Reduction in surgical site infections by localized administration with D-PLEX$_{100}$ in patients with multiple risk factors undergoing colorectal surgery

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TITLE: Reduction in Surgical Site Infections by Localized Administration with D-PLEX$_{100}$ in Patients with Multiple Risk Factors Undergoing Colorectal Surgery

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ABSTRACT

Background: D-PLEX$_{100}$ is a novel drug-eluting lipid polymer matrix that supplies a high, local concentration of doxycycline for approximately 30 days. The objective of this post-hoc analysis was to assess the efficacy of D-PLEX$_{100}$ in preventing superficial and deep SSIs in patients with ≥2 risk factors.

Patients and methods: A post-hoc analysis of a previously reported prospective randomized trial assessing D-PLEX$_{100}$ plus Standard of Care (SOC) versus SOC alone in colorectal surgery was performed to assess SSI rate in patients with ≥ 2 risk factors.

Results: The overall incidence of SSI was significantly lower for the D-PLEX$_{100}$ arm (9.9%) versus SOC (21%), p = 0.033. Patients with ≥2 risk factors, SSI incidence was 37.5% for SOC and 15.8% in D-PLEX$_{100}$ treated patients.

Conclusions: D-PLEX$_{100}$ reduces the incidence of SSIs beyond benefits associated with SOC treatment alone and including patients with ≥2 risk factors. D-PLEX$_{100}$ may be a promising addition to established SSI prophylaxis bundles.

Keywords: Surgical site infection, localized antibiotic therapy, doxycycline, risk factors

INTRODUCTION

Although there have been significant advances in surgical technique, adoption of procedural guidelines, increased treatment options, and better understanding of surgical wound microenvironments, surgical site infections (SSIs) remain substantial cause of morbidity, prolonged hospitalization, and mortality among patients undergoing both elective and emergent surgeries.[1,2] At 42.4% of all healthcare-associated infections (HAIs), SSIs have surpassed catheter-associated urinary tract infections (CAUTIs) as the most common HAI in the United States and are the single most frequently cited reason for unplanned readmission following surgery, accounting for 19.5% of all readmission reasons across major surgical procedures and nearly 26% after colorectal surgery.[3,4]

The association between preoperative patient risk factors and SSI rate has long been an area of clinical interest and concern. Comorbidities such as obesity, hypertension, smoking, diabetes, and peripheral vascular disease are closely associated with post-operative complications including increased incidence of surgical site infections.[5,6] Given how common many of these conditions are both individually and in combination with others in the general population, efforts such as the American College of Surgeons (ACS) National Surgical Quality and Improvement Program (NSQIP) Surgical Risk Calculator have been made to quantify surgical risk for complications.[7] However, the ubiquity of these patient risk factors and their association with dramatically increased SSI rates reveal a significant unmet need regarding the specific pathophysiology of SSI despite current prophylaxis.

D-PLEX$_{100}$ is a locally applied extended release doxycycline formulation developed to address the gap in effective prophylaxis against superficial and deep surgical site infections. D-PLEX$_{100}$ pairs the broad-spectrum antibiotic, doxycycline, with an innovative Polymer-Lipid Encapsulation matriX (PLEX). This drug delivery system contains a polymer-lipid based matrix which forms a protected reservoir for the active drug. D-PLEX$_{100}$ is applied to the soft tissue wound surfaces following myofascial closure (Figure 1) which allows for a localized, continuous release of doxycycline for approximately 30 days with negligible systemic drug levels.[8] In this post-hoc analysis of a Phase 2 study evaluating D-PLEX$_{100}$ in addition to standard of care (SOC) in elective colorectal surgery (publication out for review), we sought to examine the effect of D-PLEX$_{100}$ administration on SSI incidence with increased patient risk factors.

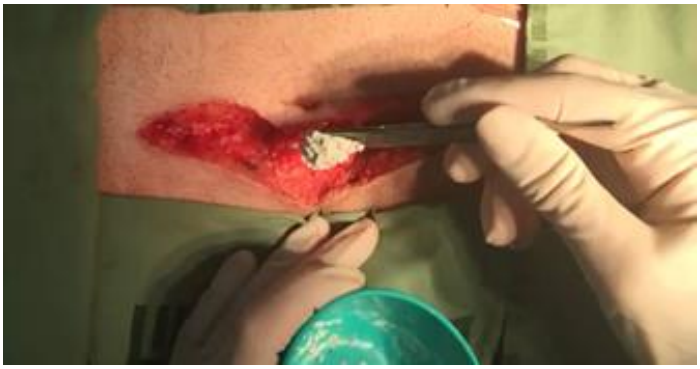

Fig. 1 D-PLEX$_{100}$ being applied to the incision edges at closure.

METHODS

Patients

The trial was conducted in eight medical centers in Israel with each center supervised by a principal investigator. Eligible patients were adults, 18 years and older, undergoing elective colorectal surgery. Female patients of childbearing age were required to have a negative serum pregnancy test prior to the procedure. Patients planned for a laparoscopic approach were included if a 5 cm or greater incision was performed as part of the procedure and/or as a specimen extraction site. Key exclusion criteria included patients who were scheduled for emergency surgery or who had received doxycycline within the 4 weeks prior to screening. Patients undergoing concomitant surgical procedures via the same incision(s) were included pending consultation and approval of the site sponsor. Patients who had received neoadjuvant radiation to the abdominal area or systemic chemotherapy within four weeks of surgery were excluded. Patients with known hypersensitivity to doxycycline and/or the tetracycline family of drugs, to D-PLEX$_{100}$ excipients, or who had allergies to more than 3 substances as determined from the screening questionnaire were also excluded.

Materials

D-PLEX$_{100}$ was provided by PolyPid Ltd. (Petah-Tikva, Israel). D-PLEX$_{100}$ is a new formulation of prolonged-release doxycycline, consisting of beta-tricalcium phosphate particles and a polymer-lipid based matrix encapsulating doxycycline [Kachel 2020]. D-PLEX$_{100}$ is supplied as a sterile powder and is mixed with normal

saline to form a paste. D-PLEX$_{100}$ is administered as a single application following myofascial closure and the active material is continuously released for approximately 30 days.

Study Design

The study protocol was reviewed and approved by the institutional review board at each participating site and was implemented following the principles of Good Clinical Practice and the Declaration of Helsinki, and in accordance with International Council of Harmonization guidelines and local regulations before enrollment of participants began. PolyPid employees participated with the primary investigators in the design of the trial and PolyPid was the study sponsor and funded the study. All patients provided written informed consent prior to any study procedures. The study was registered at the clinicaltrials.gov: NCT03633123. The patients were randomized to receive D-PLEX$_{100}$ administered along with SOC or the SOC. The prophylactic antibiotic SOC treatment, based on the Israel Ministry of Health (IMOH) guidelines and standardized for all participating sites, included a 1st or 2nd generation cephalosporin plus metronidazole administered intravenously within 30-60 minutes prior to surgery. Mechanical bowel preparation (MBP) was at the discretion of the surgeon. No oral antibiotic bowel preparation (OABP) was given to either arm. For patients randomized to the treatment arm, at the time of fascia closure D-PLEX$_{100}$ was applied along the entire length of the surgical wound, inclusive of the fascial suture line and soft tissues of the abdominal wall, subcutaneous fat, and dermis. The D-PLEX$_{100}$ dose was determined based on the length of the surgical incision: a 5-10 cm incision received 5g D-PLEX$_{100}$, an 11-20 cm incision received 10g D-PLEX$_{100}$, and an incision ≥21 cm received 15g D-PLEX$_{100}$. Immediately before application, the entire content of D-PLEX$_{100}$ vials is emptied into a sterile mixing bowl. The reconstitution is then performed as follows (according to required dose): one vial is reconstituted with 2mL sterile 0.9% saline solution, two vials are reconstituted with 3.5mL sterile 0.9% saline solution, three vials are reconstituted with 5mL sterile 0.9% saline solution to form a paste that is applied within the surgical site. All surgeons were trained on the use and application of D-PLEX$_{100}$.

Analysis and Outcomes

Patients were randomized to either the SOC or D-PLEX$_{100}$ plus SOC in a 1:1 ratio at Day 0 via an interactive web randomization system integrated with an electronic case record form (eCRF) based on the patient's sex, age (18-40,

41-65, and above 66), and if there was a planned ostomy creation. Patients were blinded to their study designation. Primary outcomes assessed included 30-day superficial and deep SSI and treatment-emergent adverse events (TEAEs).

The incisional site was assessed at post-operative Days 1, 5, 14, 30, and 60 by a blinded assessor (responsible for identifying all potential SSI's) and by a separate and blinded independent endpoint adjudication committee (EAC). The EAC was composed of 3 physicians: two surgeons with expertise in colorectal surgeries and an infectious diseases expert. The blinded EAC members independently reviewed the clinical data, wound culture results, and photo documentation of the wound for each suspected SSI event and determined whether it met the efficacy event criteria. In the event of a dispute between the blinded assessor and the committee, the committee's adjudication prevailed. SSIs were classified following the National Healthcare Safety Network and Centers for Disease Control and Prevention Surgical Site Infection Event Reporting Manual as Superficial SSI (SSSI), where the infection involved the skin and subcutaneous tissues (and not including cellulitis or stitch abscess alone) or Deep SSI (DSSI), when the infection involved the fascial and/or muscle layers. Organ/organ space SSIs (e.g., an intra-abdominal abscess or anastomotic leak) were assessed as TEAEs rather than SSI endpoints.

For this post-hoc analysis, 30-day SSI rates were examined among patients in the Intention-to-treat (ITT) population and those with ≥2 preoperative risk factors. Individual risk factor categories were diagnoses of diabetes, chronic obstructive pulmonary disease (COPD) or a history of smoking, obesity/overweight as defined as a body mass index (BMI) of 25 or more, hypertension, and peripheral vascular disease.

The study planned to enroll 200 patients, with 100 subjects allocated to each treatment group. This sample size was determined to provide adequate initial data for evaluating the study objectives. Assessments were made using Fisher's exact test with a two-tailed P-value. P-values of <0.05 were considered statistically significant. All calculations were made on the combined results of all centers, there was no selective pooling of study centers for analyses.

RESULTS

From October 2018 to October 2019, 207 patients were screened and 202 proceeded for randomization to either the SOC arm (n=101) or the D-PLEX$_{100}$ arm (n=101). In the SOC arm, one patient did not proceed to surgery. Analyses reported here were performed on the ITT Population (Figure 2).

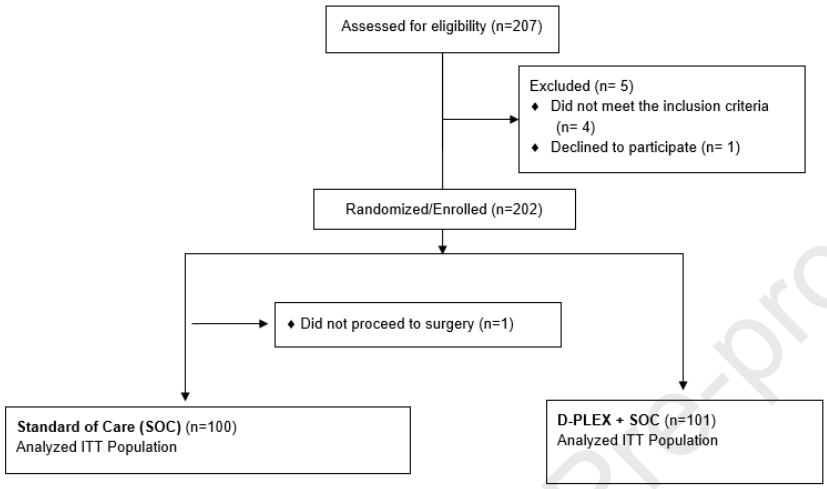

Fig. 2

The groups were stratified based on patient baseline demographics and surgical considerations and these well balanced data have been previously published.[9] All surgical wounds were classified as clean-contaminated. All incisions were closed via primary intention. The distribution of the assessed comorbid conditions are shown in Table 1.

Table 1. Distribution of Comorbid Conditions between the two groups. **(**Intention to Treat Populations n=201**)**

Comorbid Condition	D-PLEX (N=101)	CONTROL (N=100)	Overall (N=201)
Diabetes	28 (27.72%)	25 (25.00%)	53 (26.37%)
Chronic Obstructive Pulmonary Disease (COPD)/Smoking	19 (18.81%)	16 (16.00%)	35 (17.41%)
Obesity/Overweight	25 (24.75%)	31 (31.00%)	56 (27.86%)
Hypertension	47 (46.53%)	48 (48.00%)	95 (47.26%)
Peripheral Vascular Disease (PVD)	2 (1.98%)	2 (2.00%)	4 (1.99%)

*Patients in the study group have multiple comorbidities whereas the comparator group have 0-1.

The rate of superficial and deep SSIs within 30 days post-index surgery showed a 53% relative risk reduction in the D-PLEX$_{100}$ cohort (N=10/101 [9.9%]) compared to SOC (N=21/100 [21%]); p = 0.033 (Table 2). When assessed by risk groupings, patients with ≥2 risk factors had an SSI incidence of 15.8% (15/40) if treated with D-PLEX$_{100}$ plus SOC compared to 37.5% (6/38) if treated with SOC alone (Relative Risk Reduction = 58%, p = 0.042).

Table 2. Incidence of SSI through post-operative Day 30.

Endpoint	D-PLEX + SOC N=101	SOC N=100	P-value
SSI Infection rate, n (%)	10 (9.9)	21 (21.0)	0.033
SSI Infection rate, n (%) for patients with ≥2 Risk Factors	6 (15.8)	15 (37.5)	0.042

DISCUSSION

Given how common the assessed comorbidities are and the numerous analyses which reveal their association with increased SSI risk, there remains an obvious but unmet need for this large and vulnerable patient population. One of the most significant efforts in SSI prophylaxis measures has been the development and adoption of Surgical Site Infection Bundles. While these SSI bundles have undoubtedly reduced the overall incidence of SSIs, there remains important issues which deserve attention.[10] The first is the discrepancy between whether and to what extent a specific bundle component contributes to a reduced SSI rate and often there is a tradeoff between clinical benefits and harms. For example, the 2017 CDC Guidelines for the Prevention of Surgical Site Infections found that many of the antiseptic prophylaxis measures such as the use of microbial sealants or plastic adhesive drapes, with or without antimicrobial properties was not necessary in preventing SSIs.[11] This same analysis found the evidence behind triclosan-coated sutures supported a weak recommendation, which echoes findings from the recent National Institute of Health Research meta-analyses which did not find a benefit from either triclosan-coated sutures or alcoholic chlorhexidine skin preparation.[11] This analysis also noted the additional costs these interventions contribute to overall healthcare expenditure. In a meticulous assessment of evolving bundle interventions, *Dellinger et al.*

demonstrated undulating rates of potentially preventable SSIs as additional interventions were added to their institution's SSI prevention bundle.[12]

Efficacy of SSI prophylaxis bundles suffer from two major gaps. Importantly, none of the bundle elements, other than SOC antibiotics, demonstrate a high level of evidence showing a consistent reduction in the level of bacterial contamination of the wound cavity which is maximal at the time of skin closure.[11] Secondly, many bundle elements may not be performed reliably as intended and compliance across the spectrum of multidisciplinary specialties and ancillary health staff, or lack thereof, is directly related to successful SSI reduction.[2,12] In considering how D-PLEX$_{100}$ may address these gaps, the high, local concentration of doxycycline frequently exceeds the minimum inhibitory concentrations for most of the commonly implicated SSI organisms [data on file] and this level is maintained for 30 days which is significantly longer than other locally applied antibiotic-eluting agents.[8,13] Given it is applied by the surgeon at the time of closure as a single application, it is not subject to required compliance or maintenance across multiple care providers or teams. These advantages support a reasonable consideration for the role of D-PLEX$_{100}$ in SSI prophylactic bundle recommendations.

A number of topical antimicrobial agents (both antibiotics and antiseptics) have been investigated in the effort to complement current systemic prophylaxis methods, however, most demonstrate questionable results or are not validated with a high quality of evidence.[13] For example, *Bennett-Guerrero et al.* evaluated a bioresorbable release gel containing gentamicin and vancomycin (DFA-02) in a Phase 2b trial and found it was not associated with a signification reduction in SSI compared to matching placebo gel or SOC.[15] More surprisingly, in a Phase 3 trial in colorectal surgery assessing the efficacy of a gentamicin-collagen sponge for infection prophylaxis found that it was paradoxically associated with an increased risk for SSI [Bennett-Guerrero 2010].[16] The authors noted a rapid depletion of reserve antibiotic in the topical agent and low local concentration of antibiotic, and importantly a need to rethink the proposed drug formulation. A recent meta analysis by Chen et al confirmed the lack of apparent benefit of prior approaches for delivering intra wound antibiotics to reduce the SSI burden in wounds healing by primary intention.[16] The same issues apply to wound irrigation strategies which have provided minimal, if any, significant benefits in terms of successful primary wound healing when used as an adjunct to SOC intravenous prophylaxis.[17]

This Phase 2 safety and efficacy trial demonstrated that the addition of D-PLEX to SOC SSI prophylaxis significantly reduces the incidence of superficial and deep surgical site infections, and in our post-hoc analysis, we found a statistically significant reduction in SSI rates for patients with at least 2 risk factors. While this study was not powered to address patient populations with SOC risk for SSI ≤10%, given that this long-duration, local drug delivery platform bypasses many of the pharmacodynamic limitations associated with systemic antibiotics, it is reasonable to postulate its maintained efficacy in patients with a lower baseline SSI risk even if the effect size becomes more modest.[5,6] Given the cost and large sample sizes needed to demonstrate statistically significant SSI reduction in populations with lower but clinically important SSI rates, future Phase 3 and Phase 4 trials primarily assessing the reduction in SSI treatment burden in addition to relative risk reduction are needed to address this gap in clinical evidence.

CONCLUSIONS

D-PLEX$_{100}$ was effective at significantly reducing the incidence of superficial and deep surgical site infections beyond benefits associated with SOC prophylaxis alone. Additionally, the data showed a statistically significant SSI reduction of 58% in patients with ≥2 risk factors. As such, D-PLEX$_{100}$ may be a promising addition to established SSI bundles and is currently being evaluated in several large Phase 3 clinical trials (ClinicalTrials.gov Identifier: NCT04411199; NCT04233424).

Disclosures

Funding: Research funding support was provided by PolyPid, Ltd.

Conflict of Interest: A.S., Y.S., O.B., and M.R. are all employees of PolyPid, Ltd. and own stock/stock options; O.Z. is an *ad hoc* speaker for PolyPid, Ltd.; N.W., H.T., and L.S. declare they have no conflicts of interest.

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Peripheral Vascular Disease (PVD)	2 (2.0%)	2 (2.0%)	4 (2.0%)

*Patients in the study group have multiple comorbidities whereas the comparator group have 0-1.

SSIs are the most common healthcare-associated infection in the United States.

Comorbidities are closely associated with post-operative complications including SSIs.

D-PLEX$_{100}$ was developed to address the gap in effective SSI prophylaxis.

D-PLEX$_{100}$ provides local antibiotic release with negligible systemic drug levels.

D-PLEX$_{100}$ in addition to SOC significantly reduces the incidence of SSIs.