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Original Article

The Use of an Oral Mixture of Arginine, Glutamine and β-Hydroxy-β-Methylbutyrate (Hmb) for the Treatment of High Grade Pressure Ulcers: A Randomized Study

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ABSTRACT

Background/Purpose: Pressure ulcers are highly prevalent in health care facilities. Provision of nutritional support is considered as a modality for pressure ulcer management. The aim of this study is to investigate the effect of a commercial mixture of arginine, glutamine and β-hydroxy-β-methylbutyrate (HMB) on pressure ulcer healing among subjects with high-grade pressure sore.

Methods: 87 subjects, mean age 82.5 (SD 12.15), with stage III-IV pressure sore, were randomized to a HMB, arginine and glutamine mixture twice daily or standard nutritional care for 4 weeks. Pressure ulcers were measured every 2 weeks for area, depth, undermine and PUSH (Pressure Ulcer Scale for Healing) scores. Laboratory parameters including haemoglobin and C-reactive protein level were measured every 2 weeks. Secondary outcomes were length of hospitalization, in-patients' and 6-month mortality and number of hospital readmission.

Results: Overall, there was a statistically significant improvement of pressure ulcer size and depth. A statistically significant reduction in pressure ulcer size (p=0.048) and depth (p=0.002) was observed in the intervention group while the PUSH score showed a significant improvement in the control group (p <0.001). However, there was no between group difference on pressure ulcer healing in term of pressure ulcer area, depth, undermine and PUSH score. Biochemical parameters, the median length of hospitalization and number of hospital readmission also showed no between group difference.

Conclusion: Use of a nutritional formula enriched with arginine, glutamine and HMB does not improve late state pressure ulcer healing after 4 weeks.

1. INTRODUCTION

Pressure ulcers occur due to circulation compromise and tissue damage as a result of pressure or pressure with shearing forces in subjects with immobility.[1] It is associated with morbidity, mortality, length of hospital stay and health care cost.[2,3] Prevalence of pressure ulcer is high, ranging from 3-30% in some

studies.[4,5] Elderly patients are an exceptionally high risk group and are those with specific conditions that predispose to morbidity such as hip fracture. Of them, approximate 66% have been reported to develop pressure ulcer.[6]

The process of wound healing can be disrupted by many intrinsic and extrinsic factors. Preventing and treating pressure ulcer requires a complex interaction of interventions. The approach to pressure ulcer healing is multifaceted. However, the mainstay of management is the avoidance of persistent pressure at bony sites. Many other interventions were studied although their efficacy needs to be established.[7] Pressure ulcers and malnutrition are frequently coexist.[8] The rate of pressure ulcer development is up to two to three-fold high in a malnourished individual after accounting for other demographic variables and risk factors.[9] Recent weight loss,[10] impaired food intake and low dietary protein intake appear to be associated with pressure ulcer development. Patients with pressure ulcers frequently have a negative energy balance[11] and optimizing nutritional status may benefit patients who were at risk of developing pressure ulcers or currently have pressure ulcers. Previous studies have shown that improving the nutritional status of patients with oral nutritional supplements is associated with a lower incidence of pressure ulcer development. A nutritional formula enriched with arginine, zinc and antioxidants may have healing benefits.[12–14] Arginine is a semi-essential amino acid that improves protein synthesis. It helps the promotion of nitrogen balance, cell proliferation, T lymphocyte function and collagen accumulation.[15] It is a donor of nitric oxide that increases tissue blood flow and acts as a mediator for immune response.[16] Glutamine is another conditionally essential amino acid. Under extreme stress, its level will be depleted. Glutamine depletion can lead to a reduction in the healing process. β-hydroxy-β-methylbutyrate (HMB), which is a metabolite of leucine, is associated with increased muscle mass accretion through its effect of inhibition of muscle proteolysis and modulation of protein turnover.[18]

1.1. Objective

This study aims to investigate the effects of a commercial mixture of arginine, glutamine and HMB on patients with high-grade pressure sore.

1.2. Material and Methods

Patients were recruited from inpatients of convalescence units of two hospitals during the period from January 2017 to December 2018. Inclusion criteria were patients age greater than 18 years old, with at least one stage III–IV pressure ulcer according to the revised European Pressure Ulcer Advisory Panel Classification system.[19] Exclusion criteria were those with cellulitis, infected wounds, osteomyelitis or sepsis; patients requiring dietary restriction; patients with poorly controlled diabetes mellitus as defined by an Hba1c >8.5% and patients receiving palliative care. Written consents were obtained from the patients or their legal guardian.

This study was approved by the regional cluster research ethics committee of the Hong Kong Hospital Authority.

This was a randomized, open-labelled prospective study. Patients were screened by the authors for inclusion or exclusion. Subjects were randomized to nutritional supplement group or conventional treatment group by use of a sealed envelope. All participants were assessed by a dietitian and provided with nutritional support of at least 30 kcal/kg/day and 1.2 g/kg/day of protein regardless of their feeding methods. The intervention group were given two sachets of a mixture of arginine, glutamine and HMB (Abound®) diluted with 200 ml water daily for a total of 4 weeks. During the study period, vitamin C and zinc supplement would not be given.

Baseline demographics including age, sex, mode of feeding, the presence of diabetes mellitus, comorbidity as measured by Charlson Comorbidity Index (CCI)[20], haemoglobin level, albumin level, C-reactive protein (CRP) level were recorded. Body weight and body mass index (BMI) were measured at baseline, week 2 and week 4. Haemoglobin level and C-reactive protein (CRP) were measured at baseline, week 2 and at week 4.

1.3. Primary Outcome

The primary outcome was pressure ulcer healing as assessed by the change in pressure ulcer surface area over time. Pressure ulcer was assessed every two weeks by the transparency-based method. Transparency was placed over the ulcer; the ulcer margins were traced with an indelible pen. Wound depth and wound undermine were measured by a sterile probe. Pressure Ulcer Scale for Healing (PUSH) score[21] was used to monitor the progress of wound healing. The tool assigns sub-scores according to the surface area (length x width), exudate amount and type of wound tissue in the ulcer bed. The final total score categorized the severity of ulcers from 0 (completely healed) to 17 (greatest severity). All the parameters were measured at baseline, week 2 and week 4. If a patient has multiple pressure ulcers, the largest ulcer was selected for assessment throughout the study.

1.4. Secondary Endpoint

Hospital length of stay, in-patient mortality and 6-months mortality, number of hospital admissions

and length of stay 6 months after the study were also collected.

1.5. Sample Size Estimation

Based on Cereda study[16] using a nutritional formula enriched with arginine, zinc and anti-oxidants which reported a reduction of pressure area of 37.2% over 4 weeks. We estimated that with a 30% improvement of ulcer size in the study group, with the power of 0.8 and the estimated error of 0.05, the estimated sample size will be 90 (45 in each group).

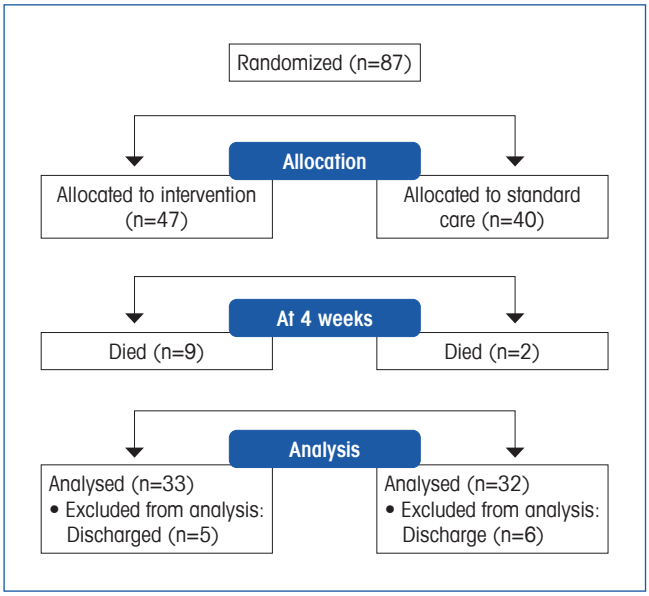
1.6. Statistical Method

Data are presented in mean +/- SD. Differences between proportions were tested by chi-square or Fisher exact where appropriate. Within-group comparison of ulcer size, ulcer depth and undermine were done by repeated-measures ANOVA. Between-group differences on demographics and ulcer characteristics were compared using t-test or Mann Whitney test. Repeated-measures ANOVA were used to detect between-group differences on primary outcomes. A p value <0.05 is considered as statistical significant.

2. RESULTS

87 subjects were recruited with a mean age of 82.48 (SD 12.15). 47 (54%) were assigned to the intervention group and 40 were receiving standard care. 33 (37.9%) were male. Figure 1 shows the patient recruitment workflow. 41 (47.1%) were on tube feeding. The mean BMI was 18.2 (SD 5.68) and the mean CCI was 2.53 (SD 1.56). The baseline albumin level was low at 22.9 g/dL (SD 6.6) and Haemoglobin level was only 10.8 g/dL (SD 9.54). Diabetes was present in 25 (28.7%) subjects. The inpatient mortality was high (47.1%) while the 6 months' mortality was 54%. The median length of stay was 36 days.

Figure 1. Consort flow diagram



A total of 28 subjects did not complete the 4 weeks' study, among them, 11 died. 9 (64.2%) were in the intervention group while 2 (15.4%) were in the control group (p=0.018).

There was no statistically significant difference between the intervention and control group on baseline demographics, biochemical parameters and size and depth of pressure ulcers except PUSH score which was higher in the control group (Table 1). Overall, there was a statistically significant improvement in the pressure ulcer size and depth with time among the whole cohort. However, there was no difference in the undermine of pressure ulcer. A statistically significant reduction in pressure ulcer size and depth was observed in the intervention group. For the control group, it has been found that only ulcer depth showed a significant improvement with time. For the PUSH score, there was an improvement in the control group only (Figure 2).

Between-group comparison on nutritional intervention showed no statistically significant difference between the 2 groups on pressure ulcer size, depth, undermine and the PUSH score.

There was no statistically significant difference between the intervention group and the control group on inpatient mortality. Biochemical parameters including CRP and albumin level did not show any significant difference with time. There was also no significant between-group difference in the number of hospital readmission and the average length of stay. However, there was a trend in loss of body weight in the intervention group compared with the control group (Table 2).

2.1. Adverse Event

There was no reported gastrointestinal intolerance of the nutritional supplement during the study period. 12 died during the study period, but we did not attribute any death to the intervention. No other treatment-related adverse event occurred.

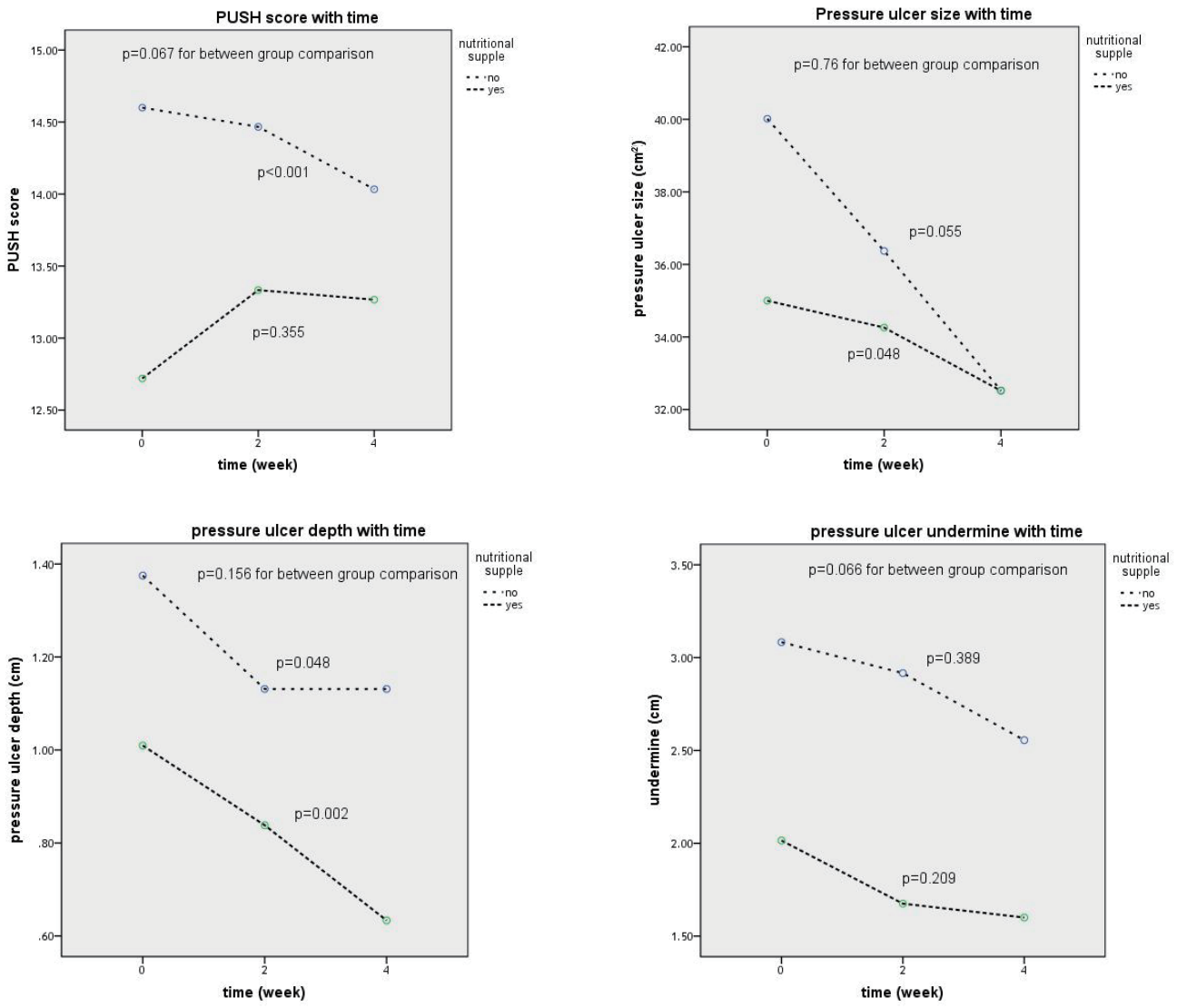
3. DISCUSSION

Malnutrition in the elderly population is associated with poor clinical outcome. It is an indicator of many complications and mortality.[22] Our study population have poor nutritional status as evidenced by a low average BMI of 18.2 and low albumin level (22.3 g/dL). There is not much evidence on the effect of nutritional intervention in the management of pressure ulcer. Since pressure ulcer is a common problem, it is reasonable that early treatment including the use of nutritional supplement may be an effective strategy in

improving wound healing which will eventually lead to a reduction in morbidity, mortality, the average length of hospital stay and overall healthcare cost.[23]

Our study found that pressure ulcer healing did not improve with a specialized amino acid mixture containing arginine, glutamate and HMB among our cohort of frail and malnourished elderly subjects. We did show a general reduction in wound size, depth and undermine, but there was no difference between the intervention and control group. A few studies have demonstrated the effectiveness of nutritional supplementation on pressure ulcer and wound healing. Several studies on the use of omega-3 fatty acid lead to a reduction in new ulcer occurrence and delay ulcer progression.[24,25] Further studies on the use of arginine, zinc and vitamin C have also shown a reduction in the wound area and PUSH score.[26] This is not replicated in our trial. Our study showed that there was an overall reduction in the wound area and the intervention group did show a statistically significant reduction in the wound area, although there was no difference compared with the control group. Similarly, both groups showed a significant reduction in depth of pressure ulcer, but the between-group difference did not reach a statistically significant level. Undermine of the pressure ulcer did not improve with time in both groups. Visible wound closure can occur without regeneration of underlying tissue. This may not be a good reflection of wound healing. It has been suggested by Wong[27] that assessment of the proportion of viable tissue and use of a validated scoring system such as PUSH score may represent a more accurate measurement of wound healing. It is interesting to note that PUSH score did improve at week 2 and week 4 among the control group only and there was no statistically significant difference between the control and intervention group. We postulate that there may be certain categorical subscores for tissue type of the PUSH score which is

Figure 2. Within group and between group difference on pressure ulcer characteristics



better in the control group that may lead to an overall improvement. Unfortunately, we did not have detail records of the PUSH sub-scores that could help us to explain the finding.

Blood parameters including albumin level and CRP showed no between-group difference on any time point. CRP level increase with time in both the intervention and control group while albumin level did not show any improvement. It is suggested that our patient groups were too frail and malnourished and their wounds were too poor that even after 4 weeks of nutritional supplement and extensive wound care, the conditions did not show significant improvement. Most studies on pressure ulcer healing, performed in hospital setting among patients who were not critically ill, had found a raised CRP level.[28] In our study, all subjects have a raised CRP level with a low serum albumin level. The acute phase response to infected wounds could lead to high CRP and may decrease protein synthesis.[27] Moreover, a low albumin level could also be due to malnutrition. Both the intervention and control group had received energy supplementation after dietitian assessment to ensure that at least 30 Kcal/Kg/day of energy supplementation was given. However, as the subjects were managed conservatively and the nutritional intake were only increased gradually during the study period, we were not able to increase the calorie intake within the first few days to meet the calorie requirement. This might affect the overall energy and protein intake over the treatment period. For our study, the overall healing rate in the first 2 weeks was only 0.15 cm^2/day while there was no further improvement over week 2 to week 4. The healing rate in the first 2 weeks among the intervention and control group was 0.05 cm^2/day and 0.26 cm^2/day respectively and the healing rate in week 2 to week 4 was 0.12 cm^2/day and 0.27 cm^2/day respectively. The PUSH score did not differ with time. This low overall healing rate in both the intervention and control group was probably related to the poor nutritional state which is a well-known aetiology of delay wound healing.[29] In an open-label cohort study among malnourished and well-nourished subjects who had received the same specific oral nutritional supplement for 9 weeks reported a faster healing rate of 0.23cm^2/day at first 3 weeks which later decreased to 0.13 cm^2/day subsequently.[30] Another study using the same oral nutritional supplement also showed an average healing rate of 0.34 cm^2/day of stage III/IV ulcer in 3 weeks.[31] This high healing rate might be due to the combination of inclusion of subjects with better nutritional state and the average size of pressure ulcer at baseline is not as large as our study (22.6 cm^2 vs 37.5 cm^2). Our subjects might be too ill, too malnourished and with a large pressure ulcer size that any nutritional intervention may be too late and too short to be able to achieve a positive outcome on pressure ulcer

Table 1. Baseline demographics

	Intervention group (N=47)	Control group (N=40)	*P* value
Age	83.04 (SD 11.46)	81.42 (SD 13.03)	0.539
Sex (female)	29 (61.7%)	25 (62.5%)	1
BMI	18.57 (SD 6.38)	17.76 (SD 4.77)	0.518
Charlson comorbidity index (median)	2	3	0.415
Presence of diabetes	14 (30.4%)	11 (27.5%)	0.815
Albumin level (g/dL)	23.16 (SD 7.45)	21.26 (SD 5.4)	0.187
Haemoglobin level (g/dL)	11.81 (SD 12.97)	9.67 (SD 1.44)	0.31
Pressure ulcer			
Size (cm^2)	34.97 (SD 26.7)	38.15 (SD 36.7)	0.652
Depth (cm)	1.04 (SD 0.82)	1.39 (SD 0.96)	0.17
Undermine (cm)	1.92 (SD 1.48)	2.88 (SD 2.75)	0.122
PUSH score (mean)	12.99 (SD 3.6)	14.64 (SD 1.83)	0.01 95% CI 0.41, 2.89

Table 2. Between group differences on secondary outcomes

	Intervention group N=47	Control group N=40	*P* value
Body weight (kg)			
Baseline	41.32 (SD 11.4)	44.51 (SD 12.75)	
Week 2	39.1 (SD 9.43)	44.31 (SD 10.65)	0.047
Week 4	40.57 (SD 12.07)	45.06 (SD 10.46)	
Albumin level (g/dL)			
Baseline	23.16 (SD 7.45)	21.28 (SD 5.34)	
Week 2	24.53 (SD 11.63)	22.03 (SD 5.14)	0.164
Week 4	22.97 (SD 6.22)	21.48 (SD 5.09)	
CRP			
Baseline	47.07 (SD 36.62)	42.82 (SD 31.42)	
Week 2	59.88 (SD 55.19)	60.29 (SD 48.47)	0.967
Week 4	72.34 (SD 63.37)	61.4 (SD 53.16)	
Median length of hospitalization (days)	33	49	0.307
Number of readmission	1.71 (SD1.64)	1.27 (SD 1.03)	0.382
In-patient mortality	26 (55.3%)	16 (40%)	0.282
6 months' mortality	34 (72.3%)	22 (59.5%)	0.249

CRP: C-reactive protein

healing. There is a possibility that if well-nourished patients were included, the wound healing rate can be improved and comparable to other study.[26]

It has been shown[23,32] that the combination of macro and/or specific micronutrients help to prevent pressure ulcer or improve wound healing. Use of protein, vitamin A, vitamin C and Zinc is shown to be associated with improved wound healing.[15,33] Provision of extra calories alone has not affect wound healing and elderly subjects with ulcer did not need extra energy requirement.[34] According to the European Pressure Ulcer Advisory Panel (NPUAP) guidelines,[19] the recommended energy intake for older patients under stress with the presence of a pressure ulcer is no different to those of the general elderly population.[35] This led to a general belief that energy requirement is not an essential factor in patients with pressure ulcer and that the recommendations for treatment of malnutrition using nutritional support is only ranging from 25 to 30 Kcal/kg/day.[34] Similarly, there is also no expected significant effect on protein intake. It has been reported by Bos[36] that there was a significant anabolic effect for short term supplement of 1.5 g/kg/day protein in under-nourished elderly. There was an improvement in the healing of existing lesion using high protein (1.8 g/kg/day) treatment.[37] Study[38] has proved that ageing is associated with unbalanced protein to metabolism and that increased protein intake at 1.5 g/kg/day may not be able to improve nitrogen balance and may even lead to dehydration.[37]

The current trial using this supplemental formula may not be adequate to produce any effect on the rate of wound healing and that the effect of the overall treatment formula might have masked the healing effect. It is difficult to have any practical suggestion on the amount of protein that should be included in the nutritional supplement. With reference to previous studies,[36,37] a protein intake of 1.5 g/kg/day might be the first step in the provision of nutritional supplement in elderly people. We cannot exclude the additional benefit of a higher intake of calories and protein would have on the rate of pressure ulcer healing.

3.1. Limitation

A total of 28 subjects did not complete the study period. Among them, 11 died during the study period (9 in the intervention group, 2 in the control group). This 32% of subjects not completing the 4 weeks' study period were substantial with a predominant of death occurred in the intervention group. This may lead to the failure of getting a positive result with the nutritional supplement.

Nutritional status can be improved with nutritional therapy. However, common to all nutritional intervention studies, adherence to treatment is a major problem. It is difficult to detect compliance among the study subjects except those who were dependent on tube feeding. Despite of this, since all the subjects were receiving in-patient management, patients' compliance can be assessed and managed accordingly.

It was difficult to have a standardized wound care regime for all patients. Each patient has pressure ulcer at a different stage and site and may have been managed differently before the present admission. As the pressure ulcers' characteristics were variable, we aim to optimize wound healing based on wound nurses' expertise. With strict exclusion criteria that exclude those with poor DM control, infected pressure sore, osteomyelitis and those that require extensive debridement of their wound, the influence of confounding factors can be reduced to a minimal.

There may be bias in interpreting the wound healing. Although the wound nurse was blinded from the study, inter-observer variation can occur. The determination of viable tissues was based on-site examination by different wound nurses and that retrospective analysis of wound photograph could also lead to bias.

Pre-morbid nutritional status is suggested to be an important factor that leads to our negative finding. The average BMI of our subjects was 18 which is much lower than those reported by Cereda[16] and Wong[27] with a BMI around 20-21. It is difficult to stratify our sample into a well-nourished and malnourished group based on this relatively small sample size. There is also a problem to identify those patients who were well nourished on admission that deteriorated during their hospital stay due to acute illness.

Finally, the duration of the trial period may be inadequate. With the poor nutritional status among our study subjects, nutritional supplement given for only 4 weeks may not be adequate to produce any improvement. The time to wound healing is difficult to determine within this limited period of trial.

4. CONCLUSION

This study showed that use of a nutritional formula enriched with arginine, glutamine and HMB does not improve pressure ulcer healing in 4 weeks' time. Further study with larger sample size and determination of pre-morbid nutritional status are required to determine the role of this specialized nutritional formula in pressure wound healing.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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