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Effect of Taurolidine on Thickness of SCAR Tissue in Rabbits

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Abstract: The effect of taurolidine on wound healing and thickness of scar tissue in rabbits was investigated and compared to commonly used povidone iodine and sodium chloride. Taurolidine applied wounds showed less adherence and a lesser degree exudate. The contraction in taurolidine gauze-applied wounds to was more apparent than other groups. The granulation tissues on all wounds appeared within postoperative days 3-5. The epithelization on all wound boundaries was seen within postoperative days 5-7. The epithelization on taurolidine applied wounds was completed on postoperative day 12. In conclusion, 2% taurolidine has positive effect on the healing of full thickness skin wounds. It also reduced the thickness of scar tissues and may be alternative to the conventional treatments in rabbit model.

Key words: Rabbit, scar tissue, taurolidine

INTRODUCTION

Despite the use of antibiotics and modern sterile technique, infection is the major factor. Proper healing can not occur if infection is present (Goldenheim, 1993). Clinicians has used numerous strategies to combat wound infections, including topical and systemic administration of antibiotics and various antiseptic agents (Willatts *et al*., 1995). The ideal result is rapid regeneration, leading to the perfect restoration of form and function (Selcukbiricik *et al*., 2004) that may result in certain undesirable complications including keloid formations, a poor final cosmetic appearance and the formation of fragile epithelial layer (Kilic *et al*., 2002). Scars arise after almost every deep dermal injury. Scars are regarded as the outcome of prolonged inflammation, which causes excessive proliferation of fibroblast and overproduction of collagen (Chen *et al*., 2005).

The antiseptic agent taurolidine is a derivative of taurinamid which is a naturally occurring aminosulphonic acid and formaldehyde. Taurolidine has an expectionally broad spectrum of antimicrobial activity including activity againts Gram-negative and Gram-positive bacteria and fungi. Taurolidine has also antiendotoxic and antiadherent properties. Emergence of bacterial resistance to taurolidine has not been demonstrated. Taurolidine has been shown to be nontoxic to human and animals (Koldehoff, 2004). Clinically, intraperitoneal taurolidine has been used for the treatment of diffuse peritonitis, either as mono-therapy or in combination with systemic antibiotics and there have not been observed acute or chronic toxic effects on hematological and biochemical parameters (Ribizzi *et al*., 2001).

The purpose of this study was to compare thickness of scar tissue and features of wound healing clinically and histologically in rabbits treated with taurolidine, povidone iodine and sodium chloride.

MATERIALS AND METHODS

The study was performed according to the Helsinki convention for the use and care of animals. All rabbits [6 male and 6 female rabbits (mean weight: 2300±300 g)] were anesthetized with intramuscular administration of xylazine hydrochloride 10 mg kg^{-1} (Rompun, Bayer, Turkey) and ketamine hydrochloride 50 mg kg^{-1} (Ketanes, Alke, Turkey).

Right and left costal regions of rabbits were clipped and the skin was prepared for aseptic surgery. Then full-thickness skin wounds were created using a template prepared from on x-ray film on each animal 2 cranial and 1 caudally located (3 cm in diameter). Two percent Taurolidine solution (Taurolin, Saba, Turkey), 10% povidone iodine solution (Biokadin, Biokan, Turkey) 0.9% sodium chloride solution (İzotonik Sodyum Klorür, İ.E. Ulagay, Turkey) with gauze satured was applied to the defects occurred experimentally. The wounds were then covered with sterile gauze and stabilized with a

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bandage. The dressing was changed every day until wound healing completed. During the postoperative period, all rabbits were checked daily for general health condition, bandage slippage and other unspecified abnormalities.

Skin samples at the wounded sites for histopathologic examination were collected from the same animal on postoperative days 4, 8, 12 and 16. For standardization, samples which were taken from different sites of the wound were fixed in 10% formalin. After fixation, the tissues were placed into ototechnician for routine tissue processing. They were embedded in paraffin blocks cut into 4 μm thickness slices and stained with Hemotoxylin-Eosin for routine light microscophic evaluation. The tissues were evaluated according to several histopathologic parameters, such as the thickness of scar tissues, the density of vascular proliferation, the degree of inflammatory cell infiltration. The density of vascular proliferation and the degree of inflammatory cell infiltration were scored as follows: 0 = normal, 1 = light increase, 2 = mild increase and 3 = marked increase. At 40x magnification field localization of 3-10, 11-30, or > 30 cells in the wounded tissue was considered as a light, mild or marked increase, respectively.

Statistical analyses were performed by using statistical analysis system configured for computer (SPSS, Relase 11.0, SPSS. Inc). The thickness of scar tissue were evaluated using variance analysis and Tukey test. Non parametric values (the density of vascular proliferation, the degree of inflammatory cell infiltration) were analysed by Kruskal Wallis and Mann-Whitney U test.

RESULTS AND DISCUSSION

All rabbits survived until the end of study with no sign of pain or discomfort. All wounds surface were covered by a thin gelatinous exudate on postoperative day 4 (POD 4). The clinical examination showed that the wounds treated with 0.9% sodium chloride and 10% povidon iodine appeared to have marked fibrinous exudate and crust formation which caused adherence to the gauze. Therefore, they required greater tearing force for removal of the dressing. On the other hand, 2% taurolidine gauze-applied wounds showed less adherence and a lesser degree exudate. The expansion process (to POD 4) was followed by the contraction process (to PODs 6-8). The contraction in 2% taurolidine gauze-applied wounds (to POD 12) became more apparent than other wounds. The granulation tissues on all wounds were appeared within PODs 3-5. The epithelization in all wound boundaries was observed on PODs 5-7. So, the epithelization in 2% taurolidine and 10% povidone iodine gauze-applied wounds were completed on PODs 12-14 and 16-17, respectively. But 0.9% sodium chloride gauze-applied wounds wasn't completed on POD 16 and ulceration in central wounds continued to PODs 18-20. Current study suggests that daily applied 2% taurolidine reduced the thickness of scar tissues when compared to other 2 antiseptics. Regarding the thickness of scar tissue, statistically significant difference ($p<0.05$) was found on PODs 4, 8 and 16 (Table 1).

Density of vascular proliferation and the degree of inflammatory cell infiltration were similar in all groups during post operative period ($p>0.05$).

Some authors (Norman, 2003; Yavuzer *et al*., 1997) do not recommend iodine application in patients with extensive lesions or a known allergy to iodine and additionally warn us using it cautiously on pregnant women, children, diabetics and patients with known thyroid disordes or compromised renal function, as well as in patient receiving lithium therapy, although it is reported that the impairment of epithelization in addition to increased vascularization in wounds treated with povidone iodine (Kjolseth *et al*., 1994). In the current study, duration of epithelization in povidone iodine group was longer than that of taurolidine group.

The degree of attachment between a dressing material and the wound surface is important (Kilic *et al*., 2002). The subjective examination showed that the 2% taurolidine conformed well to the wound surface and it was easily separable from underlying wound and had a positive effect on the wound healing. Povidone iodine and sodium chloride solution adhered strongly to the wound surfaces and required an extra force to separate adherence. This force could cause epithelial damage and thus may delay the healing. Lineaweaver *et al*. (1985) identified 0.05% as a safe concentration of povidone-iodine for fibroblasts; higher concentrations (including the 10% concentration that is commonly used in clinical practice) were 100% cytotoxic. However, Brennan and Leaper (1985) reported that, saline and 1% povidone iodine had "little or no effect" on microcirculation in

Table 1: The thickness of scar tissue in the groups (μM) (mean±S.D)

Groups	Day 4	Day 8	Day 12	Day 16
Taurolidine (2%)	748.33±49.89*	941.66±49.89*	1051.66±46.29	1068.33±43.92*
Povidone Iodine (10%)	1048.33±47.35*	1248.33±52.68*	1185.83±73.28	1565.83±78.59*
Sodium Chloride (0.9%)	996.66±56.25*	1105.83±13.44*	1394.33±20.28	1701.66±55.23*

Statistical significant*($p<0.05$) (n = 12)

wounds. But, Kjolseth *et al.* (1994) reported the impairment of epithelization in addition to increased vascularization in wounds treated with povidone iodine.

The proven treatment methods for pathological scars, including intra lesional injection of steroids, radiation therapy and surgical resection, only show some limited benefits in reducing scarring. So, a simple, feasible and acceptable method to prevent scarring is required in clinics (Chen *et al.*, 2005). In the current research, the most reducement in the scar tissue of skin wounds was observed in 2% taurolidine group.

CONCLUSION

Daily applied taurolidine reduced the thickness of scar tissues when compared to other two antiseptics. In conclusion, application of taurolidine is more effective than other solutions in the healing of full thickness skin wounds in rabbits.

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