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EFFECT OF NIFEDIPINE AND AMLODIPINE ON WOUND HEALING IN RATS

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Abstract : The wound healing effect of two calcium channel blockers, nifedipine and amlodipine was studied in rats using incision and excision wound models. In incision wound, two straight paravertebral skin thickness incision were made and on tenth day skin tensile strength was measured by using continuous water flow technique. In excision wound, circular piece of skin excised in its full thickness and wound contraction monitored by alternate day wound tracing and epithelisation period was monitored by noting the number of days required for escher to fall. Drugs enhanced the skin tensile strength in incision wound model. In excision wound model, wound contraction is increased on 4th and 16th day but epithlisation period was not significantly altered. In conclusion, calcium channel blockers can be used to enhance wound healing, especially if wound healing was suppressed by steroids.

Key words : calcium channel blockers, nifedipine, wound healing, amlodipine

INTRODUCTION

Calcium channel blockers (CCBs) have been used extensively in various cardiovascular conditions and they may have a role in non-cardiac conditions too (1). There are reports that cellular calcium metabolism appears to regulate extra cellular matrix and collagen production as well as wound healing (2, 3). It has been reported that antioxidants (Vitamins A and E, Trolox) have enhanced wound healing (4). Nifedipine and amlodipine by acting on voltage gated Ca^{2+} channels alter the intracellular calcium and also have antioxidant activity in invitro study (5). Hence the present study was taken up to assess the effect of two CCBs, mainly nifedipine and amlodipine, on normal and steroid depressed wound healing, using incision and excision wound models in rats.

METHODS

Animals : Healthy Wistar rats of either sex, bred in the department of

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Pharmacology, Kasturaba Medical College, Manipal and weighing around 150–250 g were used. They were housed individually, fed animal chow and water ad libitum. Ethical clearance was taken from Kasturba Medical College Ethical Committee.

Wound models:

All wounding procedures were carried out under light ether anesthesia. In present study no animal have shown signs of infection in all the groups.

i) **Incision wound:** On the depilated backs of the animals, two para vertebral incisions of 6 cm length were made cutting through the full thickness of the skin. Interrupted sutures, 1 cm apart, were placed to approximate the cut edges of skin (6). The sutures were removed on the 7th post-wounding day and skin tensile strength was measured on the 10th day by continuous water flow technique of Lee 1968 (7).

ii) **Excision wound:** One excision wound was inflicted by cutting away 500 mm^2 full thickness of a pre-determined area on the depilated back of each rat. Epithelisation period was noted as the number of days after wounding required for the eschar to fall off leaving no raw wound behind. Wound contraction rate was monitored by planimetric measurement of the wound area every alternate day. This was achieved by tracing the wound on a graph paper. Reduction in the wound area was expressed as percentage of the original wound size (8).

Treatment schedule

The animals were divided into 2 sets of 6 groups (n = 8). Six groups for incision model and six groups for excision model used separately. Group I, group II, group III, group IV, group V and group VI were administered 0.5 ml of normal saline, nifedipine (2 mg/kg), amlodipine (1 mg/kg), dexamethasone (0.17 mg/kg), nifedipine (2 mg/kg) + dexamethasone (0.17 mg/kg) and amlodipine (1 mg/kg) + dexamethasone, (0.17 mg/kg), respectively. All drugs were administered per orally except dexamethasone, which was given intramuscularly.

In incision wound model, all the drugs except dexamethasone were given from 0 day to 9th day in the above mentioned dosage. Dexamethasone was given in the dose of 0.37 mg/kg on 0 day and 0.17 mg/kg from days 1 to 9. In excision wound model, the same regime was followed but for a period of time till the wound was completely healed (about 21 days).

Statistical analysis

Statistical analysis was done using one way analysis of variance (ANOVA) followed by Scheffi's test using SPSS package and student's 't' test wherever required.

RESULTS

Incision wound: Animals treated with nifedipine (406 ± 16 g) and amlodipine

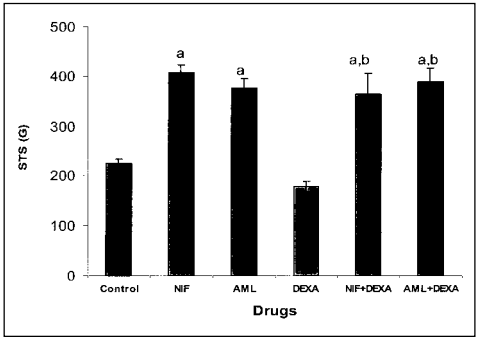

Fig. 1 : Effect of drugs on skin tensile strength (STS) of ten days old incisional wound.

(375 ± 20 g) showed significantly higher skin tensile strength as compared to controls (225 ± 8 g). Nifedipine had a slightly better action than amlodipine (Fig. 1). Dexamethasone (178 ± 10 g) treated animals showed very poor tensile strength when compared to controls (255 ± 8 g). However, when the steroid was administered along with the CCBs, this healing suppressant action was overcome. The action of amlodipine (387 ± 29 g) was better than nifedipine (364 ± 40 g) in overcoming the steroid suppressant effect although not significant statistically.

Excision wound: There was no significant change in the epithelisation period between the control and drug treated groups (Table I). Upon treatment with dexamethasone, epithelisation period was prolonged to almost 34 days (control 20–21 days). When dexamethasone was administered along with the CCBs, epithelisation was faster but could not be brought to the normal control values (Control – 20 days; CCBs – about 20 days, dexamethasone – 34 days, dexamethasone + CCBs – About 24–26 days). Both the drugs enhanced the rate of wound contraction, especially between days 4 and 16. Initially, the action of amlodipine was more effective, but from day 8, both the drugs seemed to have comparable action. They were also able to overcome the steroid suppressant action of dexamethasone but only up to about 75% of the control values.

TABLE I: Effect of drugs on wound contraction and epithelisation period in excision wound.

Drugs	*Wound contraction (%) Mean ± SE Day*				*Epithelisation period (days) Mean ± SE*
	4th	*8th*	*12th*	*16th*	
Control	16.2±1.4	36.7±1.7	78.2±1.9	91.2±1.3	20.5±0.4
Nifedipine (NIF)	28.2±5.2	55.8±4.2	86±3.3	96.1±1.3	19±1.8
Amlodipine (AML)	30.6±5.2	55.9±3.5	81.2±1.6	95.8±1.9	18.8±0.5
Dexamethasone (DEXA)	–17.9±10	0.5±10.5	28±9.1[a]	55.5±8.3[a]	33.6±1[a]
NIF + DEXA	–14.3±12	1.9±22	54.8±11	78.3±3.7	24.6±0.8[b]
AML + DEXA	–11±8.2	6.8±12	43.5±6.8	72.1±2.9	26.3±0.4[b]

n = 9
[a]P<0.05 vs Control
[b]P<0.05 vs Dexamethasone

DISCUSSION

The use of chemotherapeutic agents as adjutants to surgical therapy is common. Many protocols call for their use in perioperative period or post operatively before completion of scar maturation. It is thus reasonable to question whether or not such agents have an effect on the healing wound. Nifedipine and amlodipine belong to the dihydropyridine group of calcium channel blockers; commonly used in hypertensive patients, Nifedipine has been reported to reverse adriamycin-induced injury on wound healing (3). From the present study, it was observed that both the CCBs increased skin tensile strength, enhanced wound contraction rate and could also partially reverse steroid suppressed healing. CCBs are known to cause vasodilatation, which increases blood supply to wounded region. Hence these CCBs could be used safely in patients undergoing surgery since they do not adversely affect healing. This prohealing action could be utilized favorably, especially if the patient is on some known suppressor of wound healing like corticosterroid and antimalignant agents (9).

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