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Original Research Article

To Compare the Efficacy of Nitric Oxide Dressing and Standard Dressing in Diabetic Foot Ulcers in A Tertiary Care Centre

[1]Dr. Alagappan P. R., [2]Dr. Ganapathy Raman Nitish Dayanand, [3]Dr. Vimal Kumar Govindhan.

[1]Assistant Professor, Department of General and GI Surgery, PSG Institute of Medical Sciences and Research, Coimbatore, Tamil Nadu, India.

[2]Senior Resident, Department of General Surgery, Chettinad Hospitals and Research Institute, Kelambakkam, Chennai, Tamil Nadu, India.

[3]Professor, Department of General and GI surgery, PSG Institute of Medical Sciences and Research, Coimbatore, Tamil Nadu, India.

Corresponding Author

Dr. Ganapathy Raman Nitish Dayanand, Senior Resident, Department of General Surgery, Chettinad Hospitals and Research Institute, Kelambakkam, Chennai, Tamil Nadu, India.

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ABSTRACT

BACKGROUND

This Study was conducted and all patients were admitted with Diabetic foot ulcer and was about 40 patients and were Randomized into two groups of 20 each. Subjects of one group received treatment with Nitric oxide dressings, which was revised every alternative day and was observed for a period of three weeks. Subjects of other group received treatment with standard saline dressing and their healing outcome was also observed for a period of three weeks. Wound healing was assessed using Wound assessment tool (Bates - Jensen wound assessment tool) scoring from 1 - 65. Serum levels MMP-9 levels were measured in each group before and after dressing. Efficacy of Nitric oxide dressing over standard saline dressing was recorded.

METHODS

This was a hospital-based Interventional Study, Randomized (Comparative Study) group conducted among 40 patients diagnosed with diabetic foot ulcer at the Department of General Surgery, PSG Hospitals, Peelamedu, Coimbatore, India, and the duration period was from January 2021 to December 2022 after obtaining clearance from the institutional ethics committee and written informed consent from the study participants.

RESULTS

When the results of the study were analysed, it became clear that participants who received nitric oxide dressings fared better in terms of healing than those who received regular saline dressings. According to our findings, diabetic ulcers treated with nitric oxide had significantly less ulcer area

ISSN: 0975-3583, 0976-2833 VOL 15, ISSUE 03, 2024

than ulcers treated with saline after 3 weeks. While the control group exhibited a reduction of 50.5%, the group that had nitric oxide dressing showed a reduction of 66.9% (p value<0.05)

CONCLUSION

The study summarizes that chronic diabetic foot ulcers lack nitric oxide which impairs wound healing. Administration of exogenous nitric oxide facilitated angiogenesis and vasodilation, thereby promoting would healing. Nitric oxide dressings increase the area of wound healing and showed reduced levels of serum MMP levels when compared to standard saline dressings. Hence, nitric oxide dressing which is cost effective and also reduces the frequency of dressings can be used in regular clinical practice for the management of diabetic foot ulcer.

KEYWORDS

Nitric oxide, Diabetic foot Ulcers, Saline.

INTRODUCTION

Diabetes is one of the most important general population problems due to its high prevalence and extensive social and economic consequences. Diabetic foot ulcers are one of the chronic complications of diabetes and the leading cause of non-traumatic lower limb amputation. Approximately15% of the diabetic population will develop ulcers during their lifetime.

Ulcer usually result due to poor glycemic control, underlying neuropathy, peripheral vascular disease, or poor foot care. It is one of the most common cause for osteomyelitis of the foot and amputation of lower extremities. These ulcers commonly appear in the areas of the foot which undergoes repetitive trauma and pressure sensations.[1]

The disease is typically chronic and an inter-professional approach yields the best results. The collaborative involvement of podiatrists, endocrinologists, general practitioners, vascular surgeons, and infectious disease specialists is highly beneficial.

Several factors contribute to the failure of the healing process, including:-

1. Absence or inadequate secretion of growth factors leading to microbial colonization,
2. Reduced or absent angiogenic activity,
3. Lack of oxygen supply, and reduced release of nitric oxide (NO).[2]

Another major cause for the diminished wound healing process in diabetic patients is related to weakened angiogenesis. Hyperglycemia normally impairs the functional activity of endothelial nitric oxide synthase (eNOS), resulting in the release and reduction of reduced amounts of NO, affecting angiogenic processes.[3]

In diabetes mellitus, the pro-inflammatory phenotype of macrophages is altered/converted to a pro-repair phenotype[4] and thus resulting in decrease of angiogenesis-related mRNA and resulting in negligible amount of especially vascular endothelial growth factor (VEGF) which promotes angiogenesis and wound healing process.[5]

Usually, the healing of acute wounds occurs about in thirty days from the event of injury to complete closure whereas most of the chronic wounds remain to be obstructed and fail to recover indefinitely.[6]

Epidermal or dermal wounds less than 1 cm in area heal faster because the skin has enough potential to replace the damaged tissue.[7]

Nevertheless, deep damage to the dermis and subcutaneous areas of the skin slows skin recovery and requires replacement of skin patches to speed up the regeneration process.[8,9]

ISSN: 0975-3583, 0976-2833 VOL 15, ISSUE 03, 2024

The significance of NO has long been recognized due to its broad efficacy in various biomedical fields.[10,11]

Delivery of endogenous NO donors can enhance wound healing through multiple benefits such as antibacterial potency, vasodilation, anti-inflammatory activity .[12] Moreover systemic supplementation of NO donor improves collagen deposition at the wound site without interfering with the matrix metalloproteinase pathway.[12]

Thus this study will compare the efficacy of Nitric oxide dressing with saline dressing in diabetic patients having foot ulcers.

Aim

- To compare the efficacy of Nitric oxide dressings and standard dressing in diabetic foot ulcers in a tertiary care centre

Objectives

- To study the efficacy of Nitric oxide dressing on diabetic foot ulcers
- To compare outcomes of diabetic foot ulcer between nitric oxide dressings and moist gauze dressings

MATERIALS AND METHODS

The study was conducted in the PSG Hospital in the Department of General Surgery. Patients was randomized into two groups of 20 patients each. While one group treated with the Nitric oxide generating dressing and other group continue to receive standard care (saline dressings). The efficacy and the tolerability of the dressing will be measured. The Nitric Oxide dressing will be changed at least every 2-3 days and the standard care changed as in normal clinical practice. At weekly clinical visits, the diameter and area of the wound will be measured until healed or 4 weeks of treatment is reached. Wound assessment scoring chart was done for better evaluation. Photographical evidence will be created during change of each dressing to measure the outcomes.

Inclusion Criteria

- Male or female patients aged over 18 years.
- Diagnosed with diabetic foot ulcer.
- With a full-thickness foot ulcer (on or below the malleoli) with a cross sectional area between 25 and 2500 sq.mm
- Able to read and understand the Volunteer Information Sheet and to provide meaningful written informed consent
- Able and willing to follow the Protocol requirements

Exclusion Criteria

- Patients not willing to participate in the study
- Female patients who are pregnant or breast-feeding
- Any other serious disease likely to compromise the outcome of the trial
- Wound area greater than 2500 square mm;
- Patients with severe ischemia. Measurable as absence of palpable pedal pulse or ABPI <0.5 or between1.0-1.2, Audible Doppler sound.

ISSN: 0975-3583, 0976-2833 VOL 15, ISSUE 03, 2024

Statistical Methods

Data were analysed with IBM SPSS Statistics for Windows, Version 23.0.(Armonk, NY: IBM Corp). To describe about the data descriptive statistics frequency analysis, percentage analysis were used for categorical variables and the mean & S.D were used for continuous variables. To find the significant difference between the bivariate samples in Independent groups the Independent sample t-test Wound Assessment score used. To find the significance in categorical data Chi-Square test Wound Assessment score used similarly if the expected cell frequency is less than 5 in 2×2 tables then the Fisher's Exact Wound Assessment score used. In all the above statistical tools the probability value .05 is considered as significant level.

RESULTS

	Age Distribution	
	Frequency	**Percent**
41 - 50 yrs	7	17.5
51 - 60 yrs	21	52.5
61 - 70 yrs	9	22.5
Above 70 yrs	3	7.5
Total	40	100.0

Table 1: Age Distribution

The above table shows Age distribution were 41-50 years is 17.5%,51-60 years is 52.5%, 61-70 years is 22.5%, >70 years is 7.5%.

	Gender Distribution	
	Frequency	**Percent**
Female	8	20.0
Male	32	80.0
Total	40	100.0

Table 2: Gender Distribution

The above table shows Gender distribution were Female is 20.0%, Male is 80.0%.

			Dressing				
			Nitric oxide	**Saline**	**Total**	**χ2 Value**	**p-value**
Age	41 - 50 yrs	Count	2	5	7	5.587	0.134 #
		%	10.0%	25.0%	17.5%		
	51 - 60 yrs	Count	13	8	21		
		%	65.0%	40.0%	52.5%		
	61 - 70 yrs	Count	5	4	9		
		%	25.0%	20.0%	22.5%		
	Above 70 yrs	Count	0	3	3		
		%	0.0%	15.0%	7.5%		
Total		Count	20	20	40		
		%	100.0%	100.0%	100.0%		

No Statistical Significance at p > 0.05 level

Table 3: Comparison of Age between Dressing by Pearson's Chi-Square test

ISSN: 0975-3583, 0976-2833 VOL 15, ISSUE 03, 2024

The above table shows comparison of Age between Dressing by Pearson's ChiSquare test were $\chi 2$=5.587, p=0.134>0.05 which shows no statistical significance between Age and Dressing.

			Dressing		Total	$\chi 2$- value	p-value
			Nitric oxide	Saline			
Gender	Female	Count	6	2	8	2.500	0.235 #
		%	30.0%	10.0%	20.0%		
	Male	Count	14	18	32		
		%	70.0%	90.0%	80.0%		
Total		Count	20	20	40		
		%	100.0%	100.0%	100.0%		
# No Statistical Significance at p > 0.05 level							

Table 4: Comparison of Gender between Dressing by Fisher's exact test

The above table shows comparison of Gender between Dressing by Fisher's exact test were $\chi 2$=2.500, p=0.235>0.05 which shows no statistical significance between Gender and Dressing.

Assessment Score	Dressing	N	Mean	SD	t-value	p-value
Week 1	Nitric oxide	20	34.4	3.6	0.143	0.887 #
	Saline	20	34.5	3.0		
Week 2	Nitric oxide	20	27.9	3.5	1.601	0.118 #
	Saline	20	29.5	3.0		
Week 3	Nitric oxide	20	20.9	2.6	4.344	0.0001 **
	Saline	20	24.9	3.2		
** Highly Significant at p < 0.01 and # No Statistical Significance at p > 0.05						

Table 5: Comparison of Wound Assessment Score between Dressing by Independent sample t-test

The above table shows comparison of Wound Assessment Score between Dressing by Independent sample t-test were Week1, Week2 shows no statistical significance difference at p>0.05 level whereas in Week3 it shows highly statistical significance difference at p<0.01 level.

Variable	Dressing	N	Mean	SD	t-value	p-value
Pre Dressing Sr.MMP	Nitric oxide	20	20.4	4.4	0.518	0.608 #
	Saline	20	21.0	2.8		
	# No Statistical Significance at p > 0.05 level					

Table 6: Comparison of Pre Dressing Sr.MMP between Dressing by Independent sample t-test

The above table shows comparison of Pre Dressing Sr.MMP between Dressing by Independent sample t-test were t-value=0.518, p-value=0.608>0.05 which shows no statistical significance difference at p > 0.05 level.

ISSN: 0975-3583, 0976-2833 VOL 15, ISSUE 03, 2024

Variable	Dressing	N	Mean	SD	t-value	p-value
Post Dressing Sr.MMP	Nitric oxide	20	7.8	1.8	7.808	0.0005 **
	Saline	20	14.0	3.0		
	** Highly Statistical Significance at p < 0.01 level					
Comparison of Post Dressing Sr.MMP between Dressing by Independent sample t-test						
Variable	**Dressing**	**N**	**Mean**	**SD**	**t-value**	**p-value**
Healing time	Nitric oxide	20	2.8	0.6	8.560	0.0005 **
	Saline	20	4.7	0.7		
	** Highly Statistical Significance at p < 0.01 level					
Table 7: Comparison of Healing time between Dressing by Independent sample t-test						

The above table shows comparison of Post Dressing Sr.MMP between Dressing by Independent sample t-test were t-value=7.808, p-value=0.0005<0.01 which shows highly statistical significance difference at p < 0.01 level.

The above table shows comparison of Healing time between Dressing by Independent sample t-test were t-value=8.560, p-value=0.0005<0.01 which shows highly statistical significance difference at p < 0.01 level.

Dressing	Wound Assessment Score	N	Mean	SD	t-value	p-value
Nitric oxide	Week 1	20	34.35	3.62	29.990	0.0005 **
	Week 3	20	20.85	2.62		
Saline	Week 1	20	34.50	3.00	21.933	0.0005 **
	Week 3	20	24.90	3.24		
	** Highly Statistical Significance at p < 0.01 level					
Table 8: Comparison of Dressing between Wound Assessment Score by Paired Samples t-test						

The above table shows comparison of Dressing between Wound Assessment Score by Paired sample t-test were Nitric oxide t-value=29.990, p-value=0.0005<0.01 which shows highly statistical significance difference at p < 0.01 level similarly in Saline, t-value=21.933, p-value=0.0005<0.01 which shows highly statistical significance difference at p<0.01 level respectively.

Variable	Dressing	N	Mean	SD	t-value	p-value
Wound Assessment Score difference in 1 to 3 Week	Nitric oxide	20	13.50	2.01	6.212	0.0005 **
	Saline	20	9.60	1.96		
** Highly Statistical Significance at p < 0.01 level						
Table 9: Comparison of Wound Assessment Score Difference 1 to 3 week between dressing by Independent sample t-test						

The above table shows comparison of Wound Assessment Score in difference of 1 to 3 week between Dressing by Independent sample t-test were t value=6.212, p-value=0.0005<0.01 which shows highly statistical significance difference at p < 0.01 level.

ISSN: 0975-3583, 0976-2833 VOL 15, ISSUE 03, 2024

DISCUSSION

A randomized controlled study was done to compare the efficacy of Nitric oxide and saline dressing in diabetic foot ulcers. This study also includes the analysis of the expression serum Matrix metallo protinease (MMP) 9 in diabetic patients with foot ulcers and their influence on wound healing.

It has been well established that diabetic foot ulcers increase the morbidity and, consequently, the financial toll on the society. Therefore, early prevention of diabetic foot ulcers is of paramount importance. Once an ulcer has formed in a diabetic patient, proper care should be instituted at the earliest to prevent it from progressing to produce extensive damage and possible need for an amputation.

Diabetic foot ulcer care involves the choice of an ideal dressing to aid in satisfactory healing of wounds. Of the many dressing materials available, nitric oxide dressing which improves the blood supply and preventing infection has been the subject of research and the use of this as a dressing has been extensively studied in various fields of medicine and dentistry.

Literature review on the use of nitric oxide, as a dressing on diabetic foot ulcers revealed that there are not too many studies. A study was done during 2007 on diabetic foot ulcers and nitric oxide dressings were found to have promising results.

One of the main non-communicable diseases (NCDs) that pose a risk to development in the twenty-first century is diabetes mellitus. Diabetes can lead to a number of issues, including diabetic foot ulcers. The cause of diabetic ulcers is multifactorial and includes polyneuropathy, biomechanical stress, infection, inadequate footwear, and, to a lesser extent, ischemia. The fundamentals of ulcer treatment include relieving pressure, restoring skin perfusion, treating infections, providing intensive wound care, and having the patient take good care of themselves.

Minor trauma may result in ulcers in Diabetes Mellitus patients with altered immune systems, and because the immune systems are weaker, the healing process takes longer, leading to chronic ulcers. Patients with diabetic peripheral neuropathy frequently experience shooting and scorching pain in their distal extremities as well as loss of feeling, which can eventually cause foot ulcers, infections, and amputation due to the non-healing nature of the condition caused by hyperglycemia.

It is widely known that diabetic foot ulcers increase mortality rates, which raises societal costs. In order to prevent diabetic foot ulcers at an early stage. When a diabetic patient develops an ulcer, appropriate care should be started as soon as possible to stop it from spreading and possibly causing extensive damage and need for an amputation. It has been proven from a study that a diabetic foot ulcer precedes 75 - 85 % of amputations in people with Diabetes. Thus, Diabetic foot ulcers pose a growing disease with debilitating consequences and no adequate treatment.

Care for diabetic foot ulcers includes selecting the best dressing to promote successful wound healing. Nitric oxide dressing, which improves blood flow and prevents infection, has been extensively researched in several medical and dental specialties. It is one of the numerous dressing materials that are readily available. Furthermore, studies on the use of nitric oxide in the management of painful peripheral neuropathy have yielded encouraging results.

Historically, there has been a scarcity of evidence based topical therapy to hasten the wound healing process in chronic wounds like Diabetic foot ulcer. But recently, new evidence-based treatments have emerged from multi center, randomized, controlled trials.

A study done by Joseph V Boykin in clinical practice have shown that preliminary wound healing studies have shown that threshold wound fluid nitrate values may function as an effective diagnostic indicator of successful wound healing for the diabetic foot ulcer patients.

ISSN: 0975-3583, 0976-2833 VOL 15, ISSUE 03, 2024

High levels of nitric oxide (NO) metabolites have shown a positive regulatory effect on the repair process of wound healing, while inhibition of NO production is related to impaired healing.

Studies have shown that the pathogenesis of Diabetes Mellitus contributes to the decreased formation of NO metabolites in the wound environment and lack of vascularization of the peripheral nerves which harnesses the wound healing since it is a proven fact that endogenous Nitric oxide facilitates wound healing and promotes angiogenesis.

Studies by Schaffer et al, have demonstrated reduced Nitric oxide production in isolated wound cells of Diabetic mice and on treatment with insulin, the cells showed enhanced production of Nitric Oxide. This enhanced Nitric oxide facilitated collagen deposition and wound mechanical strength causing rapid wound healing.

Sandra Y Silva et al in their study have shown that an estimate of 15 % of the diabetic population develop ulcer at some point of their lives. They also demonstrated that topical use of NO accelerates the wound healing process of wounds whereas Nitric oxide inhibitors prolonged the healing time of these lesions. The use of colloid Nitric Oxide donors in diabetic subjects proved adequate granulation tissue formation and early closure of wounds.

A study by Aristidis Veves et al who studied the endothelial mediated micro vascular blood flow in neuropathic patients to determine the endothelial regulation of micro circulation to its association with endothelial constitutive Nitric Oxide synthetase (ecNOS) in the skin concluded that both endothelium dependent and independent vasodilation are impaired in Diabetic patients predisposed to foot ulceration and that Neuropathy is the major factor associated with this abnormality. Their study demonstrated the importance of Nitric oxide by citing that reduced expression of ecNOS may be a major contributing factor for endothelial dysfunction.

A multicenter, Randomized Controlled, observer blinded study of a nitric oxide generating device in the treatment of Diabetic foot ulcer demonstrated a primary end point by attaining a median percentage area reduction of 88.6 % compared to its 46.9% for the control group at 12 weeks in the intention- to - treat population.

Owing to the historical studies favoring the use of Nitric oxide as a mode of treatment to hasten the healing process of Diabetic foot ulcer, we emphasized the objective of our study in the efficacy of Nitric oxide over standard saline dressings in the management of Diagnostic foot ulcers.

This study is mainly based on two outcomes, the primary being reduction in ulcer size rather than complete wound healing with a scientifically legitimate reason that complete healing of a wound is measured by the investigator which can subject to bias in favor of the study. The second outcome was to visualize the influence of MMP 9 on wound healing.

This randomized control prospective study included 40 Diabetic patients who were admitted with Diabetic foot ulcer. The study then randomized patients into two groups of 20 each wherein one group received treatment with Nitric oxide dressing on alternative days for a period of three weeks. The other group received treatment with standard saline dressing.

Adequate wound care was given and during their weekly visits, the diameter and the area of the wound was measured and results obtained were based on the Wound assessment tool by Bates - Jensen Wound assessment tool.

According to our study's findings, diabetic ulcers treated with nitric oxide had significantly less ulcer area than ulcers treated with saline after 3 weeks. The control group exhibited a reduction of 50.5% while the nitric oxide group showed a reduction of 66.9%.

In view of the statistical significance of the percentage reduction after 3 weeks (p value 0.01), it was determined that nitric oxide dressings are more effective in promoting healing than saline dressings. Nitric oxide dressings were also discovered to be effective in treating diabetic

ISSN: 0975-3583, 0976-2833 VOL 15, ISSUE 03, 2024

ulcers, By reducing the need for additional dressing supplies. Nitric oxide is practical for dressings because to its simplicity of preparation.

The nitric oxide dressing can be changed once in three days, reducing the patient's need for frequent hospital visits. Thus, its use is highly beneficial for patients who are confined to beds since it allows for better wound care and the prevention of wound soakage.

The impact of MMP-9 on wound healing is covered in the second section of this study. MMP-9 is important in determining how quickly a wound seems to be healing.

Matrix metallo proteinases (MMP) are a group of endopeptidases that play a vital role in the restoration of damaged skin. They mediate cellular events like angiogenesis and increased vascular permeability, thereby making them very crucial for wound healing.

Growth factors, bio- engineered tissues, stem cell therapy, gene therapy and peptide therapy also have some supporting evidence in Diabetic ulcer management. The development of nanotechnology has created a means of prolonging the bioavailability of target molecules at the wound site, with the use of glass / hydrogel nano particles, polyethylene glycol and hyaluronic acid.

With so many newer modalities coming into trend in the healing of Diabetic foot ulcer, Nitric oxide also has its own significance proven by studies and our study has helped to conclude that Nitric oxide dressings facilitate early healing of chronic Diabetic foot ulcers and alleviates peripheral neuropathy. And since it’s benefits like low cost, better healing, easy accessibility, low frequency of dressings when compared to standard saline dressings overweight the disadvantages, it is a preferable option for the management of Diabetic foot ulcers.

In this study, we compared the percentage reduction of ulcer area between the Nitric oxide and the saline group at the end of 3 weeks. The two groups of 20 patients were evenly matched. Findings in our study show that there is a significant reduction in ulcer area at the end of 3 weeks in Nitric oxide treated diabetic ulcers than in the saline. The nitric oxide group showed 66.9 % reduction whereas the control group showed a reduction of 50.5 %.

The percentage reduction at the end of 3 weeks showed a statistical significance (p value <0.01) and it was thus concluded that Nitric-oxide dressings produce better healing than saline dressings. It was also found that the use of nitric oxide dressings in diabetic ulcers can minimize the exhaustion of dressing materials. The ease of preparation of nitric oxide makes it convenient for dressings.

On the strength of the findings of these studies, we conducted our study comparing the efficacy of nitric oxide over saline dressings and the expression and association of MMP-9 with wound healing.

In this study, 20 patients from the control and nitric oxide groups each had MMP-9 detected. MMP-9 levels were measured in the control and test groups both before and after dressing. It was observed that in serum MMP-9, the expression after dressing with nitric oxide dressing shows highly statistical significance difference at $p < 0.01$ level.

The better reduction in area and low levels of serum MMP 9 obtained with Nitric oxide dressing proves to be a better treatment option for the management of chronic Diabetic foot ulcer than the normal standard dressings. Also, the reduced frequency of dressings, low cost and easy accessibility adds on to the benefits of Nitric oxide dressings.

Apart from the various advantages of Nitric oxide, the disadvantages would be its short half-life in biological systems, being unstable and thereby requiring frequent application. Which has been combated by the development of multilayer polymeric transdermal patch produced by electrospinning technique that guarantees a constant nitric oxide release and the use of

ISSN: 0975-3583, 0976-2833 VOL 15, ISSUE 03, 2024

spectroscopic and electrochemical methods has proved best in the direct measurement of nitric oxide The nitric oxide showed betted reduction in ulcer area than saline dressing. However the statistical significance was achieved. The limitation of this study was that it was conducted in a small sample size.

CONCLUSION

A deficiency of nitric oxide synthase in diabetic patients may lead to lack of vascularization of the peripheral nerves, which causes Diabetic peripheral neuropathy (DPN). Lower concentrations of Nitric oxide in diabetic foot ulcers may be responsible for the impaired healing in this disease. The present study has shown that the Nitric oxide dressings are more efficacious than standard saline dressings in enhancing the process of wound healing which is evident from the marked reduction in wound size. A reduction in serum MMP 9 levels post Nitric oxide dressing than post saline dressing indicates it is statistically significant and better than the standard dressing. A nitric oxide dressing is envisioned for the treatment of Diabetic peripheral neuropathy and Diabetic wound ulcers by increasing vasodilation.

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