To compare the efficacy of topical phenytoin over conventional wound care (5% povidone-iodine) in diabetic ulcer

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Abstract

Background: Diabetic foot ulcers is one of the common complication of diabetes mellitus. It has become a significant health care problem affecting 15%. In this study Phenytoin is used for diabetic foot ulcers comparing its efficacy over conventional dressing.

Methodology: This is a prospective study of 70 patients admitted in JSS hospital, with diagnosis of Diabetic foot ulcer between 2017-2019. They were divided into two group after a detailed clinical examination, and appropriate work up satisfying inclusion and exclusion criteria. One group underwent phenytoin dressing and other group conventional dressing and were assessed on 14th day.

Results: This study observed that group for which Phenytoin dressing was done underwent SSG over conventional dressing.

Conclusion: Wound healing was faster with Phenytoin dressing compared to conventional, hence reducing the duration of hospital stay in turn being cost effective. Thus this method can be implied.

Keywords: Diabetic foot, phenytoin, conventional dressing

1. Introduction

Diabetes is group of metabolic disorder characterised with hyperglycemia. Diabetic foot ulcers is one of the common complication of diabetes mellitus. It has become a significant health care problem by affecting 15% of all diabetics during their lifetime of which 15%-20% can lead to amputation. In India approximately 40,000 legs are amputated every year of which 75% are neuropathic with secondary infection which is potentially preventable. For many decades various technique have been tried like sucralfate dressing, mupirocin dressing, hemocoagulase dressing, oxum solution etc. Despite extensive effort to improve wound healing, the outcome of existing method are far from optimal. One such agent that has been tried in wound healing is Phenytoin. It was introduced in 1937 for effective control of convulsive disorder. A common side effect with phenytoin is development of fibrous overgrowth of gingiva. This apparent stimulatory effect of phenytoin on connective tissue suggest an existing possibility for its use in wound healing.

2. Method

This is a prospective comparative study conducted on 70 patients admitted in JSS hospital between 2017-2019 with the diagnosis of diabetic foot ulcers after taking the consent. They were randomly allocated into two groups and one group underwent Topical Phenytoin dressing and the other group underwent conventional dressing after taking thorough history, general physical, local and loco regional examination. Baseline blood investigation, Doppler, x ray was taken, diabetic status was evaluated and treated. Pus culture sensitivity was done on admission, 7th day and 14th day. Wound size was measured using surgical gauze-measuring tape using Walker’s Formula and progress evaluation was done in terms of slough, discharge and appearance of granulation tissue at the end of 14th day.

2.1 Inclusion criteria

Patient aged >18yrs
Duration of ulcer >2 weeks
Wound surface area <10cm²
In patients in JSS hospital

2.2 Exclusion criteria
Non healing ulcers of other etiologies like varicose vein, arterial disease, burns.
Grade 3, 4, 5 of Wagner’s classification
Renal failure
Generalised debility
Anaemia

2.3 Data analysis
The study population was divided into two groups by random method. Group A underwent phenytoin dressing and Group B underwent conventional dressing i.e; 5% povidone iodine daily. Wound contracture is measured using Walker’s formula.
Topical phenytoin dressing was done by giving normal saline wash followed by placing sterile gauze soaked in phenytoin suspension (phenytoin dissolved in 5ml NS).
Dosage used
0 to 5cm²-100mg, 5.1 to 9cm²-150mg, 9.1 to 15cm²-200mg.
Conventional dressing is done with 5% povidone iodine solution and hydrogen peroxide wash followed by povidone iodine dressing.
Efficacy of phenytoin over conventional dressing were studied using statistical methods.
Progress evaluation was done in terms of appearance of granulation tissue, reduction of slough, discharge and wound contracture.
Statistical method that was used were:
1. Phi
2. Cramer’s v
3. Mean
4. Standard deviation
5. Standard error mean
6. P value of <0.05

3. Result
3.1 Age and gender distribution

Table 1: Comparing the age distribution in each group

| Group      | N   | Mean   | Std. deviation | Std. error mean |
|------------|-----|--------|----------------|-----------------|
| Age        |     |        |                |                 |
| Conventional | 35  | 56.8571| 11.74519       | 1.98530         |
| Phenytoin  | 35  | 58.6286| 10.88465       | 1.83984         |

Mean age in each group is comparable
Mean age in conventional group is 56.8671 yrs
Mean age in Phenytoin group is 58.6286yrs
The difference in mean age is statistically insignificant

Table 2: Statistics of the gender in each group

| “Symmetric Measures” | Value | Approx. Sig. |
|----------------------|-------|--------------|
| Nominal by Nominal   | Phi   | .174         |
|                      | Cramer’s V | .174         |
| N of Valid Cases     | 70    |              |

“a. Not assuming the null hypothesis”
“b. Using the asymptotic standard error assuming the null hypothesis”

In this study though it is male predominant, the male female ratio in each group is comparable and is statistically insignificant with p=0.14

3.2 Microbiological consideration

The most common organism isolated in pus culture growth was Staphylococcus >E. Coli >pseudomonas, which were not seen in repeat pus culture in patient who underwent Phenytoin dressing.

3.3 Progress evaluation in terms of slough, discharge and granulation Slough

Fig 1: Pie chart of organisms in pus culture taken from wound
### Table 3: Comparing the progress evaluation in terms of reduction of slough

| Groups        | Progress_Evaluation_Slough | 1Day | 14 Day | Total |
|---------------|---------------------------|------|--------|-------|
| Conventional  | Yes                        | 35   | 14     | 70    |
|               | % within Session          | 100.0% | 40.0% | 66.7% |
|               | Count                     | 35   | 35     | 105   |
|               | No                        | 0    | 21     | 35    |
|               | % within Session          | 0.0% | 60.0%  | 33.3% |
|               | Count                     | 35   | 35     | 105   |
| Phenytoin     | Yes                        | 32   | 3      | 38    |
|               | % within Session          | 91.4% | 8.6%  | 36.2% |
|               | Count                     | 32   | 32     | 67    |
|               | No                        | 3    | 32     | 66    |
|               | % within Session          | 8.6% | 91.4%  | 63.8% |
|               | Count                     | 35   | 35     | 105   |

### Table 4: Statistics of reduction of slough in each group

#### “Symmetric Measures”

| GRPS          | Value  | Approx. Sig. |
|---------------|--------|--------------|
| Conventional  |        |              |
| Nominal by Nominal | Phi | 0.529 | .000 |
|                | Cramer's V | 0.529 | .000 |
| N of Valid Cases | 105 |        |
| Phenytoin     |        |              |
| Nominal by Nominal | Phi | 0.813 | .000 |
|                | Cramer's V | 0.813 | .000 |
| N of Valid Cases | 105 |        |

*a. Not assuming the null hypothesis*.  
*b. Using the asymptotic standard error assuming the null hypothesis*.

### Discharge

### Table 5: Comparing the progress evaluation in terms of reduction in discharge

| Groups        | Day_1__Discharge | 1Day | 14 Day | Total |
|---------------|------------------|------|--------|-------|
| Conventional  | Yes              | 35   | 32     | 102   |
|               | % within Session | 100.0% | 91.4% | 97.1% |
|               | Count            | 35   | 35     | 105   |
|               | No               | 0    | 3      | 3     |
|               | % within Session | 0.0% | 8.6%  | 2.9%  |
|               | Count            | 35   | 35     | 105   |
| Phenytoin     | Yes              | 35   | 34     | 104   |
|               | % within Session | 100.0% | 97.1% | 99.0% |
|               | Count            | 35   | 34     | 104   |
|               | No               | 0    | 1      | 1     |
|               | % within Session | 0.0% | 2.9%  | 1.0%  |
|               | Count            | 35   | 35     | 105   |

### Table 6: Statistics of reduction of discharge in each group

#### “Symmetric Measures”

| GRPS          | Value  | Approx. Sig. |
|---------------|--------|--------------|
| Conventional  |        |              |
| Nominal by Nominal | Phi | .243 | .046 |
|                | Cramer's V | .243 | .046 |
| N of Valid Cases | 105 |        |
| Phenytoin     |        |              |
| Nominal by Nominal | Phi | .139 | .364 |
|                | Cramer's V | .139 | .364 |
| N of Valid Cases | 105 |        |

*a. Not assuming the null hypothesis*.  
*b. Using the asymptotic standard error assuming the null hypothesis*.

### Granulation

### Table 7: Comparing the progress evaluation in terms of granulation tissue appearance

| Groups        | Day_1_Granulation | 1Day | 14 Day | Total |
|---------------|-------------------|------|--------|-------|
| Conventional  | Yes               | 0    | 26     | 39    |
|               | % within Session  | 0.0% | 74.3%  | 37.1% |
|               | Count             | 35   | 9      | 66    |
|               | No                | 35   | 35     | 105   |
|               | % within Session  | 100.0% | 25.7% | 62.9% |
|               | Count             | 35   | 35     | 105   |
Table 8: Statistics of appearance of granulation tissue in each group

| GRPS         | Value | Approx. Sig. |
|--------------|-------|--------------|
| Conventional | Phi   | .628         |
|              | Cramer's V | .000       |
| N of Valid Cases | 105   |              |
| Phenyoitn    | Phi   | .727         |
|              | Cramer's V | .000       |
| N of Valid Cases | 105   |              |

"a. Not assuming the null hypothesis".
"b. Using the asymptotic standard error assuming the null hypothesis".

Progress evaluation of wounds in each group was compared in terms of reduction of slough, discharge and time taken for appearance of granulation tissue and when both the groups were compared, Phenytoin was found to be more efficacious in each parameter and was statistically significant with p value of 0.0001.

3.4 Reduction in area

Table 9: Comparing the area of the wound on day 1 and 7

| Group            | N  | Mean   | Std. deviation | Std. error mean |
|------------------|----|--------|----------------|-----------------|
| Ulcer_Area_Day_1 |    |        |                |                 |
| Conventional     | 35 | 28.9771| 24.09505       | 4.07281         |
| Phenyoitn        | 35 | 28.7714| 24.84669       | 4.19986         |
| Ulcer_Area_Day_7 |    |        |                |                 |
| Conventional     | 35 | 27.5911| 23.46914       | 3.96701         |
| Phenyoitn        | 35 | 20.7549| 19.91622       | 3.36646         |
| Difference_Week_1|    |        |                |                 |
| Conventional     | 35 | 1.3860 | 1.95978        | .33126          |
| Phenyoitn        | 35 | 8.0166 | 5.17724        | .87511          |
| Percent_area_Day_7|   |        |                |                 |
| Conventional     | 35 | 93.8734| 8.89887        | 1.50418         |
| Phenyoitn        | 35 | 64.4932| 10.94864       | 1.85066         |

Table 10: Statistics of reduction in wound area on day 1 and 7

“Independent Samples Test”

| Group            | N  | Mean   | Std. deviation | Std. error difference |
|------------------|----|--------|----------------|-----------------------|
| Ulcer_Area_Day_1 | 68 | .035   | .972           | .20571                |
| Ulcer_Area_Day_7 | 68 | 1.314  | .193           | 6.83629               |
| Difference_Week_1| 68 | -7.086 | .000           | -6.63057              |
| Percent_area_Day_7| 68 | 12.320 | .000           | 29.38019              |

T-Test

Table 11: Comparing the wound contracture on day 14

“Group Statistics”

| Group            | N  | Mean   | Std. deviation | Std. error mean |
|------------------|----|--------|----------------|-----------------|
| Ulcer_Area_Day_14|    |        |                |                 |
| Conventional     | 35 | 25.1017| 22.13608       | 3.74168         |
| Phenyoitn        | 35 | 13.9083| 14.11358       | 2.38563         |
| Difference_Week_2|    |        |                |                 |
| Conventional     | 35 | 2.4666 | 2.15928        | .36499          |
| Phenyoitn        | 35 | 6.8466 | 5.86349        | .99111          |
| Percent_area_Day_14|   |        |                |                 |
| Conventional     | 35 | 83.0784| 13.09719       | 2.21383         |
| Phenyoitn        | 35 | 40.7781| 10.43439       | 1.76373         |
| Area_Reduction   |    |        |                |                 |
| Conventional     | 35 | 3.8754 | 3.37199        | 56997           |
| Phenyoitn        | 35 | 14.8631| 10.93201       | 1.84785         |
Table 12: Statistics of wound contracture on day 14

|                          | t  | df | Sig. (2-tailed) | Mean difference | Std. error difference |
|--------------------------|----|----|-----------------|-----------------|-----------------------|
| Ulcer_Area_Day_14        | 2.522 | 68 | .014            | 11.19343        | 4.43750               |
| Difference_Week_2        | -4.147 | 68 | .000            | -4.38000        | 1.05618               |
| Percent_area_Day_14      | 14.944 | 68 | .000            | 42.30037        | 2.83051               |
| Area_Reduction           | -5.682 | 68 | .000            | -10.98771       | 1.93375               |

Wound contracture is one of the most important parameters in determining the efficacy of phenytoin over conventional dressing. In this study, the area of reduction in phenytoin is better than conventional dressing by the end of 14th day, and it is also statistically significant with p value of < 0.0001.

3.5 Duration of stay and average number of dressings

Table 13: Comparing the percentage of wound contracture and duration of hospital stay

|                          | Group   | N  | Mean   | Std. deviation | Std. error mean |
|--------------------------|---------|----|--------|----------------|-----------------|
| Percentage_Reduction     | Conventional | 35 | 17.1359 | 12.99742       | 2.19696         |
|                          | Phenytoin | 35 | 59.2219 | 10.43439       | 1.76373         |
| Number_of_days_to_end_point | Conventional | 35 | 53.7143 | 31.60749       | 5.34264         |
|                          | Phenytoin | 35 | 26.5714 | 13.81663       | 2.33544         |
| No_of_dressings          | Conventional | 35 | 26.9143 | 15.81766       | 2.67367         |
|                          | Phenytoin | 35 | 13.5714 | 6.78357        | 1.14663         |
In this study the duration of stay in hospital is significantly lesser in phenytoin dressing over conventional dressing and also the number of dressings is also lesser in case of phenytoin dressing, hence indirectly being cost effective for the patient. It is also statistically significant with p value of <0.0001.

4. Discussion

“Wound healing is a mechanism whereby the body attempts to restore the integrity of the injured part”. There are lot of factors that influence wound healing like site, structure, mechanism of wounding, contamination, loss of tissue, vascular insufficiency, malnutrition, immune deficiencies etc. Normal wound healing occurs in three phases, they are: 1. “The inflammatory phase 2. The proliferative phase 3. The remodelling phase”.

These acute wounds are managed with “cleansing, exploration and diagnosis, debridement, repair of structures, replacement of loss of tissue, skin cover/closure”. These wound healing is of important concern to surgeons and there are various method incorporated, but there is not a single method that is ideal. Phenytoin is one such agent which improves the wound healing. Phenytoin— it was synthesized by German Chemist Heinrich Biltz in 1908. The usefulness of this in controlling of seizures was discovered by H. Houston Meritt and Tracy Putnam One of the side effect of phenytoin is hyperplasia of gum which prompted its assessment in wound healing.

The mechanism of wound healing with phenytoin is multifactorial. They are formation of granulation tissue, reducing the slough, bacterial load/reducing the wound size. “In a study by Vijaya Patil, Rashmi Patil; phenytoin has been proved to be useful topical agent in promoting wound healing and control of infection in diabetic ulcers, study was conducted on 100 patients and results were—significant reduction of discharge and slough in wound by 14days in phenytoin group and 21days in control group, mean duration of stay in hospital was 20days in phenytoin group and 26days in control group”.

“A study conducted by Leo F Tauro in 2013, total of 200 patients were taken, 100 patients underwent phenytoin dressing, 100 patients were subjected to conventional dressing, at the end of 14days wounds were inspected, the mean rate of granulation tissue formation in study group was 87+7.33% and control group was 74.64+8.04%, mean hospital stay was 36.26+2.64(SD) in study group and 40.97+3.31(SD) in control group and bacterial load was reduced(negative culture sensitivity) in 70% of study group and 54% of control group. The results were analysed by unpaired students ‘t’ test which showed highly significant (p<0.0001) difference”. In this study the phenytoin hastens the wound healing by increasing the granulation tissue, decreasing the slough/bacterial load/area of the wound which is statistically significant.

5. Conclusion

According to this study, Topical phenytoin significantly hasten the wound healing by formation of granulation tissue, reducing the slough, Discharge from wound, bacterial load/reducing the wound size. Phenytoin dressing efficacy over conventional dressing in terms of requirement of dressing is less. The duration of stay in hospital is decreased, hence being cost effective for the patient. Now a days where time is essence, the patient can resume to their daily activities early with phenytoin dressing.

6. References

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