to dry in an inverted position on filter paper and, after that, on the back of each of the dishes, 2 points were drawn, one in the center of the upper left and lower right quadrant of each plate. Two samples of 5 microL of ClxIPA are placed over the dots in the culture on the other side of the dish and they are left to dry for 1 min. After this, a square of Ioban2 (approximately 1 cm x 1 cm cut with a sterile scalpel) was placed over one of the samples with sterile clamps. Thus, in one of the points there is only ClxIPA and in the other, ClxIPA plus Ioban2. The dishes were allowed to dry for another 5 min and then incubated in aerobic conditions at 37 ° C (for 24 hours if the plate contained any of the bacteria or 48 if it was yeast). With PVP-I, we proceeded in the same way, except that the initial drops of 5 microL were allowed to dry for 5 min instead of 1, before placing the Ioban2 on half of these antiseptic drops.

After incubation, the inhibition zones (minimum and maximum) of both samples were evaluated for each antiseptic and microorganism.

As a control of the inhibition diameter for each microorganism, the antiseptic was replaced by 5 microL of sterile distilled water and left to dry for 5 min, before proceeding as above (with or without Ioban2).

The experiment was performed three times with each microorganism.

2.3.2. In vivo study

To improve the classic collection of cutaneous microbiota by means of brushing 2-4 cm^2 of the skin, we used a much larger cutaneous surface: The back of the second phalanges of the 2nd to 5th fingers of both hands. This surface could be 15-25 cm^2, depending on the size of the volunteer's hand.

The experiment consisted of the following:

First: After washing with a pH 5,5 soap for 30 seconds and air drying, we collected the initial microbiota by immersing the sampled area of each hand in 10 ml of a culture broth (in a sterile Petri dish), and rubbing the these phalanges against the bottom of the disch for one minute. After that, we shook the liquid in the plate for another minute to homogenize the microbiota collected in the sampling. Finally, 3 blood agar dishes were seeded, each with 0.1 ml of the previous 10 ml broth, and incubated at 37 ° C for 48 hours, to count their c.f.u.

Second: Antisepsis was performed on both hands with two applications of ClxIPA (back and forth on the same surface of each finger, including its joints) and, after air drying, in the non-dominant hand, a band of Ioban2 was wrapped around the sampling surface and the 2 adjacent joints of these second phalanges. The volunteers were working on their computer for the next two hours, so that the hand without Ioban2 would have limited contact with other surfaces and the hand with Ioban2 was used somewhat in the work (the thumb was free and the other four fingers together joined).

Third: After that time, they returned to the laboratory where the cutaneous microbiota of both hands was collected in the same way as in the beginning, except that instead of using culture broth, sampling was done with 10 ml of culture broth plus an antiseptic inhibitor (described in methods,). Thus any antiseptic residues that might have remained on finger surfaces did not inhibit the growth of microorganisms that might have survived the two hours since the initial sampling. Then, from each hand and volunteer, three 0.1 ml aliquots were seeded in three blood agar dishes, and, after 48 h incubation at 37ºC, their c.f.u. were counted.

Last, we compared the $\log_{10}$ reduction, obtained on each of the volunteer's hands after two hours, and assessed the effect of Ioban2 by paired mean of the logarithmic differences of c.f.u. of the hand with Ioban2 vs the hand without Ioban2, in each volunteer.

As a comparison, we used 10% PVP-I (or distilled water as control) in similar experiments carried out on the following weeks.

3. Result

In vitro experiment: The mean results of the inhibition zones of each microorganism are shown in Table 1.

Table 1 Descriptive analysis of the results of the in vitro experiment placing Ioban 2 on the area with PVP-I or ClxIPA.

Microorganism	**Mean inhibition halo diameter* (mm) per product**			
	ClxIPA	**ClxIPA + Ioban2**	**PVP-I**	**PVP-I + Ioban2**
S. aureus	33	37	14	18
S. epidermidis	25	27	13	18
S hominis	17	20	7	NE
E faecium	18	21	5	NE
E. coli	13	24	14	17
P. aeruginosa	18	22	6	NE
C. albicans	25	29	16	25
T. glabrata	26	28	15	23
Mean of all the microorganisms	23 ± 5	26 ± 5	14 ± 1**	20 ± 3**

* = mean of the diameters of the maximum inhibition zones obtained in the 3 dishes corresponding to each microorganism and product
**= the inhibition zone for *P. aeruginosa*, *S. hominis* and *E. faecium* were not measurable, so were not evaluated in ANOVA.
Abbreviations: ClxIPA= Chlorhexidine 2% in isopropanol 70%; PVP-I = iodinated polyvinyl pyrrolidone 10%. NV= not evaluated, NS= not significant.

Bonferroni test: ClxIPA +Ioban2 > ClxIPA ($p<0,05$)

ClxIPA +Ioban2 > PVP-I+Ioban2 ($p<0,01$)

PVP-I+Ioban2 > PVP-I ($p<0,01$)

ClxIPA >PVP-I ($p<0,01$)

ClxIPA and PVP-I+Ioban2 : NS

The inhibition zones show a significant increase of the inhibition diameters when using Ioban2 after either of the two antiseptics, although the increase was less with ClxIPA (3 mm) than with PVP-I (6 mm). If we compare these inhibition zones with those from the controls for only Ioban2 with the same microorganisms (very small inhibition areas that only exceeded the Ioban square by approximately 1 mm) it is seen that the previous halo increase, when using antiseptic plus Ioban2, is due to a synergistic effect between both products. In addition, the inhibition area had a rounded shape, not square, as would have corresponded to the shape of the antimicrobial drape placed on the dishes, so it can be deduced that the predominant effect was that of the antiseptic, and Ioban2 only helped to achieve greater microbial inhibition. However, this synergy was important and statistically significant, except in PVP-I with three microorganisms (*P. aeruginosa, S. hominis* or *E. faecium*), which, when producing inhibition zones smaller than the surface of the Ioban2 square, could not be measured, which is why they have not been included in the calculations. But the effect was analogous, that is, Ioban2 increased the inhibition zone due to PVP-I, as we have seen in other experiments (not included in this work) when placing a greater volume of PVP-I (15 instead of 5 microL), on dishes sown with those three microorganisms.

In vivo experiment: When designing this study we also considered examining time periods of less than two hours (30 and 60 min) but we saw that microbial growth after the antisepsis was reduced making it more difficult to observe significant differences between the hand with Ioban2 compared to the one that did not have it. After two hours, the skin

microbiota had greatly increased (and the number of c.f.u. stabilized), so if we add this advantage to that 120 min being a reasonable duration for many surgical interventions, we chose two hours for this experiment.

Table 2 Descriptive analysis of the results (in log10 c.f.u.) of the experiment in volunteers when putting on Ioban2 on skin, after using PVP-I or ClxIPA as an antiseptic.

Variable	**ClxIPA**	**p value**	**PVP-I**	**p value**	**control***
	Mean±SD		Mean±SD		Mean±SD
Dom hand before antisepsia	3.71 ± 0.77	NS	3.78 ± 0.61		
Non-Dom hand before antisepsia	3.84 ± 0.78	NS	3.72 ± 0.85	NS	3.52 ± 0.9
Dom hand 2h after antisepsia	2.22 ± 1,31	p<0.01	3.25 ± 0.91		
Non-Dom hand 2 h after antisepsia+Ioban2	1,72 ± 1.57	p<0.01	2,85 ± 1,14	NS	3.38 ± 0.76
Log10 reduction due to antiseptic	1.49 ± 1,13	p<0,01	0.52 ± 0.68		
Log10 reduction due to Ioban2 + antiseptic (water in control)	2.04 ± 1.47	p<0,01	0.87 ± 0.81	p<0,05	0.21 ± 0.
Log10 reduction due to antiseptic VS. Log10 reduction due to Ioban2 + antiseptic (water in control)	** p<0.05		** p<0.05		

c.f.u. = colony forming units; Dom = dominant; No-Dom = non-dominant; ClxIPA= Chlorhexidine 2% in isopropanol 70%; PVP-I = iodinated polyvinyl pyrrolidone 10%; *= Control= no antiseptic; ** = increase in the antiseptic effect; NS= not significant

The results of this experiment with the 40 volunteers are presented in Table 2. The three results from each sampling were averaged (obtaining the mean c.f.u. corresponding to 0.1 ml, so we could calculate the c.f.u. for the sample 10 ml, simply multiplying the average of 0.1 ml by 100. From that figure, the respective decimal logarithm was calculated and introduced in the SPSS-14 program for subsequent calculations.

All these values were equal to or greater than 2 $\log_{10}$ except in cases where only one or two c.f.u. grew in the three dishes (originating a "mean" of 0.3 x 100 = 33 c.f.u., or 0.66 x 100 = 66 c.f.u., which determined $\log_{10}$'s of 1.5 and 1.8 respectively). But, if no colony grew in the three dishes, the result would have been 0 x 100 = 0, which would result in a log10 = "less infinite". To avoid this problem, we have chosen to employ “0” as the logarithmic result, in these cases.

This result occurred when applying ClxIPA in 22% of the volunteers on the hand without Ioban2 and in 42% on the hand with Ioban2 (Fisher's p <0.05). When using PVP-I, these "0" results had a very low frequency (2.5% on the hand without Ioban2 and 10% on the hand with Ioban2, Fisher´s p was not significant). In the control experiment (only Ioban2), we don´t obtained that result in any occasion. This is a qualitative demonstration of the greater completeness in the microbial destruction of ClxIPA with respect to PVP-I, and that, moreover, with Ioban2 almost half of the volunteers still had a very reduced skin colonization two hours after performing an antisepsis with ClxIPA.

In the quantitative analysis (Table 2) the mean colonization was similar on both hands of the volunteers in the three experiments (3.52-3.84 $\log_{10}$), without statistical differences between dominant and non-dominant hand. If there were significant differences 2 h after application between the antiseptic treatments, ClxIPA was 10 times more effective than PVP-I, and significant difference was maintained when Ioban2 was also used. But the most important thing was to control the effect derived from the numerical diversity in the microbiota on the different volunteers. So, each volunteer was compared with him/herself when studying the residual efficacy after two hours. Thus, we verified the low residual efficacy of PVP-I (0.52 $\log_{10}$) and that this efficacy significatively increased ($p<0.05$) when carrying Ioban2 (0.87 $\log_{10}$). With ClxIPA the mean logarithmic reduction in each volunteer was more than twice that obtained with PVP-I (1.49 $\log_{10}$) and it increases significatively ($p<0.05$) when carrying Ioban2 (2.04 $\log_{10}$). In the control experiment, when Ioban2 was applied on the skin without previous antiseptic treatment, the initial microbiota were reduced in only 0.21 $\log_{10}$.

The logarithmic reduction due to ClxIPA or PVP-I, added to that produced by Ioban2 is lower than that obtained when using, together, one of these antiseptics with Ioban2 (1.49 + 0.21 = 1.7 vs 2.04 in ClxIPA or 0.52 + 0.21 = 0.73 vs. 0.87 in PVP-I) demonstrating a synergy between Ioban2 and both antiseptics.

4. Discussion

The efficacy of these incision drapes in reducing cutaneous colonization in surgical procedures in which PVP-I was used as a previous antisepsis has been demonstrated in the Davies meta-analysis [11] and by Rezapoor [12]. In the latter, skin was sampled by means of a swab at several time points during the surgery. However, only when the result at the end of the intervention was described as "positive or negative" (ie "one or more" c.f.u. versus "no" c.f.u.) was it consistently found that Ioban2 could reduce skin colonization after iodine antisepsis.

Other studies [16, 17] also based on applying these iodized incision drapes over a previous antisepsis with PVP-I, have shown a positive effect of Ioban2 on SSI, but they are retrospective and do not control for the patient to whom the field belonged. Consequently, the comparison may have biases, and, in addition, in a recent work [17] they do not include the "non-use of surgical incision drapes", as a point of comparison, and used plastic surgical incision drapes without iodine. So the ostensible reduction in SSI that was observed may be due to the antagonism to the greenhouse effect produced by non-iodinated plastic incision drapes, but cannot answer the question of whether or not it is better to use Ioban2 to reduce SSI.

Our experiments reveal a quality that should be valued in Ioban2: it acts synergistically, with the pre-existing antiseptics, ClxIPA and PVP-I, increasing the final reduction of the skin microbiota.

According to the manufacturer of Ioban2, the sheets are impregnated with approximately 0.078-0.115 mg iodine / cm^2, a very low concentration, which allows them to be applied without problems on most people, but which may be subject to the "inoculum effect" (their effectiveness depends on the magnitude of the microbial contamination that it faces). PVP-I has a reduced residual effect (0.52 log_{10} vs 1.49 log_{10} with ClxIPA), as we have seen in several studies and has been described on many occasions [5, 6, 14,15], so, the colonization of the skin is relatively high at two hours after the antisepsia. Not only has this been the basis for preferring ClxIPA over PVI-I, but it may also explain the failure of Ioban2 to reduce SSI after PVP-I antisepsis, since the antimicrobial incision drapes do not compensate the lack of efficacy of PVP-I. This "inoculum effect" also explains the reduced microbicidal efficacy of ioban2 (0.21 log_{10}) in the control-experiment.

However, ClxIPA reduces colonization of the skin better, and also, maintains it in almost half of the volunteers at undetectable levels (0 c.f.u. in the three sampling dishes). Therefore, we can deduce that the iodine that is released can better control the scarce cutaneous microbiota left by ClxIPA with respect to the microbiota left by the PVP-I. That means it is likely combining Ioban2 with ClxIPA improves and prolongs antisepsis in volunteers and in vitro, as we have seen here, and it also means we could reduce SSI in real life.

But this must be verified with randomized studies using a proper antisepsis with ClxIPA and that, in addition, cover different types of clean and clean-contaminated surgery (for example, heart interventions, hip prosthesis, liver, etc.) to be able to affirm that the possible improvement occurs. If the sample size is not large enough, a meta-analysis may help to achieve adequate statistical power.

Limitations of this study:

-There was a great deal of variability in the amount of skin colonization between the different volunteers, making it difficult to draw statistically significant conclusions, but this also occurs in the real surgical world.

- The greatest limitation is that, despite the double *in vitro* and *in vivo* experiment structure with a considerable number of volunteers, the conditions that occur in the operating room can not be reproduced. The temperature of the skin under the foci, the humidity, stress and passive mobilization of the patient, etc., will probably increase perspiration, or the removal of the Ioban2, more frequently than in our experiment. Any of these occurrences will increase the amount of cutaneous microbiota on the patient, and automatically decrease the effect of the Ioban2. That is why it is so important to perform the surgical studies mentioned above.

If the conclusion of all the surgical investigation is that Ioban2 reduces the SSI, it could be indicated in prevention bundles, based on measures of proven efficacy in surgical interventions. Until this happens, we condition Ioban2 use with a recommendation like the one made by the NICE Guide [18], that is, not using plastic fields, and in the case of their use, in any surgical indication, to use iodophore-impregnated incision drapes. Although we can now add something more: Ioban2 could be placed after a previous antisepsis with ClxIPA instead of PVP-I.

5. Conclusion

The alcoholic solutions of chlorhexidine act synergistically, in vitro, with the antimicrobial incision drapes that release iodine. These antimicrobial incision drapes improve the reduction of the colonization of the underlying skin achieved by surgical antisepsis, whether it is PVP-I or ClxIPA, but the global reduction of microbiota is more intense with the latter antiseptic (2.04 vs 0.87 log10). Although the incision drapes with iodine have not been shown to decrease SSI if the initial antisepsis is with PVP-I, they could do so after antisepsis with ClxIPA. For this reason, it is necessary to carry out controlled studies in several types of surgeries to check whether this greater reduction in colonization obtained by the new antisepsis also decreases SSI when using Ioban2 compared to when it is not used.

Abreviations

ClxIPA= Chlorhexidine 2% in isopropanol 70%; PVP-I = iodinated polyvinyl pyrrolidone 10%; NV= not evaluated; NS= not significant. c.f.u. = colony forming units; Dom = dominant; No-Dom = non-dominant; SSI= surgical site infection; SEMPSPH = Sociedad Española de Medicina Preventiva, Salud Publica e Higiene.

Compliance with ethical standards

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Disclosure of conflict of interest

There is no potential conflict of interest regarding the publication of this manuscript.

Statement of ethical approval

All procedures performed in our volunteers were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standard, as it is declared by the Comite de Etica de la Investigacion (Universidad Autonoma de Madrid).

Statement of informed consent

All participants gave their informed consent prior to inclusion in the study.

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