

BASIC SCIENCE

The Effect of Bupivacaine on the Efficacy of Antibiotic Coating on Penile Implants in Preventing Infection



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ABSTRACT

Background: In an effort to reduce dependence on opioids following inflatable penile prosthesis placement, intra-operative soaking of the implant in Bupivacaine (BUP) has been proposed as part of a multimodal approach to pain control. However, no study has shown if the addition of BUP affects the antimicrobial properties of InhibiZone on AMS700 (Boston Scientific, Marlborough, MA) and/or of antibiotic soaked Titan Coloplast (Coloplast Corporation, Minneapolis, MN).

Aim: To determine if BUP alters the zone of inhibition (ZOI) against *Staphylococcus epidermidis* (*S epidermidis*) and *Escherichia coli* (*E coli*), common gram-positive and gram-negative bacterial causes of infection, respectively, created by InhibiZone coated AMS and/or by antibiotic-soaked Coloplast implant.

Methods: *S epidermidis* and *E coli* were spread on agar plates. After a 30-minute incubation, four AMS with InhibiZone strips treated with sterile saline or BUP (1.25 mg/mL) were placed on a plate. 4 Coloplast strips were dipped in varying routinely used concentrations of Rifampin (0–10 mg/mL) plus Gentamicin (0–1 mg/mL; rifampin and gentamicin (R+G)) solution with or without BUP. The ZOI for AMS with InhibiZone and Coloplast dipped in antibiotic solution was measured using ImageJ software. Normalized ZOI was calculated as (ZOI area/plate area) × 100. Unpaired *t*-test compared the mean ± SD ZOI between BUP and no BUP groups (n = 4/group).

Outcomes: The primary outcome of the study was the ZOI against *E coli* and *S epidermidis* at 24 and 48 hours.

Results: Growth of both *S epidermidis* and *E coli* at 24 and 48 hours of incubation was inhibited in both implants and the addition of BUP did not alter the ZOI. Coloplast strips dipped in R+G produced a ZOI in a dose-dependent manner. Interestingly, the ZOI against *S epidermidis* compared to that of *E coli* was much wider for both implants.

Clinical Implications: This suggests that the use of BUP does not affect the protective effects of antibiotic dips and can potentially be used during penile prosthesis surgery pending clinical trials.

Strengths and Limitations: This is the first study to evaluate the effect of BUP on anti-bacterial dips. As with all in vitro analysis, further research must be done to see if these findings hold true in the clinical setting.

Conclusions: The addition of BUP does not impede the in vitro antibacterial activity of InhibiZone-coated AMS or R+G-soaked Coloplast. Whether these in vitro findings translate to surgical outcomes needs to be evaluated in future preclinical trials. **Lokeshwar SD, Horodyski L, Lahorewala SS, et al. The Effect of Bupivacaine on the Efficacy of Antibiotic Coating on Penile Implants in Preventing Infection. J Sex Med 2019;7:337–344.**

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Key Words: Anesthetic; Antibiotic Dips; Bupivacaine; Erectile Dysfunction Treatment; Infection; Inflatable Penile Prosthesis; Penile Implants; Penile Implant Surgery; Sexual Dysfunction

Received June 11, 2019. Accepted June 16, 2019.

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<https://doi.org/10.1016/j.esxm.2019.06.007>

INTRODUCTION

Erectile Dysfunction (ED) is a disease that affects >50% of men between the ages of 40 and 76.¹ With an increase of comorbid conditions in the general population, such as diabetes² and obesity, the prevalence of ED has increased in recent years.³ The rising prevalence of ED has led to an increasing need for penile prostheses, including inflatable penile prostheses (IPPs). Since their original description in 1973,⁴ IPPs have greatly improved in mechanical functionality. However, infection still remains the most feared complication of penile implant surgery due to limited options for salvage apart from full removal and/or replacement of the infected prosthesis.⁵ Although historically most infections (almost 80%) were caused by gram-positive bacteria,⁶ recently, infections have shifted toward other sources, including gram-negative bacteria and fungus.⁷ This shift has signaled a changing landscape of postoperative penile prosthesis surgical infections.

IPPs used in the United States are manufactured by 2 companies, Boston Scientific and Coloplast (Coloplast Corporation, Minneapolis, MN), and popular models used in this study are the AMS 700 with InhibiZone (AMS; Boston Scientific, Marlborough, MA) and the Titan Coloplast (Coloplast), respectively. The Boston Scientific implant is coated with a blend of rifampin and minocycline called InhibiZone. The Coloplast implant offers a hydrophilic coating and can be soaked in various antibiotic dips, based on surgeon preference, during implantation.⁸ The combination of rifampin and gentamicin (R+G) as an antibiotic dip for Coloplast is commonly used and has been found to be effective.⁹ Previous in vitro assessments of Coloplast coated with R+G and AMS have shown that both have comparable protection against infection in vivo.¹⁰

With the recent opioid epidemic, alternatives for postoperative pain control for IPP placement have been proposed.¹¹ One strategy is the intraoperative use of local anesthetic. One study soaked a Coloplast implant, coated in a solution of antimicrobials, in a mixture of 0.75% ropivacaine and 0.5% Marcaine (the brand name of Bupivacaine [BUP]; Hospira Inc., Lake Forest, IL). The study reported that passive drug elution was above the minimum inhibitory concentration, and that patients' pain scores were greatly reduced.¹² An in vivo study on BUP, in the form of a liposome injectable suspension known as Exparel, showed better postoperative pain control in patients receiving the BUP-soaked implants.¹³

No study has yet shown if BUP alters the antibacterial effect of these various antibiotic dips on penile prostheses. We tested the hypothesis that the use of BUP does not alter the protective effect of the antibiotic coating on penile implants. We examined if the zone of inhibition (ZOI) against gram positive *Staphylococcus epidermidis* (*S epidermidis*) and gram-negative *Escherichia coli* (*E coli*), created by InhibiZone in AMS and by R+G-soaked Coloplast implant, is altered by BUP.

METHODS

Materials

E coli was obtained from the American Type Culture Collection and *S epidermidis* and Mueller-Hinton Agar plates were obtained from ThermoFisher Scientific in Waltham, MA. R+G were obtained from Sigma Aldrich.

Testing of Antibiotic Sensitivity

Overnight cultures of *E coli* or *S epidermidis* were uniformly spread on 10-cm agar plates. Strips were cut from the cylinder component of each implant using sterile techniques in a laminar-flow hood and measured approximately 0.5 × 0.5 cm. The cylinder component of the implant was chosen because it has the highest surface area of any component besides the reservoir, which, since it is placed in the abdomen and not in the penis or scrotum, is a less common site for infection. Following a 30-minute incubation at room temperature, AMS strips treated with either saline or BUP (1.25 mg/mL) were placed directly on a plate; 4 strips per plate. The strips were placed with their external side placed down onto the plate. Additionally, Coloplast strips dipped in various concentrations of R (0–10 mg/mL) + G (0–1 mg/mL) solution with or without BUP (1.25 mg/mL) were placed, external side down, on a plate; 4 strips per plate (Table 1). Strips were cut from the cylinder component of each implant using sterile techniques in a laminar-flow hood. Following 24 and 48 hours of incubation, the area of the ZOI was measured using ImageJ software (National Institute of Health).

Statistical Analysis

GraphPad Prism software (version 4.03) was used for analyses. Normalized ZOI was calculated as (ZOI area/plate area) × 100. Measurements in each control or treatment group were performed in quadruplicate and the data are expressed as mean ± SD. Unpaired *t*-test was used to compare the mean ± SD of the ZOI between various treatment groups and their respective control groups as well as between BUP and non-BUP groups (n = 4/group), because the data showed a normal distribution. All reported *P* values are 2-tailed. The SD in the ZOI for each treatment group was ≤10%. The quadruplicate measurement had >90% power to detect a difference as small as 1.2-fold between a control group and a treatment group and, therefore, the study was sufficiently powered.

RESULTS

The Addition of BUP does not Affect the ZOI Against *S epidermidis*

We tested whether BUP, used at standard dosage (1.25 mg/mL) affects the bactericidal activity of AMS or Coloplast with R+G against *S epidermidis*. Normalized ZOI was measured at 24 hours and all results were statistically equivalent at 48 hours.

Table 1. Treatment groups used in study

A: <i>S epidermidis</i>	
Treatment group	Antibiotic dip + IPP
Coloplast	
1	Saline
2	BUP 1.25
3	0.157 R + 0.0157 G
4	0.157 R + 0.0157 G + BUP 1.25
5	0.313 R + 0.0313 G
6	0.313 R + 0.0313 G + BUP 1.25
7	0.62 R + 0.062 G
8	0.62 R + 0.062 G + BUP 1.25
9	1.25 R + 0.125 G
10	1.25 R + 0.125 G + BUP 1.25
11	2.50 R + 0.25 G
12	2.50 R + 0.25 G + BUP 1.25
13	5.0 R + 0.5 G
14	5.0 R + 0.5 G + BUP 1.25
AMS	
15	Saline
16	BUP 1.25
B: <i>E coli</i>	
Treatment group	Antibiotic dip + IPP strip
Coloplast	
1	Saline
2	BUP 1.25
3	0.62 R + 0.062 G
4	0.62 R + 0.62 G + BUP 1.25
5	1.25 R + 0.125 G
6	1.25 R + 0.125 G + BUP 1.25
7	2.50 R + 0.25 G
8	2.50 R + 0.25 G + BUP 1.25
9	5.0 R + 0.5 G
10	5.0 R + 0.5 G + BUP 1.25
11	10.0 R + 1.0 G
12	10.0 R + 1.0 G + BUP 1.25
AMS	
13	Saline
14	BUP 1.25

All antibiotic and BUP doses are in mg/mL.

A: *S epidermidis* = *Staphylococcus epidermidis*.

B: *E coli* = *Escherichia coli*.

BUP = Bupivacaine; IPP = inflatable penile prosthesis; G = gentamicin; R = rifampin.

Because the antibiotic sensitivity measurements are typically performed at 24 to 48 hours we chose these time periods in our study and maximum ZOI was already obtained at these time periods.⁹

Both AMS and Coloplast with R+G showed bactericidal activity against *S epidermidis*. The difference in the ZOI of AMS

in the absence compared with the presence of BUP was not statistically significant (Figures 1A and 2A, Table 2). Coloplast coated in R+G solution generated a ZOI in a dose-dependent manner (Figures 1B and 2B). Furthermore, BUP did not affect the ZOI at each R+G dosage (Figures 1B and 2B, Table 2). The antibiotic sensitivity was independent of whether the strips were dipped in antibiotic first followed by BUP or vice versa.

BUP does not Affect the ZOI Against Gram-Negative *E coli*

Both AMS and Coloplast showed bactericidal activity against *E coli*. The ZOIs for AMS at 24 and 48 hours were similar (Table 3). The ZOIs of AMS in the absence or presence of BUP were not statistically significant (Figures 3A and 4A, Table 3). Coloplast coated in R+G solution generated a ZOI in a dose-dependent manner at 24 and 48 hours (Figures 4B,C, Table 3). Furthermore, BUP did not affect the ZOI at each R+G dosage (Figures 3B, 4B,C, Table 2).

AMS and Coloplast R+G are More Effective Against *S. epidermidis* than *E. coli*

For *S epidermidis*, the ZOI of AMS was 5-fold higher against *S epidermidis* when compared to *E coli* and this difference was statistically significant ($P < .0001$). BUP did not affect this difference (Figure 5A). As in the case of AMS, the ZOI for Coloplast, even at the lowest R+G combination (0.157 mg/mL Rifampin and 0.0157 mg/mL Gentamicin), was 4-fold higher for *S epidermidis* than for *E coli* ($P < .0001$; Figure 5B). For both AMS and Coloplast, the addition of BUP did not alter this difference (Figure 5A,B).

DISCUSSION

Between 2006 and 2017, an average of 233.7 million opioid prescriptions were filled in retail pharmacies each year.¹⁴ From 2001–2016, there was a 345% increase in opioid-related deaths.¹⁵ This steep rise in opioid-related deaths has been described as an opioid crisis and has resulted in efforts to reduce postoperative prescription of opioids. For penile implant surgery, alternative pain control methods have been researched to reduce the burden of opioids.¹⁶ BUP may be administered in 2 ways for implant surgery: by dorsal nerve block or by dipping the implant into BUP during surgery. Dorsal peripheral nerve block using BUP has shown promising results for postoperative pain reduction and control.^{17,18} However, the effect of BUP dip on the antibiotic coating on penile implants has not yet been studied. In our study, the addition of BUP did not lead to a statistically significant inhibition or reduction of the ZOI for either AMS or Coloplast with R+G against *S epidermidis* or *E coli*. There was no statistically significant difference in the ZOI between the BUP and non-BUP groups. ZOI was utilized as the mode of measurement with influence from the Dhabuwala et al¹⁰ previous study comparing the infection control of various antibiotic dips.

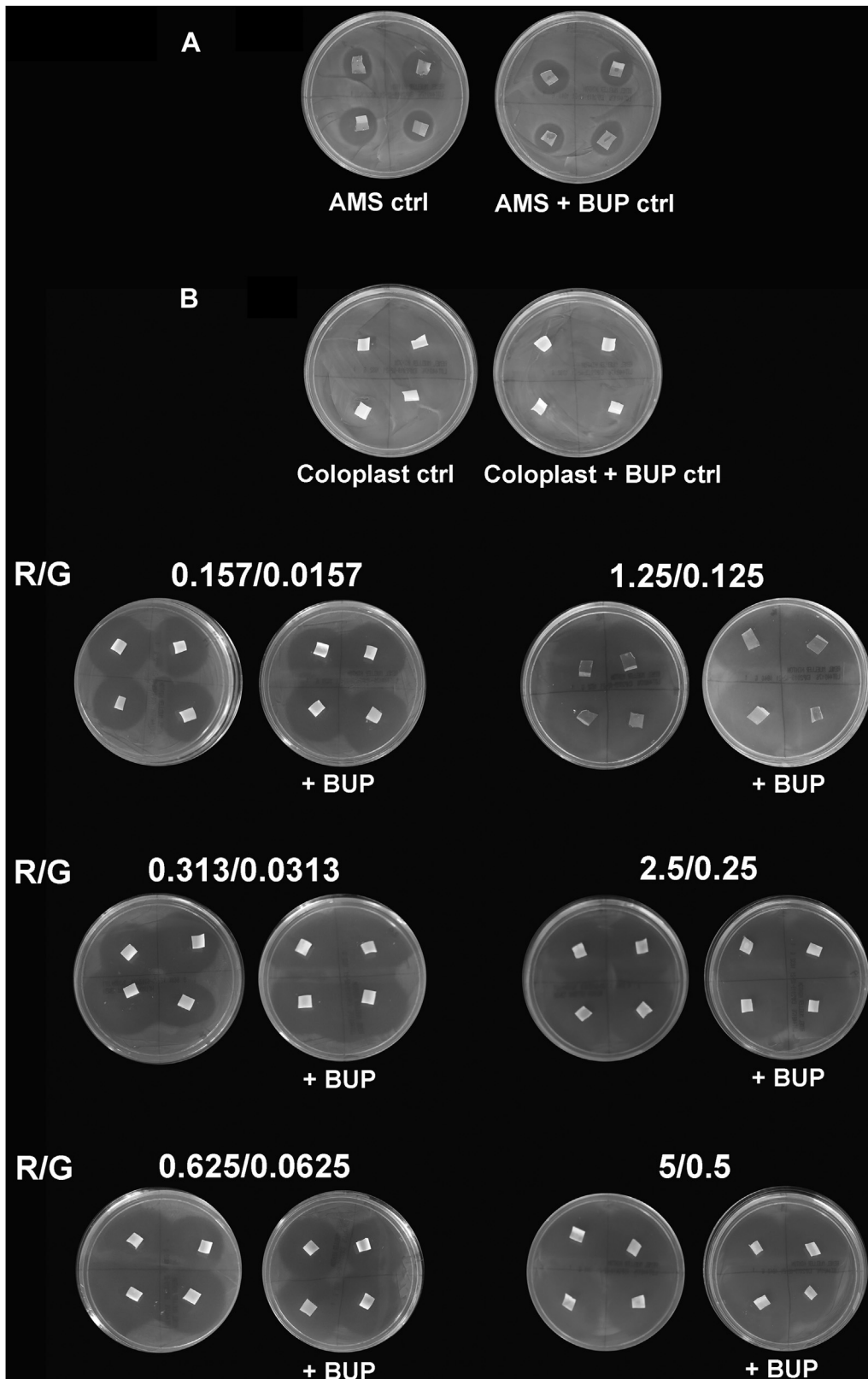


Figure 1. ZOI produced by Coloplast coated in R+G and AMS with or without BUP. *S. epidermidis* was plated on agar plates and 4 AMS or Coloplast strips dipped in various solutions were placed in each quadrangle. Plates were incubated at 37°C for 24 hours to visualize the ZOI. Panel A shows bacterial plates with AMS strips with or without BUP, which were photographed after 24-hour incubation. Panel B ZOI of Coloplast coated in R+G with or without BUP was photographed after 24-hour incubation. BUP = Bupivacaine; R+G = rifampin and gentamicin.

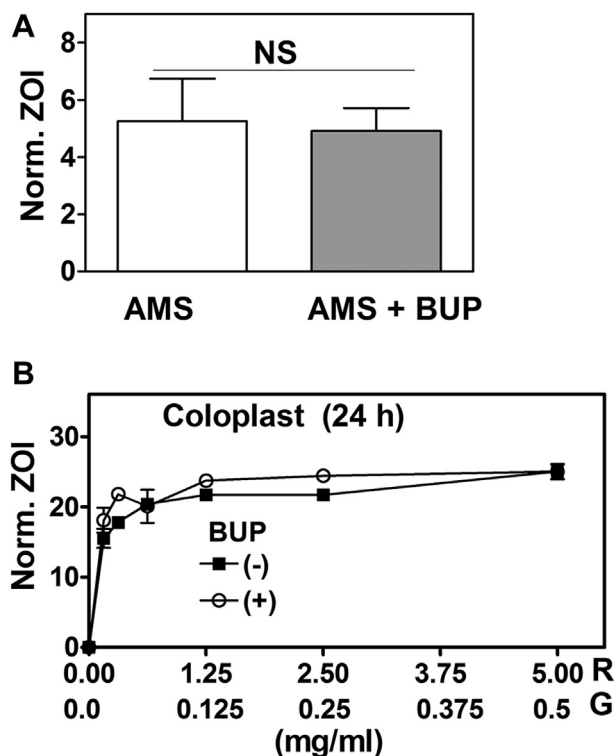


Figure 2. Comparison of the ZOI of R+G combination with or without BUP for *Staphylococcus epidermidis*. Panel A AMS700 with InhibiZone. Panel B Coloplast Titan at 24 hours. BUP = Bupivacaine; NS = not significant; R+G = rifampin and gentamicin; ZOI = zone of inhibition.

In our study, the ZOI against gram-positive *S epidermidis* was much larger than the ZOI against gram-negative *E coli*. This held true for both AMS and Coloplast (coated in all tested concentrations of R+G) strips. Additionally, the ZOI for Coloplast with R+G against gram-positive *S epidermidis* outgrew the confines of each quadrangle of the plate between 12 and 48 hours for all but the lowest tested concentration. Because *S epidermidis* was highly sensitive to the antibiotic treatment, lower concentrations were used for ZOI determination and the results were noted following only 24-hour incubation. This finding in our study could explain the currently observed changing landscape of implant infections,⁸ with a lower percentage of infections coming from gram-positive bacteria in recent years. This may be due to the improved coverage of gram-positive bacterial infections, rather than an overall increase in gram-negative and fungal infections.

In our study, BUP alone did not create any ZOI against *E coli* or *S epidermidis*, and this was the same effect seen in the control group. BUP alone was tested for its effect on ZOI because previous studies have illustrated its antimicrobial effects. In 1 study, visual growth of bacterial isolates within equine species was inhibited by BUP in 93% of common bacterial isolates and bactericidal to 81%.¹⁹ The bacterial species found most sensitive to BUP without additional preservatives included *Staphylococcus* species and *E coli*.^{20,21}

Table 2. Comparison of the ZOI for *S epidermidis* produced by penile prostheses treated with R+G with or without BUP

Prosthesis type	BUP (-)	BUP (+)	P value
AMS	5.24 ± 1.49	4.9 ± 0.77	.71
Coloplast 0.625 R/ 0.0625 G	20.4 ± 0.52	20.08 ± 2.35	.81

Mean normalized ZOI between groups were compared using the unpaired *t*-test. Data: Mean ± SD; n = 4/group. For BUP (-) and (+) comparison in the case of Coloplast Titan 2.5/0.25 R+G combination was chosen because at this concentration the ZOI produced was in the linear range. BUP = Bupivacaine; R+G = rifampin and gentamicin; *S epidermidis* = *Staphylococcus epidermidis*; ZOI = zone of inhibition.

It is a common practice to dip the Coloplast in antibiotics prior to implantation, due to its well-tested hydrophilic coating that is well-suited for antibiotic dips.²² Although AMS with InhibiZone alone has been found to reduce infection in vivo,²³ the use of additional antibiotic dip with AMS, for additional coverage, is also common in our institution. In particular, a combination of R+G may augment the antibacterial capabilities of InhibiZone. Future studies should be performed to evaluate the potential of the combination of R+G on amplifying the antibacterial coverage for AMS.

To our knowledge, this is the first study to test the effects of BUP on the antibacterial qualities of various antibiotic dips. Previous studies on BUP have shown its ability to control pain.¹³ This study also tested the widest array of concentrations of R+G for Coloplast-soaking solutions. All concentrations of R+G inhibited the growth of gram-positive and gram-negative bacteria. Therefore, further research may be done to test whether lower concentrations of antibiotic dip may be sufficient for anti-infection coverage.

Some of the limitations of our study are: we used *E coli* and *S epidermidis* as the representative examples of gram-negative and gram-positive bacteria, however, these may no longer be the most common pathogens causing infection, and, therefore, a wide variety of pathogens, like pseudomonas, clostridium species, and

Table 3. Comparison of the ZOI for *E coli* produced by penile prostheses treated with R+G with or without BUP

Prosthesis type	BUP (-)	BUP (+)	P value
24 h			
AMS	1.21 ± 0.11	1.34 ± 0.06	.062
Coloplast 2.50 R/ 0.25 G	2.2 ± 0.5	2.81 ± 0.42	.122
48 h			
AMS	1.27 ± 0.14	1.33 ± 0.12	.533
Coloplast 2.50 R/ 0.25 G	2.38 ± 0.23	2.93 ± 0.26	.02

Mean normalized ZOI between groups were compared using the unpaired *t*-test. Data: Mean ± SD; n = 4/group. For BUP (-) and (+) comparison in the case of Coloplast Titan 2.5/0.25 R+G combination was chosen because at this concentration of the combination, ZOI produced was in the linear range. BUP = Bupivacaine; *E coli* = *Escherichia coli*; R+G = rifampin and gentamicin; ZOI = zone of inhibition.

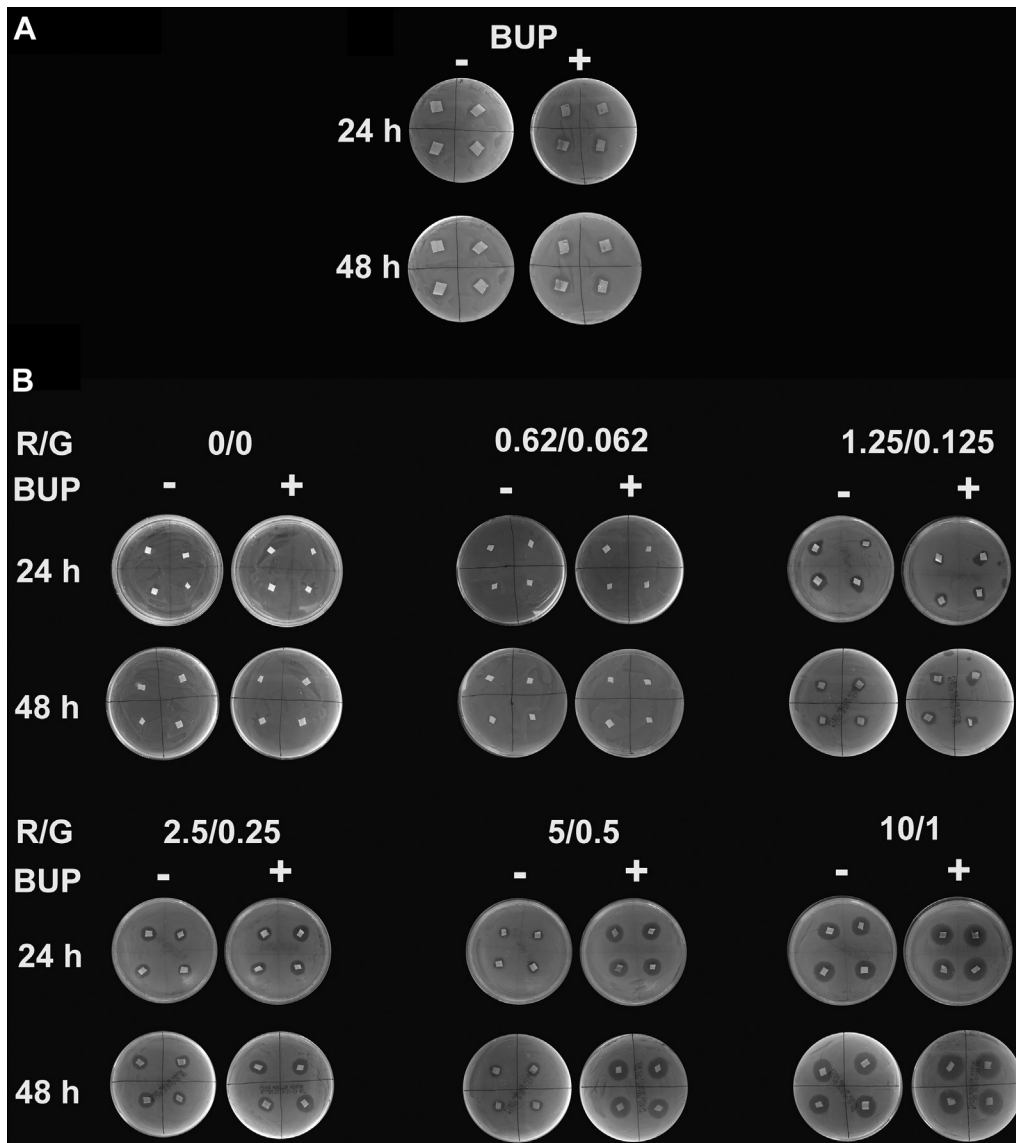


Figure 3. Zone of inhibition (ZOI) produced by Coloplast coated in R+G and AMS with or without BUP. *Escherichia coli* was plated on agar plates and 4 AMS or Coloplast strips dipped in various solutions were placed in each quadrangle. Plates were incubated at 37°C for 48 hours for visualization of the ZOI at 24 and 48 hours. Panel A Bacterial plates with AMS strips with or without BUP were photographed after 24 hour and 48 hour incubations. Panel B ZOI of Coloplast coated in R+G with or without BUP were photographed after 24 hour and 48 hour incubations. BUP = Bupivacaine; R+G = rifampin and gentamicin.

fungi, need to be investigated. BUP may have an influence on parameters other than bacterial growth in causing the development of infection. For example, the effects of BUP on the characteristics of polymers may be a confounding factor during long-term exposure on antibiotic-coated polymers.²⁴ Further research is needed to determine the difference, if any, between BUP utilization as a dip compared to BUP use as a dorsal nerve block and a head-to-head comparison between lidocaine and BUP. Although, in our study, BUP alone did not create a significant or observable ZOI against *S. epidermidis* or *E. coli*, the preservative effects of BUP may have caused some increased antimicrobial effects with the antibiotic dips, which may have led to some of the BUP groups to have larger ZOIs than those seen

in non-BUP groups. Another major limitation of our study is that it was an in vitro study and the findings will need to be validated in vivo for incorporating BUP during penile prosthesis implantation in patients.

CONCLUSION

With the introduction of BUP dip as a pain control agent during penile prosthesis implant surgeries, it is imperative to study the effects of this anesthetic on the antibacterial protection afforded by the antibiotic dips and coating of IPPs. In this study, BUP did not impede the antibacterial activity of InhibiZone or R+G soaked Coloplast. This was exhibited by no statically

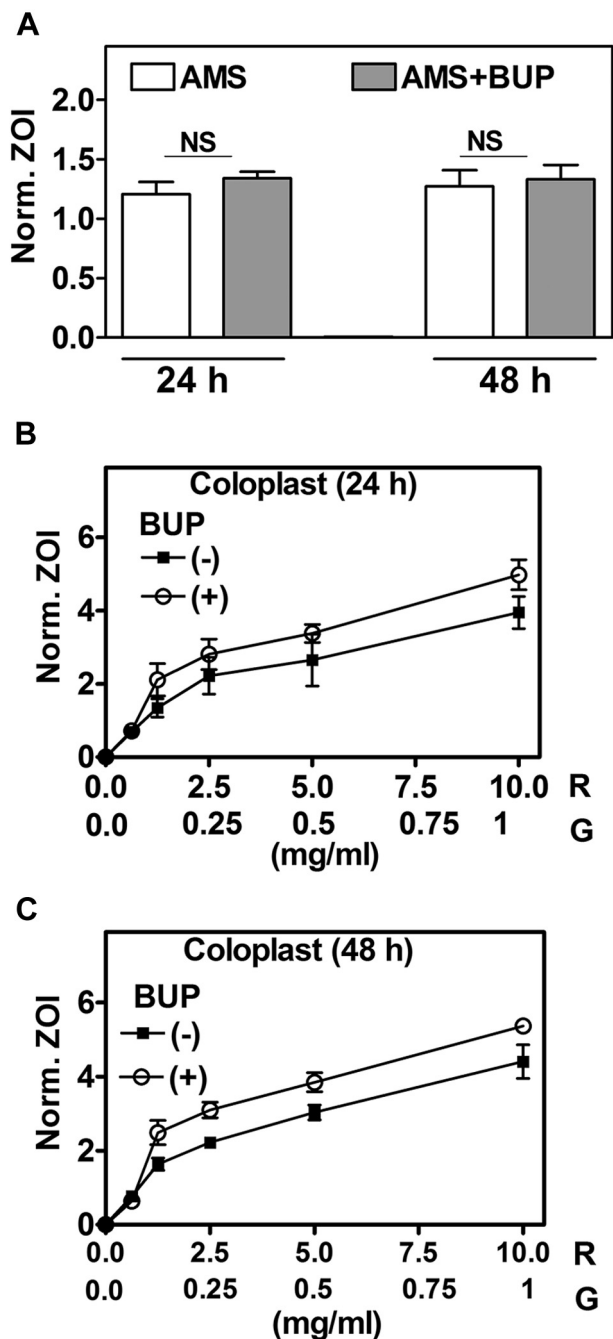


Figure 4. Comparison of the ZOI of R+G combination with or without BUP for *Escherichia coli*. Panel A AMS; Panels B and C Coloplast at 24 hours (B) and 48 hours (C), respectively. BUP = Bupivacaine; R+G = rifampin and gentamicin; ZOI = zone of inhibition.

significant reduction in ZOI for implants treated with BUP. Gram-positive coverage is greater with both InhibiZone and Coloplast dipped in R+G compared to gram-negative coverage. This study warrants further research on the effect of BUP on antibiotic coating of penile implants in preclinical animal model

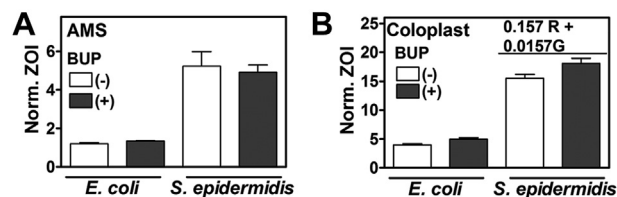


Figure 5. Comparison of the ZOI of AMS and Coloplast against *E. coli* and *S. epidermidis*. Panels A and B Comparison of the ZOI generated by AMS (A) or Coloplast (B), dipped in R+G against *E. coli* and *S. epidermidis*. BUP = Bupivacaine; *E. coli* = *Escherichia coli*; R+G = rifampin and gentamicin; *S. epidermidis* = *Staphylococcus epidermidis*; ZOI = zone of inhibition.

trials. Whether these in vitro findings translate to surgical outcomes needs to be evaluated in future research.

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Conflict of Interest: Ranjith Ramasamy is a consultant for Coloplast, is an investigator for Boston Scientific and Direx, and is an investigator and member of the advisory board for Endo and Aytu Biosciences. Bruce Kava is a consultant for Endo and Coloplast. The other authors declare no conflicts of interest.

Funding: None.

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