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# To evaluate safety and efficacy of tedizolid phosphate in the management of several skin infections

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## ABSTRACT

Tedizolid Phosphate is an oxazolidinone-class antibiotic and is used for the treatment of acute bacterial skin and skin structure infections. it is a prodrug activated by plasma or intestinal phosphatases to tedizolid following administration of the drug either orally or intravenously. Once activated, tedizolid exerts its bacteriostatic microbial activity through inhibition of protein synthesis by binding to the 50S ribosomal subunit of the bacteria. The purpose of the study was to evaluate safety and efficacy of Tedizolid phosphate and compare it with that of Lenizolid Phosphate another oxazolidinone class of drugs. The study was conducted at OMNI hospital located at dilsukhnagar, Hyderabad. 126 subjects with skin infections, who satisfied the eligibility criteria, were accrued during the study period. These patients were randomized into 2 groups, and were then evaluated according to the treatment protocol. Investigational product was then administered to evaluate safety and efficacy parameters. Subjects received treatment according to the study arm/group. Subjects were asked to take drug for 7 days daily once orally till the clinical symptoms disappear/ as per PIs discretion. Samples for microbiological evaluation were done at screening, end of the therapy. Among both the formulations the group the received Tedizolid phosphate was considered safer and more efficacious as Clinical success rate was 89.9% and the group that received Lenizolid phosphate had the clinical success rate of 81%. It can be concluded that Tedizolid phosphate could be promising drug in the treatment of various skin infections.

**Keywords:** Diseases; infection; tedizolid phosphate; skin infections; wound.

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## INTRODUCTION

Infection is the invasion of a host organism's body tissues by disease-causing agents, their multiplication, and the reaction of host tissues to these organisms and the toxins they produce[1]. Infectious diseases, also known as transmissible diseases or communicable diseases, comprise clinically evident illness (i.e., characteristic medical signs and/or symptoms of disease) resulting from the infection, presence and growth of pathogenic biological agents in an individual host organism.

Bacterial skin infections may be uncomplicated or complicated. Uncomplicated infections usually respond promptly to systemic antibiotics and local wound care. A skin infection is considered complicated when it meets 2 of the following 5 criteria:

Involves a preexisting wound or ulceration of the skin

Involves the deeper soft tissues

Requires surgical intervention

Is caused or exacerbated by underlying comorbid disease states (eg, diabetes, systemic immunosuppression)

Is unresponsive to conventional antibiotic therapy or is recurrent

All uncomplicated skin infections have the potential to become complicated. Complicated skin and soft-tissue infections may require multidrug therapy and the assistance of other consultants (eg, surgeons, infectious disease specialists), particularly in light of resistance in many strains of bacteria and the rapid loss of efficacy among more potent antibiotics. Recurrent skin infections should raise suspicion of colonization (eg, staphylococcal nasal carriage), resistant strains of bacteria (eg, methicillin-resistant Staphylococcus aureus (MRSA), cancer, poorly controlled diabetes, or other reasons for immunocompromise (eg, HIV, hepatitis, advanced age, congenital susceptibility). Bacteria are involved in the pathophysiology of acne, but acne is not primarily considered a bacterial skin infection.

**Types of acute bacterial skin infections**

**Cellulitis:** Cellulitis is acute bacterial infection of the skin and subcutaneous tissue most often caused by streptococci or staphylococci. Symptoms and signs are pain, rapidly spreading erythema, and edema; fever may occur, and regional lymph nodes may enlarge[2]. Diagnosis is by appearance; cultures are sometimes helpful, but awaiting these results should not delay empiric therapy. Treatment is with antibiotics. Prognosis is excellent with timely treatment. Cellulitis isn't usually spread from person to person. Cellulitis is an infection of the deeper layers of the skin most commonly caused by bacteria that normally live on the skin's surface. Have an injury, such as a cut, fracture, burn or scrape

Cellulitis is typically unilateral; stasis dermatitis closely mimics cellulitis but is usually bilateral. The major findings are local erythema and tenderness, frequently with lymphangitis and regional lymphadenopathy. The skin is hot, red, and edematous, often with surface appearance resembling the skin of an orange (peaud'orange). The borders are usually indistinct, except in erysipelas. Petechiae are common; large areas of ecchymosis are rare. Vesicles and bullae may develop and rupture, occasionally with necrosis of the involved skin. Cellulitis may mimic deep venous thrombosis but can often be differentiated by one or more features. Fever, chills, tachycardia, headache, hypotension, and delirium may precede cutaneous findings by several hours, but many patients do not appear ill. Leukocytosis is common. Cellulitis with rapid spread of infection, rapidly increasing pain, hypotension, delirium, or skin sloughing, particularly with bullae and fevers, suggests life-threatening infection. Following may have the occurrence of cellulitis

Have a skin condition, such as eczema, athlete's foot or shingles

Participate in contact sports, such as wrestling

Have diabetes or a weakened immune system

Have a chronic swelling of your arms or legs(lymphedema)

Use intravenous drugs

**Skin abscess causes:** A skin abscess is a build up of pus in or on the skin. Skin abscesses are typically caused by either an inflammatory reaction to an infectious process (bacteria or parasite) or, less commonly, to a foreign substance within the body(a needle or a splinter, for example). Abscesses may develop because of obstructed oil(sebaceous) or sweat glands, inflammation of hair follicles, or from minor breaks and punctures of the skin[7]. Abscesses may also develop after a surgical procedure.

The infectious organisms or foreign material cause an inflammatory response in the body, which triggers the body's immune system to form a cavity or capsule to contain the infection and prevent it from spreading to other parts of the body[8]. The interior of the abscess liquefies, and pus develops (which contains dead cells, proteins, bacteria, and other debris). This area then begins to expand, creating increasing tension and inflammation of the overlying skin.

**Internal abscesses:** Abscesses that develop inside the tummy (abdomen) are caused by an infection reaching tissue deeper within the body. This can occur as a result of:

an injury

abdominal surgery

an infection spreading from a nearby area

There are many ways an infection can spread into the abdomen and cause an abscess to develop. For example, a lung abscess can occur due to a bacterial infection in your lungs, such as pneumonia, and a burst appendix can spread bacteria within abdomen.

**Infected wound:** Infected wounds are wounds in which bacteria or other microorganisms have colonized, causing either a delay in wound healing or deterioration of the wound. Most wounds are typically contaminated by bacteria[9]. However, infected wounds result when the body's immune defenses are overwhelmed or cannot cope with normal bacterial growth. Infection of wounds caused by surgery is a serious health risk, as studies have shown that 70 percent of the deaths of patients who have undergone surgery are caused by surgical site infections

**Risk for a wound infection**

This includes any of the following:

Diseases such as diabetes, cancer, or liver, kidney or lung conditions slow healing.

Foreign objects such as glass or metal can get stuck in the wound and delay healing.

Poor blood supply to the wound increases your risk for infection. Blood flow may be decreased by high blood pressure, and blocked or narrowed blood vessels. Your risk also increases if you smoke, or have blood vessel problems or a heart condition

Repeated trauma to a healing wound may increase your risk for an infection, and delay healing.

A weak immune system caused by radiation, poor nutrition, or certain medicines increases your risk for an infection.

**Causative organism**

**MRSA:** Methicillin-resistant Staphylococcus aureus (MRSA) is a bacteria that is resistant to many antibiotics. In the community, most MRSA infections are skin infections. In medical facilities, MRSA causes life-threatening bloodstream infections, pneumonia and surgical site infections.

MRSA, also called methicillin-resistant Staphylococcusaureus or multiple-resistant, bacterium in the genus Staphylococcus that is characterized by its resistance to the antibiotic methicillin and to related semisynthetic penicillins. MRSA is a strain of S. aureus and was first isolated in the early 1960s, shortly after methicillin came into use as an antibiotic. Although methicillin is no longer used, MRSA has become widespread some 50 million people worldwide are believed to carry the organism

It is commonly found on the skin, in the nose, or in the blood or urine. Most MRSA infections occur in people who've been in hospitals or other health care settings, such as nursing homes and dialysis centers. When it occurs in these settings, it's known as health care-associated MRSA (HA-MRSA)[12]. HA-MRSA infections typically are associated with invasive procedures or devices, such as surgeries, intravenous tubing or artificial joints.

Another type of MRSA infection has occurred in the wider community among healthy people. This form, community-associated MRSA(CA-MRSA), often begins as a painful skin boil. It's spread by skin-to-skin contact. At-risk populations include groups such as high school wrestlers, child care workers and people who live in crowded conditions.

Doctors diagnose MRSA by checking a tissue sample or nasal secretions for signs of drug-resistant bacteria. The sample is sent to a lab where it's placed in a dish of nutrients that encourage bacterial growth. But because it takes about 48 hours for the bacteria to grow, newer tests that can detect staph DNA in a matter of hours are now becoming more widely available.

**Staphylococcous**

The organism may cause disease through tissue invasion and toxin production. The toxins liberated by the organism may have effects at sites distant from the focus of infection or colonization. The postulated sequence of events that leads to infection is initiated with carriage of the organism. The organism is then disseminated via hand carriage to body sites where infection may occur (either through overt breaks in dermal surfaces, such as vascular catheterization or operative incisions, or through less evident breakdown in barrier function, such as eczema or shaving-associated microtrauma).

The hallmark of staphylococcal infection is the abscess, which consists of a fibrin wall surrounded by inflamed tissues enclosing a central core of pus containing organisms and leukocytes. From this focus of infection, the organisms may be disseminated hematogenously, even from the smallest abscess. The ability to elaborate proteolytic enzymes facilitates the process[13].This may result inpneumonia, bone and joint infection, and infection of the heart valves. In immunocompromised hosts (eg, patients with cancer who are neutropenic and have a central venous line), 20-30% develop serious complications or fatal sepsis following catheter-related S aureus bacteremia.

Persistent deep-seated infections have now been linked to small-colony variants of the organism. This population is more resistant to antibiotics and grows slowly. These organisms have been described in patients with cystic fibrosis and may contribute to the persistence of S aureus in these patients.

S. aureus has long been recognized as one of the most important bacteria that cause disease in humans. It is the leading cause of skin and soft tissue infections such as abscesses(boils), furuncles, and cellulitis. Although most staph infections are not serious, S. aureus can cause serious infections such as bloodstream infections, pneumonia, or bone and joint infections.

Staphylococcus aureus belongs to the family Staphylococcaceae. It affects all known mammalian species, including humans. Further due to its ability to affect a wide range of species, S. aureus can be readily transmitted from one species to another. This includes transmission between humans and animals.

**Variety of manifestations s. Aureus may cause**

Minor skin infections, such as pimples, impetigo etc.

It may cause boils(furuncles), cellulitis folliculitis, carbuncles

It is the cause of scalded skin syndrome and abscesses

It may lead to lung infections or pneumonia

Brain infections or meningitis

Bone infections or osteomyelitis

Heart infections or endocarditis

Generalized life threatening blood infections or Toxic shock syndrome (TSS), bacteremia and septicaemia

**Types and presentation of s aureus infection include the following**

**Impetigo:** A small area of erythema that progresses into bullae (filled with cloudy fluid) that rupture and heal with the formation of a honey-colored crust

**Scalded skin syndrome (ritter disease):** A relatively rare, toxin-mediated disorder with superficial fragile blisters that burst, leaving a tender base; often accompanied by fever and occasionally by mucopurulent eye discharge

**Folliculitis:** A tender pustule that involves the hair follicle

**Furuncle:** Small abscesses characterized by exuding purulent material from a single opening; involves both the skin and the subcutaneous tissues in areas with hair follicles

**Carbuncle:** An aggregate of connected furuncles, with several pustular openings

**Bone infections(osteomyelitis):** In children, sudden onset of fever and bony tenderness or a limp; pain may be throbbing and severe; however, presentation in neonates can be subtle

**Septic arthritis:** Decreased range of motion, warmth, erythema, and tenderness of the joint with constitutional symptoms and fever; however, these signs may be absent in infants (in whom the hip is the most commonly involved joint)

**Endocarditis:** Initially presents as fever and malaise; peripheral emboli may be present; may involve healthy valves

**Toxic shock syndrome:** Fever, diffuse macular erythema, and hypotension, with involvement of 3 or more organ systems; can be rapidly progressive in previously healthy individuals

**Pneumonia:** Most common in infants, young children, and debilitated patients; a short prodrome of fever followed by rapid onset of respiratory distress; prominent GI symptoms may also occur

**Thrombophlebitis:** Fever, pain, and occasionally erythema at the insertion site of an intravenous catheter; usually affects hospitalized patients

**Deep tissue abscess and infection:** Muscles and organs can become infected, including the parotid gland, eyes, liver, spleen, kidneys, and central nervous system; deep abscesses also may occur; fever with or without localizing pain is typical

**MATERIALS AND METHODS**

**Factors to be identified:** Efficacy and safety within finished population.

**Data focus:** Efficacy, Adverse events

**Design features:** Randomized, Controlled, 2 treatment arms, interventional

**Study duration:** 3 months

**Population:** Individuals with target disease

**Sample size:** 126 Patients with proven arthritis.

- The study was conducted in omni hospital, Hyderabad.
- 126 patients, who satisfied the eligibility criteria, were accrued during the study period.
- These patients were randomized into 2-Arms, and were then evaluated according to the treatment protocol.

**Inclusion criteria**

- Males or females >/=18 years old
- Adequate venous access for a minimum of 2 I.V. doses of study drug
- Acute Bacterial Skin and skin structure infection (ABSSSI) meeting at least 1 of the clinical syndrome definitions listed below and requiring I.V. antibiotic therapy. Local symptoms must have started within 7 days before the Screening Visit
- Cellulitis/erysipelas
- Major cutaneous abscess
- Wound Infection
- Suspected or documented gram-positive infection from baseline Gram stain or culture.

**Exclusion criteria**

- Uncomplicated skin and skin structure infections such as furuncles, minor abscesses
- Infections associated with, or in close proximity to, a prosthetic device
- Severe sepsis or septic shock
- Known bacteremia at time of screening
- ABSSSI due to or associated with any of the following:
- Suspected or documented gram-negative pathogens in patients with cellulitis/erysipelas or major cutaneous abscess that require an antibiotic with specific gram-negative coverage. Patients with wound infections where gram-negative adjunctive therapy is warranted may be enrolled if they meet the other eligibility criteria
- Diabetic foot infections, gangrene, or perianal abscess
- Concomitant infection at another site not including a secondary ABSSSI lesion (eg, septic arthritis, endocarditis, osteomyelitis)
- Infected burns
- Decubitus or chronic skin ulcer, or ischemic ulcer due to peripheral vascular disease (arterial or venous)
- Any evolving necrotizing process (ie, necrotizing fasciitis)

**Use of antibiotics as follows**

- Systemic antibiotic with gram-positive cocci activity for the treatment of any infection within 24 hours before the first infusion of study drug

- Patients who failed prior therapy for the primary infection site are also excluded from enrollment
- Topical antibiotic on the primary lesion within 24 hours before the first infusion of study drug except for antibiotic/antiseptic-coated dressing applied to the clean postsurgical wound
- Administration of Linezolid within 30 days before the first infusion of the study drug
- Recent history of opportunistic infections where the underlying cause of these infections is still active (eg, leukemia, transplant, acquired immunodeficiency syndrome (AIDS))
- Previous exposure to Tedizolid Phosphate treatment

**Patient history**

- A detailed history has been ascertained and entered in the CRF.
- A detailed previous history has been recorded.
- Past history of taking any drugs, antibiotics and any history of previous hospitalization, associated illness and habits and diet has been recorded in detail.
- Any significant family history was also recorded.

**Patient screening procedure includes**

- Demography
- Medical history
- Prior medication
- Physical examination

**Vital signs:** Blood pressure, pulse, respiratory rate and oral temperature, BMI determination

**Urine pregnancy test (UPT):** Only for females of child bearing potential, Blood culture

**Demographic**

- All the patients who met the study criteria were enrolled in the study & reviewed daily.
- Name, Age and Sex of patients, hospital register number,

**Sample collection methodology**

**Laboratory Investigation**

- Complete Blood Count
- Microbiological Culture processes
- Blood Culture

**Sample Collection Procedures**

**Blood sample collection**

**Vein Puncture**

- Usually prefer the upper arm
- Primary vein: median cubital vein
- Secondary Vein: Cephalic vein
- Tertiary Vein: Basilic vein

**Torniquete Application**

- Assist in feeling good vein
- Tied three to four inch above the site of puncture
- Should not use more than one minute to avoid hemoconcentration
- Should be removed before removal needle.

**Cleaning of puncture site**

It should be done by alcohol swab in circular motion inside and outside to prevent contamination of site and specimen.

Let the site to dry for a minute

**Specimen Labelling**

Fell the requisition form which should be for each individual patient

Label with sticker by writing requisition no, subject ID for the maintenance of lab records.

**Sample Containers**

**SST Tube:** (Yellow top), Specimen withdrawn= 5ml

**Processing**

- Invert the SST tube gently five times
- Allow blood in SST tube to clot upright at room temp for 30-60 minutes (Don't allow the tubes to sit longer than one hour after collection)
- Centrifuge SST tube for 10-15 minutes at 1250 RCF. Carefully remove tube from centrifuge and maintain it in upright position.
- Transfer separated serum to serum tube (yellow cap) using disposable transfer pipette.
- **Storage:** Store serum tube at room temperature ($25^0$C or lower)

**Administration of investigational product:**

After signing the informed consent, study related procedures blood sampling for microbial testing and sensitivity is carried out. Subject will be randomized to receive empiric therapy with the study drugs on the same day of screening.

Once subjects meet the eligibility criteria, they will be continued in the study.

Subjects will receive drug treatment according to the study arm/group. Subjects are asked to administer drug for 7 days daily once orally till the clinical symptoms disappear/ as per PIs discretion. Samples for microbiological evaluation will be done at screening, end of the therapy.

**RESULTS AND DISCUSSION**

**Table 1: Demographic variables**

| Demographic baseline characters | Group(n=63) | Group(n=63) |
|---|---|---|
| Age (yrs) (mean) | 37.3 (12.1) | 36.0 (12.4) |
| Gender | | |
| Females | 20 (31.7) | 24 (38.1) |
| Males | 43 (68.3) | 39 (61.9) |

| Types of skin infections | | |
|---|---|---|
| Infected wound | 1 (1.6) | 4 (6.3) |
| Cellulitis | 13 (20.6) | 13 (20.6) |
| Abscess | 49 (77.8) | 46 (73.0) |

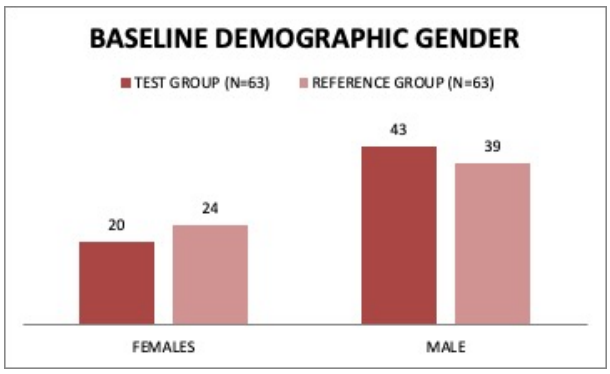


**Figure 1: Baseline demographic character gender**

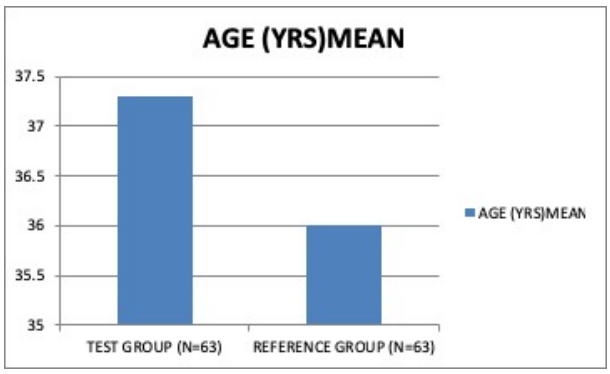


**Figure 2: Baseline demographic character age**

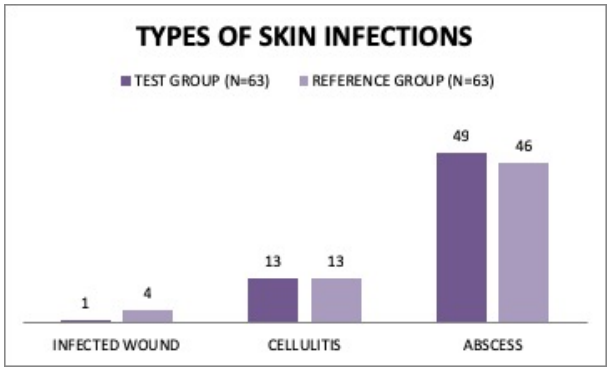


**Figure 3: Types of skin infections**

**Table 2: Early microbiological assessment**

| Clinical responseeot (micro biology) | Test group (n=63) | Reference group (n=63) |
|---|---|---|
| MRSA | 18/20 | 12/15 |
| Streptococcus aureus | 28/28 | 28/30 |
| Streptococcus pyogenes | 9/9 | 9/12 |
| Streptococcus anginosus | 4/6 | 6/6 |

**Table 3: Clinical response microbiology**

| Early clinical response (micro biology) | Test group (n=63) | reference group (n=63) |
|---|---|---|
| MRSA | 20/63 | 15/63 |
| Streptococcus aureus | 28/63 | 30/63 |
| Streptococcus pyogenes | 9/63 | 12/63 |
| Streptococcus anginosus | 6/63 | 6/63 |

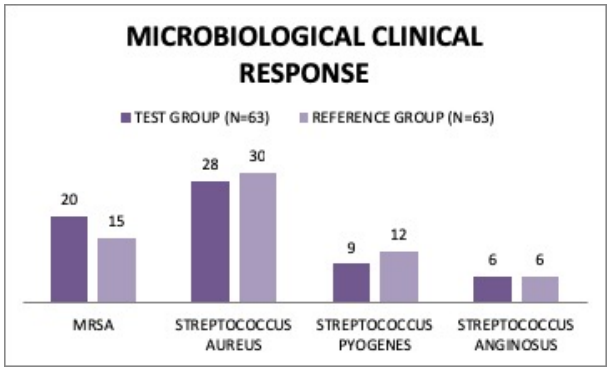


**Figure 4: Early microbiological assessment**

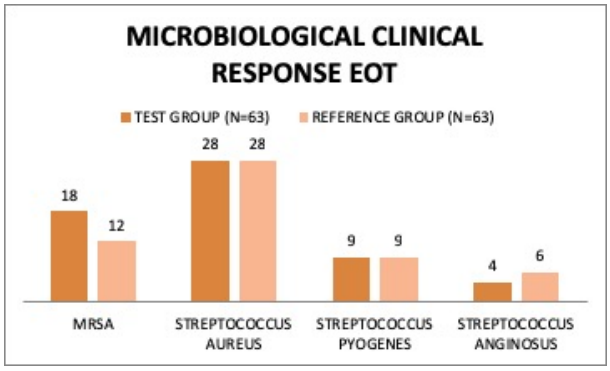


**Figure 5: Clinical Response Eot (Micro Biology)**

**Table 4: Overall clinical response**

| Clinical result | Test group(n=63) | Reference group(n=63) |
|---|---|---|
| Clinical cure | 56 (88.9) | 51 (80.9) |
| Clinical failure | 7 (11.1) | 12 (19.0) |

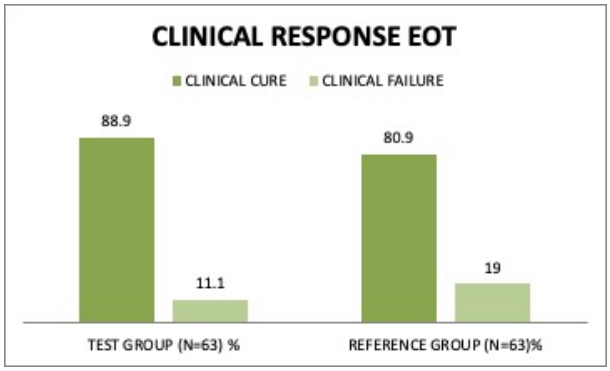


**Figure 6: Overall clinical response**

**Table 5: Adverse events reported**

| Adverse effects reported | Test group(n=63) | Reference group(n=63) |
|---|---|---|
| Decreased appetite | 1 | 2 |
| Dizziness | 11 | 11 |
| Headache | 5 | 10 |
| Insomnia | 1 | 4 |
| Vomiting | 2 | 2 |
| Increased bp | 1 | 4 |
| Fatigue | 3 | 5 |

| | | |
|---|---|---|
| Diarrhea | 3 | 7 |

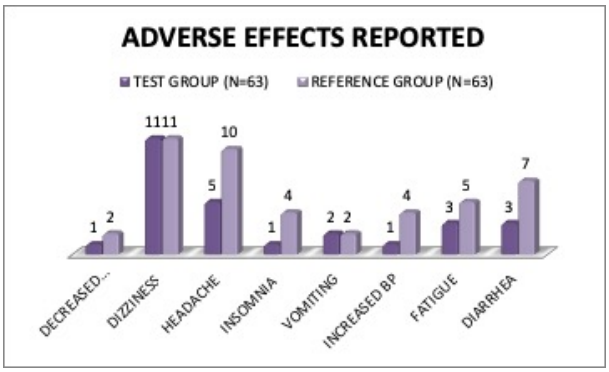


**Figure 7: Adverse events reported**

## DISCUSSION

Total 150 subjects were enrolled in the study with different types of skin infection, with MRSA resistance infections.

All the subjects were explained about the benefits of the study. Subjects were screened according to the inclusive and exclusive criteria of the protocol designed. Out of 150 patients, 24 subjects were withdrawn or dropped out from the study due to lack of interest.

126 subjects were randomized in to two groups, test group and reference group, 63 subjects in each group. The patients were asked to sign the inform consent forms.

Demographic parameters like age, gender were collected from the subjects of both groups in the case repot forms. The microbiology that is presence of MRSA, streptococcus species in blood was also taken into consideration.

Both groups were given the drug treatment for 7 days. On the day zero the ICF was collected from them, on day-1 the drug treatment was given. Subjects were asked to take drug once daily orally.

For the test group the IP was given, for reference group linezolid 400mg was given for 7days. Both groups subjects were asked to take drug for seven days daily once, after 7 days the drug treatment was stopped that is end of treatment. The clinical response was taken from subjects.

Table 1 represents the baseline demographic characters, like age, gender, types of infections which were collected from subjects before the drug treatment there were 20 females and 43 males from the test group and 24 females and 39 males were enrolled in the reference group they are represented graphically in graph no 1, 2 and 3.

There were three types of skin infections reported in the study infected wound 1 subject in test group and 4 from the test group were reported, cellulitis 1 subject and 13 from reference group were reported. Abscess 49 in test group and 46 in reference group. Presented in the graph no 3, there were more patients with abscess infection in both groups.

Table 2 presents the presence of microorganisms in the blood of subjects at baseline, there were MRSA 20 subjects out of 63 in test and 15 from the reference groups, and there were streptococcus auresusann other micro organism in the blood, before treatment, graphically presented in graph no 4.

Table 3 presents the efficacy of the drug, the reduction in the presence of microorganisms in the blood, after the drug treatment. Out of 20 subjects with MRSA resistance 18 subjects showed efficacy in test and 12 out of 15 from reference group, and streptococcousaureus -28 out of 28 responded in the test and 28 out of 30 in the reference group.

Streptococcus pyogenes -9 out of 9 responded in the test group ang 9 out of 12 responded in reference group. Streptococcousanginosus – 4 out of 6 responded and 6 out of 6 responded in the reference group. This is presented graphically in the graph no 5. There was significant response for the test drug.

Table 4 presents the overall clinical response in both groups. Both groups responded to the treatment, the clinical cure for 7 days treatment in test group was 88.9% that is 56 subjects have responded and 51 subjects (80%) in the reference group. There is no much significant response in both groups. Test group showed better efficacy.

The clinical failure rate was 11.1% in the etest group that is 7 subjects, and 19% in the reference group. The reference group had greater clinical failure compared. This is presented in the graph no 6.

Table 5 presents the safety evaluation: there were eight adverse effects reported in both group. Presented in graph no 7. The test group showed greater efficacy and safety than the reference group.

## CONCLUSION

The study was conducted in omni hospital, dilsukhnagar for a period of 6 months in the finished population. The incidence of drug-resistant Gram-positive organisms such as methicillin-resistant Staphylococcus aureus (MRSA) has reached a point where new therapeutic options are urgently needed. The results suggest tedizolid phosphate was found safe and effective than linezolid for a period of 7 days treatment in the treatment of skin infections.

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