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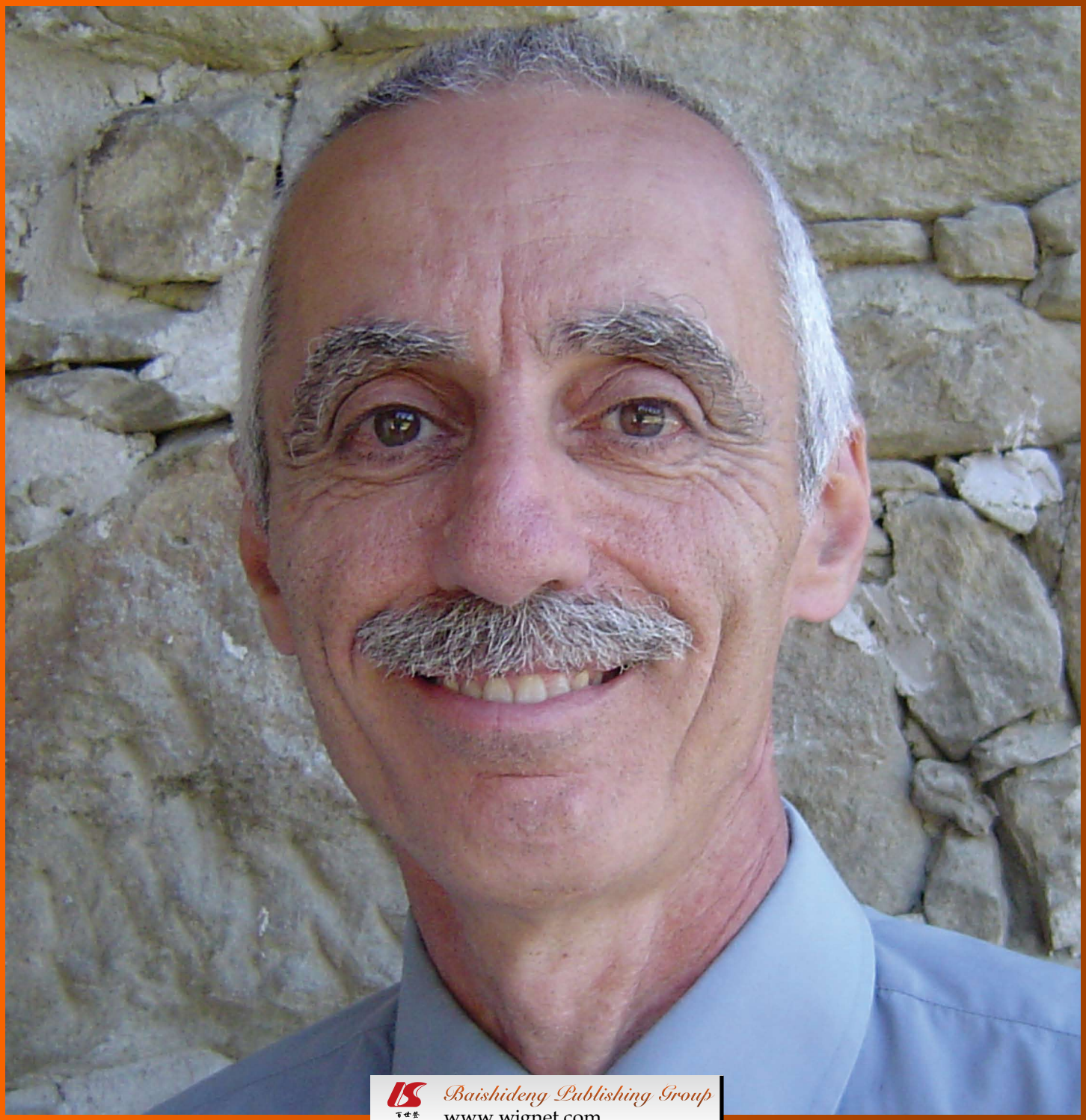

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BRIEF ARTICLE

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BRIEF ARTICLE

High-potency sucralfate prevents and rapidly reverses chemo-radiation mucositis in a patient with stage 4b head and neck cancer

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Abstract

AIM: To study usefulness of high-potency sucralfate (HPS) in a patient with chemoradiation mucositis and discuss its mechanism of action.

METHODS: HPS, a non-covalently cross-link of sucralfate, cations and bidentate anionic chelators, has a maintains a surface concentration of sucralfate 3 h following administration that is 7-23 fold that possible with standard-potency sucralfate. The accelerated mucosal healing and pain alleviation of HPS in patients with erosive esophageal reflux, prompted its use in this patient with chemoradiation mucositis of the oropharynx and alimentary tract. A literature-based review of the immuno-modulatory effects of sucralfate is discussed.

RESULTS: Within 48 h of intervention: (1) there was complete disappearance of oral mucositis lesions; tenderness with (2) patient-reported disappearance of pain, nausea and diarrhea; patient required (3) no opiate analgesia and (4) no tube-feeding supplements to regular diet. Dysgeusia and xerostomia persisted. A modified Naranjo Questionnaire score of 10 supported the likelihood that HPS intervention caused the observed clinical effects. No adverse reactions noted.

CONCLUSION: In this patient HPS was useful to treat chemo-radiation mucositis of the oropharynx and alimentary tract. HPS may directly or indirectly facilitate an immunomodulatory mechanism involving accelerated growth factor activation, which may be a new target for therapeutic intervention in such patients.

Key words: Sucralfate; Mucositis; Chemoradiation; Immuno-modulation; Cytokines; Intra-epithelial lymphocytes; Growth factors

Core tip: Mucositis is a debilitating and costly consequence of chemo-radiation. Most mucositis treatments are palliative. Conversely, high-potency sucralfate (HPS) may be definitive. Patients with stage 4b head neck cancer, at high risk for developing mucositis, require gastrostomy tubes as an alternative to oral feeding. The use of HPS in this cancer patient prevented mucositis, allowing continuance of standard oral diet. Midway through chemo-radiation, though noncompliant discontinuation of HPS, by patient led to the emergence oral and alimentary mucositis, 2 d following resumption

of HPS, mucositis disappeared, a normal oral diet was maintained and no analgesia was required.

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INTRODUCTION

Healing of mucositis erosions induced by chemo-radiation in cancer patients involves a balanced interplay between cytokines (pro- and anti-inflammatory), chemokines and growth factors[1]. Transforming growth factor β (TGFβ), which is upregulated by epithelial growth factor (EGF), TGFα, pro-inflammatory interleukin-1β and interferon γ[2] appears to be key in the pathobiology of oral mucositis, and likely in alimentary mucositis as well. Standard potency sucralfate avidly aid in growth factors[3] activation but has no significant clinical affect on chemo-radiation induced mucositis.

Signs and symptoms of oral mucositis (its associated symptoms and physical findings) have been standardized with most clinicians using the World Health Organization (WHO) grade classification system in Table 1[4]. The severity of mucositis-related alimentary toxicity, have two main grading scales one shown in Table 2, by the European Organization for Research and Treatment of Cancer/Radiation Therapy Oncology Group[5] and the other by the WHO[4]. In patients with advanced grades of mucositis (Grade 2 and 3), dose reduction is required in 60% of them, and 30% require discontinuation of chemotherapy regimens[6,7].

Adequate nutritional support is also a major problem. Regardless of cancer type or dose of treatment, 70% of patients with Grade 3 or 4 mucositis, require tube-feeding to supplement caloric and hydration needs. In patients undergoing hematopoietic stem cell transplant (HSCT), nearly 87% require tube-feeding with 80% requiring narcotic analgesics. There are economic issues related to mucositis as it increases the cost of care. Patients with solid tumors receiving chemotherapy who develop oral mucositis are hospitalized 4.3 d longer at a cost increase of 6277 per cycle[8]. Bone marrow transplant patients with oral mucositis require additional days of hospitalization resulting on average in increased hospital charges of 42749 per patient[9].

Episodes of mucositis are predictable. It is the most significant side effect of patients with head and neck cancer[10,11] receiving high-dose chemotherapy or radiation therapy. Incidence of severe oral mucositis approaches 100% in patients with stage 3 or 4b head and neck cancer receiving high dose radiation. Nearly 75% of patients undergoing HSCT experience advanced grades of both oral and gastrointestinal (GI) mucositis, particularly if methotrexate is used to prevent graft-*vs*-host disease[6]. High rates of alimentary mucositis, upwards of 20%-50%, occur with the use of 5-fluorouracil, capecitabine or tegafur to treat tumor and metastatic sites[6,12,13]. Similarly, 20%-60% of patients receiving chemotherapeutic antimetabolites such as methotrexate develop dose-dependent alimentary mucositis per cycle[6,12].

Clearly effective management of oral and alimentary mucositis would address patients' pain, rate of infection, nutritional states as well as recurrent hospitalizations, costs of care and optimization of treatment dose. Most FDA cleared interventions garner only a "standard of clinical practice" justification for their use and await expanded evidence-based examination[14]. Few cancer support therapies qualify for advanced guideline status, as the level of clinical efficacy fall short of that established by the Multinational Association of Supportive Care in Cancer (MASCC)[15,16].

The most recent guidelines on the treatment of oral mucositis include use of antimicrobial lozenges, benzydamine, oral cryotherapy, keratinocyte growth factor-1, and low-level laser therapy. To treat alimentary mucositis, MASCC panel recommends amifostine, ranitidine or omeprazole for upper GI mucositis and sulfasalazine 500 mg twice daily, sucralfate enemas, loperamide or octreotide 100 mg subcutaneously twice daily for lower GI mucositis[14].

No single agent satisfactorily addresses the occurrence of mucositis throughout the length of GI tract. Specifically, the 2005 MASCC guidelines recommended against the use of sucralfate for the prevention or treatment of radiation induced oral mucositis.

However, the patient in this report with oral and alimentary mucositis responded to high-potency sucralfate (HPS). HPS is original potency sucralfate with enhanced muco-adherence achieving high mucosal surface concentration.

Its presumed mechanism of action to be discussed later may involve engagement of nascent growth factors and neutralizing the polarity of ion-gated mucosal nociceptors.

MATERIALS AND METHODS

This was an interventional study in a patient with advanced stage 4 head and neck cancer undergoing concurrent chemoradiation and thus prone to develop severe oral and alimentary mucositis. The setting of the study was an outpatient department of medical oncology, radiation medicine and internal medicine. The patient provided informed consent and was enrolled in a compassionate use program sponsored by Mueller Medical International who provided ProThelial™ a proprietary formulation of HPS.

HPS

HPS has been shown to mitigate nausea, vomiting and diarrhea as well as accelerates healing of GI erosions in

Table 1 Grade scales for the assessment of oral mucositis

World Health Organization Grade	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Function	Painless ulcers, erythema or mild soreness	Painful erythema, edema, or ulcers but can eat solids	Painful erythema, edema, or ulcers and cannot eat solids	Alimentation is not possible; dependence on Ⅳ and feeding-tube	
Clinical Exam	Erythema of the mucosa	Patchy ulcerations or pseudomembranes	Confluent ulcerations or pseudomembranes; bleeding with minor trauma	Tissue necrosis; significant spontaneous bleeding; life-threatening consequences	Death
Symptoms	Minimal symptoms, normal diet; minimal respiratory symptoms but not interfering with function	Symptomatic but able to eat and swallow modified diet; respiratory symptoms interfering with function but not with activities of daily living	Symptomatic and unable to adequately aliment or hydrate orally; respiratory symptoms interfering with activities of daily living	Symptoms associated with life-threatening consequences	Death

Table 2 European Organization for Research and Treatment of Cancer/Radiation Therapy Oncology Group and the World Health Organization toxicity criteria acute chemoradiation morbidity

	Scale for gastrointestinal toxicity				
	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Esophagus toxicity grade	None	Mild fibrosis; Slight difficulty in swallowing solids; No pain on swallowing	Unable to take solid food normally; Swallowing semi-solid food; Dilation may be indicated	Severe fibrosis; Able to swallow only liquids; May have pain on swallowing; Dilation required	Necrosis/Perforation Fistula
Small bowel toxicity grade	None	Mild diarrhea; Mild cramping; Bowel movement 5 times daily	Moderate diarrhea and colic; Bowel movement > 5 times daily	Obstruction or bleeding, requiring surgery	Necrosis/Perforation Fistula
Colorectal toxicity grade	None	Increased frequency or change in quality of bowel habits not requiring medication, rectal discomfort not requiring analgesics; Slight rectal discharge or bleeding	Diarrhea requiring parasympatholytic drugs, mucous discharge not necessitating sanitary pads, rectal or abdominal pain requiring analgesics; Excessive rectal mucus or intermittent bleeding	Diarrhea requiring parenteral support, severe mucous or bloody discharge necessitating sanitary pads/abdominal distension (flat plate radiograph demonstrates distended bowel loops)	Acute or subacute obstruction, fistula or perforation; gastrointestinal bleeding requiring transfusion; abdominal pain or tenesmus requiring tube decompression or bowel diversion
World Health Organization colorectal Toxicity grade	None	Increase of 2-3 stools per day over pretreatment	Increase of 4-6 stools per day, or nocturnal stools, or moderate cramping	Increase of 7-9 stools per day, or incontinence, or severe cramping	Increase of > 10 stools per day or grossly bloody diarrhea, or need for parenteral support

man and animals. It is prepared by suspending regular-potency sucralfate in a select solution of cations and bidentate anionic chelators[17]. In this patient, doses of HPS suspension containing 1.5 g of sucralfate were self-administered three times daily for 2 d at the onset of mucositis symptoms and signs. Then twice daily dosing was continued throughout treatment course up to 2 wk following cancer therapy.

Outcome measures

There were two primary outcome measures and two secondary outcome measures. Primary measures consisted of the limitation or disappearance of visible oropharyngeal lesions and patient reported alimentary symptoms of pain, nausea, vomiting and diarrhea. Secondary outcome measures comprised of any need for opiate analgesia and tube-feeding supplementation of oral diet, and the score on a modified Naranjo Questionnaire[18]. The latter was employed to assess the probability of the intervention causing the observed clinical effects.

Case presentation

The patient was a 43-year-old male home health aide, divorced, with four children, who seldom drank alcohol and had stopped smoking 2 years prior to presentation to otolaryngologist but had a 17 pack year history of smoking. His mother died of metastatic breast cancer at age 52 years and his father died of unknown cause.

He presented with a 1 year history of swelling in his right neck for which he had received multiple courses of antibiotics with no appreciable change. With progressive swelling he had developed a 6-mo history of fullness in the back of his throat, a sensation occasionally associated with gagging during meals. He was referred to an otolaryngologist for evaluation of neck swelling and worsening gag.

On physical exam he was 73 inches tall, weighed 235 lbs and had an 8 cm × 6 cm neck mass below the right mandible extending to the angle of the jaw. Direct fiber-optic examination of the throat revealed a large mass at the base of the tongue. The biopsy of the right neck

Table 3 Modified naranjo probability of intervention-caused response

	Questions	Yes	No	Don't know	Case report
1	Are there previous conclusive reports on this response?	1	0	0	0 don't know
2	Did the response appear after the intervention was administered?	2	-1	0	+2 Yes
3	Did the response disappear when the intervention was discontinued?	+1	0	0	+1 Yes
4	Did the response reappear when the intervention was re-administered?	+2	-1	0	+2 Yes
5	Are there alternative causes that could on their own have caused the reaction?	-1	+2	0	+2 No
6	Did the reaction reappear when a placebo was given?	-1	+1	0	+1 No
7	Was the intervention detected in the blood in concentrations known to be toxic?	+1	0	0	0 No
8	Was the response more apparent when the dose was increased, or less apparent when the dose was decreased?	+1	0	0	0 No
9	Did the patient have a similar response to the same or similar intervention in any previous exposure?	+1	0	0	+1 Yes
10	Was the response confirmed by any objective evidence?	+1	0	0	+1 Yes
Patients total score					10

mass revealed a poorly differentiated squamous cell carcinoma. A computed tomography (CT) scan of the neck revealed massive right internal jugular lymphadenopathy from the angle of the jaw to the level of the thyroid measuring 6 cm × 4 cm in cross section. There was a 2-cm mass in the right tonsillar area at the base of the tongue which represented the primary tumor. A CT of the brain and chest was negative for metastatic disease.

Formal cancer diagnosis for this patient was squamous cell carcinoma of the base of the tongue classified as a T3N3M0 stage 4b. His case was presented to the hospital tumor board and it was recommended that he undergo a concurrent course of chemoradiation with a modified radical neck dissection.

Clinical course

Per institution protocol for all stage 4b head and neck cancer expected to develop oral and alimentary mucositis, the patient underwent placement of percutaneous G-tube and given a home supply of tube feeding solution. His concurrent chemoradiation consisted of weekly transfusion of Paclitaxel and Carboplatin with radiation totaling 71 Gy for base of the tongue, 71 Gy to the tumor mass itself and an additional radiation dose of 59 Gy to right sided regional nodes.

By week 2 patient develop WHO Grade 2 oral mucositis, and WHO Grade 1-2 esophageal and small bowel mucositis with painful swallowing, nausea, occasional vomiting and frequent loose stools. Patient was prescribed Prothelial™, a potency-enhanced sucralfate suspension 1.5 g, 3 times daily for 2 d, and then a maintenance dose of 1.5 g twice daily.

RESULTS

Primary outcome measures for HPS

All primary outcome measures were met. There was visible resolution of mucosal erosions and patient reported absence of nausea and diarrhea within 48 h. In week 4 feeling well and assuming that he no longer needed it, the patient stopped HPS for 10 d against protocol while under chemoradiation. He suffered a recurrence of oral lesions, nausea, and diarrhea. Two days following resumption of HPS suspension patient's recurrent symptoms and ulcers had cleared.

Secondary outcome measures for HPS

All secondary outcome measures were met. Patient required no opiate or non-opiate analgesia while on HPS suspension. Additionally while on HPS, the patient did not require use of the feeding tube nor of caloric supplementation as he was able to continue pre-treatment diet, tolerating both solid food and liquids. At the start of chemo-radiation, the patient was 35 lbs overweight for his height of 73 inches, weighing 235 lbs. While on HPS, he maintained his ideal body weight of 198 lbs.

Naranjo Algorithm for HPS

The Naranjo Algorithm is a validated questionnaire designed to determine the likelihood that an observed clinical effect in a patient exposed to a drug can be attributed to the drug or other factors[18]. Though generally used to investigate adverse drug reactions, the Naranjo Questionnaire, in its most basic sense, is a validated method to assess whether a drug or intervention can be linked to a subsequent clinical reaction (or response). Thus it was reasonable to use the algorithm to assess the likelihood that the observed but unexpected clinical response in this patient was due to HPS.

Most patients with stage 4b head and neck cancer treated with radiation, Paclitaxel and Carboplatin concurrently develop oral and alimentary mucositis due to required concurrent chemo-radiation[10,11,19] and indeed by week 2 this patient developed symptomatic oral and alimentary mucositis of the GI tract. Relevant to Naranjo Algorithm is that patient symptoms and signs disappear within 2 d of introduction of HPS, recurred when the patient stopped the sucralfate intervention for 10 d, but then disappeared 2 d following the resumption of HPS.

Table 3 shows the Naranjo score of 10 in this patient treated with HPS. Ordinarily, a score > 9 implies a definite drug-effect association, a score between 5-8 implies

probable association, a score between 1-4 implies a possible association while a score of "0" implies doubtful association. The Naranjo score of 10 for HPS implies that there was likely a "definite" probability that the intervention was associated with the observed clinical improvement in this patient.

DISCUSSION

Rubenstein *et al*[15] reviewed 38 agents and modalities prescribed by physicians from 1985 through 2004 for the management of both oral and alimentary mucositis. By mechanism of action these agents are grouped as anti-inflammatories, anti-infectives, anti-oxidants, immuno-modulators, muco-adhesives, cytoprotectants, anti-ulcerants and biophysical interventions. HPS is a muco-adhesive cytoprotectant that appears to facilitates immuno-modulatory prevention and reversal of mucositis through out the GI tract.

MASCC guidelines[15] do not recommend the use of standard potency sucralfate to treat or prevent mucositis. However, in the patient of this report, HPS prevented oral and alimentary mucositis. When HPS was inadvertently discontinued, when both oral and alimentary mucositis recurred, due to patient's inadvertent noncompliance, HPS treated it fairly rapidly within 48 h.

For this patient the use of HPS obviated the need to reduce or in any way alter an aggressive treatment regimen for the cancer. There was no use of opiate analgesia. Tube-feed supplementation was unnecessary as well. Obviously, an expanded evaluation of HPS is required as these responses were observed in a single patient.

Translational medicine view

Mucositis is a long-standing unmet medical need in supportive care of cancer treatment. A positive clinical effect of HPS on oral and alimentary mucositis stands in stark contrast to the exclusion of sucralfate from MASCC guidelines - guidelines that greatly impacts medical practice and research. Indeed, expanded clinical trials are necessary to ascertain the permanence (if any) of this HPS observation. Nevertheless the question remains as to mechanism whereby HPS could possibly ameliorate signs and symptoms of mucositis. The following mechanism proposed in this report utilized methods of translational medicine to integrate basic science input from multi-disciplines of study. This mechanism of action for HPS centers on the efficient activation of mucosal growth factors near the site of mucosal injury or assault. From the viewpoint of translational medicine, efficient activation of nascent mucosal growth factors is a therapeutic target for others in the field, focusing efforts on the discovery of other, potentially better, agents to treat and prevent mucositis. The remainder of this report is devoted to a fundamental standard of translational medicine - understand the actions of an intervention so as to use its principle to unearth additional potentially better interventions.

Understanding sucralfate: Its potency and multi-modal mechanism of action

Sucralfate is a polyanionic disaccharide that exerts the totality of its clinical effects through physical contact with the mucosa. It is non-systemic. The classic understanding of sucralfate's mode of action is that it acts as a "bandage", as a physical barrier covering the mucosal, supplemented by chemo-adsorption actions of sucralfate against pepsin and bile salts[20].

However, Hollander *et al*[21] reported other near-immediate mucosal effects following administration of sucralfate. Within 10 min of contact on the mucosa and at appropriate doses, sucralfate initiates epithelial regeneration and stimulates (1) secretion of a mucus gel; (2) the release of bicarbonate beneath this gel; and (3) the secretion of somastatin and prostaglandin E. Unknown at the time of their report, these effects were mediated by direct engagement of focal growth factors by sucralfate. "In appropriate doses" is the operative phrase. The effects of sucralfate reported by Hollander *et al*[21] occurred at doses five to twenty times the allowable human dose of 14 mg/kg. Rats received single doses of 70-280 mg/kg. In man, the latter high oral doses can result in bezoar formation in man.

Potency enhancement of sucralfate

Potency of sucralfate is defined as the extent of clinical effect associated with surface concentration of sucralfate achieved following administration. Standard potency sucralfate cannot treat or prevent oral or alimentary mucositis. However, the potency of sucralfate can be greatly enhanced by suspending standard potency sucralfate in a solution of multivalent cations buffered by multi-dentate anionic chelators. The resultant "cross-linked" sucralfate is believed to facilitate orderly layering of sucralfate on the mucosa and upon itself. Orderly layering on the mucosa and upon itself could account for the multifold elevation of surface concentration of sucralfate in HPS per dose without a commensurate increase in its formulary strength in grams per milliliter. Three hours following administration, HPS maintains mucosal concentrations of sucralfate at least 7 fold that expected for standard potency sucralfate of equal formulary strength[17]. On ulcerated or irritated enteric lining the mucosal concentrations of sucralfate from HPS is 23 fold above that expected for standard potency sucralfate of equal formulary strength.

These multiples of surface concentration achieved by HPS are equivalent to the augmented doses of sucralfate used unsuspectingly by Hollander *et al*[21]. This potency enhancement effect is retained when HPS suspension is dehydrated and administered as a powder in a capsule.

Immuno-modulatory and depolorization mechanism of action

The exact mechanism of action of HPS is unknown. However, relying on the literature across several disciplines of biomedical sciences, a case can be made that HPS (as well as other polyanionic compounds) provides two significant effects on contact: firstly an immuno-

modulatory effect through non-specific but high-affinity interactions with growth factors and secondly, an ionic depolarization of activated ("firing") ion-gated nociceptors embedded in the mucosa. Ion-gated nociceptors embedded within the mucosa give rise to pain, nausea and vomiting. Polyanionic stabilization of ion-fluxes in activated nociceptors reduce their firing, and thereby the sensation of pain, nausea and vomiting on contact. Activated growth factors of the GI tract maintain normal mucosal function and epithelial integrity. The following outlines salient features of GI function that are most likely influenced by the topical application of HPS.

Mucosal physiology of GI tract

The mucosal lining of the GI tract is tasked with both digestive and defensive functions[22,23]. For the purposes of defense, the GI lining has an embedded array of specialized mucosal receptors (nociceptors)[23,24], intramucosal (epithelial) lymphocytes[25-34] sub-mucosal immune cells[35-42] and sub-mucosal sensory and effector neurons[23,24]. Mucosal nociceptors are gated-ion type receptors that register acidity, pressure, stretch and pain and are innervated by A-fiber and C-fiber neurons[23-25].

Specialized mucosal lymphocytes known as intra-epithelial lymphocytes (IELs) are responsible for surveillance and detection of unwanted agents, toxins and substances[23-25]. There are three major subpopulations of such cells[26,31,32]. Two major subpopulations of α-β IEL's (αβ-IELs) that filter luminal contents for foreign antigens or toxins and are generally responsible for signaling the presence of unwanted agents by active expression of pro-inflammatory cytokines[31,32]. The third subpopulation of surveillance lymphocytes known as γ-δ IEL's (γδ-IELs) are tasked with (1) controlling and temporizing the signaling functions of the first two subpopulations of αβ-IELs; (2) defend against microbial invasions; (3) support epithelial cells; and (4) focal elaboration and feedback secretion of transforming TGFβ[26-30]. γδ-IELs are subject to direct modulation by neighboring epithelial cells. The communications between IEL's and epithelial cells are conducted *via* cytokines[28,29,33,43-45].

Submucosal immune cells, namely mast cells, are stimulated (up-regulated) by pro-inflammatory cytokines released from upregulated IELs. Up-regulated mast cells release pro-inflammatory cytokines that in turn affect (or up-regulate) sub-mucosal neurons[35-42]. Submucosal neurons up-regulate by pro-inflammatory cytokines from IEL-stimulated mast cells then elaborate and release neuron-derived cytokines and effector substances like substance-P, vasoactive intestinal protein and neurokinins[23,31,32,34].

In turn, neuro-cytokines and effector substances released by up-regulated neurons can (1) stimulate epithelial cells to secrete fluids[23,24,46]; (2) stimulate sub-mucosal muscularis and the circular muscles of the gut to contract while simultaneously causing the longitudinal muscles to relax[23-25,47,48], (actions that result in intestinal cramping and bloating); and (3) stimulate capillary vessels to expand and increase their flow[23,24]. Additionally, stimulated sub-mucosal sensory neurons release pain substances within the sub-mucosa and into the bloodstream; they also transmit up-regulating neuronal signals outside the GI tract into dorsal root ganglia of the spine[23,24,49,50] to affect segments of the GI that are proximal and distal to the area of IEL activation.

These mucosal-mediated actions are defensive and lead to a "functional mucosal syndrome", a syndrome wherein the clinical symptoms of nausea, vomiting, pain[24,49], colic, ileus[47,48], even diarrhea[50-52] arises from mucosal mediated defensive actions provoked by antigen stimulated firing of αβ-IELs. These actions structure substantially the mucosal immuno-neuronal physiology that is indirectly affected by HPS on the instance of its contact with the mucosa.

These defensive functions of the epithelium are led by an exaggerated presence of pro-inflammatory cytokines that are secreted out of balance relative to the presence of anti-inflammatory cytokines. Activated growth factors similar to fibroblast growth factor, EGF, and TGF[53-57] are tasked with restoring cytokine balance. The consequence of disproportionate concentration of pro-inflammatory cytokines is a feedback secretion of growth factors, and more importantly, a feedback increased expression of growth factor receptor sites on nascent enteric epithelial cells[58]. Activated growth factors, once inserted into their tyrosine kinase membrane receptors, spawn the release of anti-inflammatory cytokines, with a feedback reversal of expressed pro-inflammatory cytokines[58] as well as re-epithelialization of the mucosa[55].

HPS facilitate local engagement of mucosal growth factors

HPS engagement of the mucosal surface may lead to focal movement growth factors, which facilitate conformational changes to enable their insertion into tyrosine membrane receptors[53]. In this way HPS supports the "immuno-balancing" efforts of growth factors by direct physical engagement of growth factors[53,54]. Thusly, HPS accelerates a growth factor-dependent correction of "cytokine imbalance", reversing "functional mucosal syndrome", with the reversal of nausea, vomiting, diarrhea, ileus, cramping, and bloating[47,48,50,52]. Active engagement of growth factors by HPS accelerates healing of erosions and ulcerations[53,54,56].

Potency-enhanced sucralfate or HPS appears useful for treatment and prevention of chemo-radiation induced mucositis in both the upper and lower GI tract. Given that severe cases of mucositis lead to dehydration, systemic infections and unwanted reduction or postponement of optimal cancer treatment this observation in reported here could be significant. Disciplined investigations on the use of HPS in patients with mucositis are necessary to assess reproducibility of this observation and to establish efficacy and safety. The suggested mech-

anism of action is testable by multi-array cytokine analysis of mucosal biopsies prior to, during and following treatment with HPS. Obviously, like HPS, any other non-systemic polysaccharides suitable for potency-enhancement could be investigated for efficacy in the treatment of oral and alimentary mucositis.

COMMENTS

Background

An imbalance favoring pro-inflammatory cytokines over anti-inflammatory cytokines is likely involved in the disease process of chemo-radiation induced oral and alimentary mucositis. Cancer patients suffering from mucositis have limited therapeutic support options. As a result poorly treated mucositis can lead to suboptimal cancer treatment, dehydration, costly re-hospitalizations and untimely deaths.

Research frontiers

In 2012 the Mucositis Study Group of the Multinational Association of Supportive Care in Cancer/International Society for Oral Oncology reviewed 64 clinical studies involving 11 interventions for mucositis. They found only one intervention adequate for guideline recommendation. Evidence supported limited use of recombinant human KGGF-1 (palifermin) for prevention (but not treatment) of oral mucositis if given three d prior to conditioning and three d following autologous stem cell transplantation in hematological malignancies. Inconclusive evidence prohibited guideline recommendations for any other intervention. Standard potency sucralfate was not recommended.

Innovations and breakthroughs

High potency sucralfate (HPS) is new. It is a suspension of standard potency sucralfate in a cationic solution of multi-dentate chelators. HPS hyper-concentrates sucralfate on the mucosal lining such that 3 h following its administration, the surface concentration of sucralfate remains 7-23 fold greater than otherwise expected - 7 fold greater on normal mucosal and 23 fold greater on ulcerated lining. Sucralfate of standard potency binds mucosal growth factors, yet fails to demonstrate substantial clinical effects. However the use of HPS in this patient resulted in simultaneous prevention and treatment of oral and intestinal mucositis. It is assumed therefore that there is an augmented interaction between HPS and mucosal growth factors.

Applications

The use of HPS infers that there are additional mechanisms of action for sucralfate than previously thought. These would include immuno-modulation centered on engagement and activation of mucosal growth factors as well the depolarization of ion-gated nociceptors resulting in rapid relief of mucosal pain. There may be other applications of HPS particularly in clinical scenarios dependent on epithelial healing and repair.

Peer review

This paper explores HPS may directly or indirectly facilitate an immunomodulatory mechanism involving accelerated growth factor activation, which may be a new target for therapeutic intervention in such patients. It is an interesting and very well written article.

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BRIEF ARTICLE

Examining the relationship between physical fitness and spiritual fitness in cancer patients: A pilot study

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Abstract

AIM: To examine the relationship between spiritual fitness and overall physical fitness, and their resulting impact on feelings of depression and anxiety in individuals being treated for cancer.

METHODS: Thirty patients completed the McGill Quality of Life questionnaire and the Spiritual Fitness Assessment survey, and were asked to classify themselves as "Religious" or "Non-Religious". After the questionnaires were completed, each patient underwent a comprehensive fitness assessment, which included assessments for VO_{2max}, muscular strength and endurance, flexibility, and body composition, as well as height, weight, and resting heart rate and blood pressure. The data collected were averaged and analyzed using a one-way ANOVA test at the 0.05 level of significance.

RESULTS: Of the 30 participants, 17 classified themselves as "religious" (*R*) and 13 classified themselves as "non-religious" (*NR*). The *R* group had a higher body fat percentage and a lower VO_{2max} than the *NR* group. However, these results were not significant. It was also determined that the *R* group scored themselves significantly higher than the *NR* group on the Spiritual Fitness questionnaire, but reported significantly higher levels of depression and anxiety than their non-religious counterparts.

CONCLUSION: Health beliefs did not necessarily back up health practice; specifically, those respondents who classified themselves as "religious" reported that their beliefs positively influenced their health behaviors, yet physiological and psychological data did not support this claim.

Key words: Cancer; Exercise; Spirituality; Health practice; Health beliefs; Fitness; Anxiety

Core tip: The purpose of this study was to examine the relationship between spiritual fitness and overall physical fitness, and their resulting impact on feelings of depression and anxiety in individuals being treated for cancer. Thirty participants completed a quality of life and a spiritual fitness survey, and performed a comprehensive fitness evaluation. It was determined that health beliefs did not necessarily back up health practice; specifically, those respondents who classified themselves as "religious" reported that their beliefs positively influenced their health behaviors, yet physiological and psychological data did not support this claim.

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INTRODUCTION

A cancer diagnosis can affect an individual's core as-

sumptions regarding life trajectory, beliefs about the self, control, self-worth, and the existential. Oftentimes such a diagnosis leads an individual to a process of spiritual and emotional transformation[1]. It is estimated that around 58% of cancer patients experience depression[2] and approximately 23% suffer from anxiety[3]. However, a positive correlation has been found between spirituality and emotional adjustment to cancer[4,5], indicating that spirituality plays a significant role in helping patients deal with their thoughts of mortality[4].

Similarly, research documents several positive physiological and psychological changes for cancer survivors who participate in structured exercise programs. These include improvements in VO_{2max}[6], muscular strength and endurance[7], and reduced levels of fatigue[8-12], anxiety[13,14], and depression[13-15]. As such, the American Cancer Society recommends that exercise serve as an important part of an individual's cancer care plan, asserting that exercise will improve an individual's feelings of control and hope[16]. However, published reports indicate that most (85%) of the cancer population are not currently meeting these recommendations for exercise[17].

Along with the beneficial effects of habitual physical activity, research studies have shown religious involvement to positively impact mortality risk[18], health status, mental and physical well-being[19], and a sense of self-efficacy[20]. The positive impact appears to extend to all genders, races, and socioeconomic categories[21,22]. However, recent studies show that people who would classify themselves as religious individuals are more likely to be obese than their non-religious counterparts[22,23].

Now more than ever, healthy behavior choices and emotional support are being promoted in attempt to limit cancer. Traditionally, research examining the relationship between spiritual and physical fitness has focused mostly on the healthy adult population. However, in light of the physiological stress experienced by many cancer survivors, it is critical that their psychosocial needs be addressed, as well. Therefore, the purpose of this study was to examine the relationship between spiritual fitness and overall physical fitness, and their resulting impact on feelings of depression and anxiety in individuals being treated for cancer.

MATERIALS AND METHODS

Subjects

Thirty patients were recruited for participation in this investigation. The eligibility criteria included individuals who are currently undergoing cancer treatment and are able to read and write in English. Patients were recruited from local oncology offices and hospitals. All procedures were approved by the Wright State University Institutional Review Board prior to data collection.

Data collection

The 30 patients who met the eligibility criteria and agreed to participate filled out the McGill Quality of Life questionnaire and the Spiritual Fitness Assessment survey (Fletcher, D), where they were asked to classify themselves as "Religious" or "Non-Religious". Religious was defined as "having or showing belief in and reverence for God; implies both belief and practice" (The Free Dictionary). After the questionnaires were completed, each patient underwent a comprehensive fitness assessment. The fitness evaluation included assessments for VO_{2max}, muscular strength and endurance, flexibility, and body composition, as well as height, weight, and resting heart rate and blood pressure measurements.

Table 1 Subject characteristics

Characteristics		*n*
Age (yr)	40.6 ± 2.6	
Gender	Male	11
	Females	19
Type of cancer	Prostate	5
	Colon	8
	Chemotherapy	20
	Breast	17
Current course of treatment	Radiation	7
	Surgery	3

Statistical analysis

The data collected from the psychological questionnaires and the fitness assessments were averaged and analyzed using a one-way ANOVA test. All data was analyzed at the 0.05 level of significance.

RESULTS

Subjects

A total of 30 individuals (*n*, male = 11, female = 19) participated in this investigation. Of these 30 individuals, a total of 17 classified themselves as "religious" (*R*) and 13 classified themselves as "non-religious" (*NR*). Table 1 illustrates the subject characteristics, along with type of cancer and current course of treatment.

Fitness assessment data

Figure 1 presents VO_{2max} and body composition results. Although the results show a trend where the Religious group had a higher body fat percentage (R = 35.13% ± 2.4%, NR = 32.33% ± 3.4%, Figure 1), and a lower VO_{2max} (in mL/kg per minute, R = 17.25 ± 1.7, NR = 22.24 ± 1.8, Figure 1), these results were not significant.

Physiological and spiritual questionnaires

Two questions from the Spiritual Fitness Assessment were selected from the questionnaire to compare with the biometric data. The analyzed questions from the Spiritual Fitness Assessment were: "I engage in healthy behaviors to care for my body as God's temple", which received an overall mean of 2.88 ± 0.3, on a 7-point scale, from respondents; and "I draw special strength/power from God's Spirit to make health-related behavior choices and

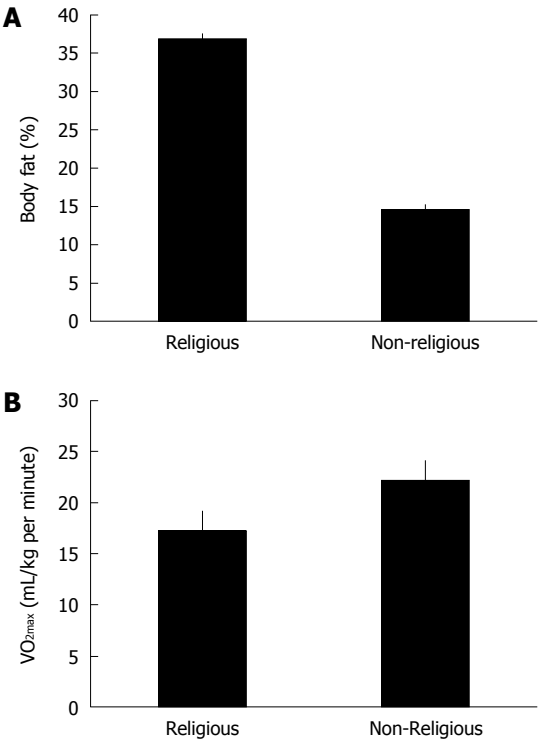

Figure 1 VO_{2max} and body composition results. A: Body fat percent; B: VO_{2max}. Values are mean ± SE.

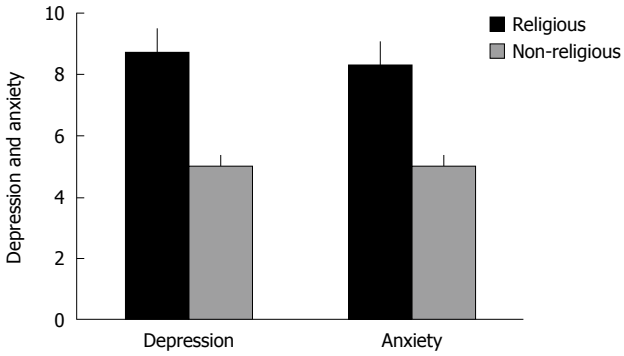

Figure 2 Depression and anxiety scores. Values are mean ± SE, on a 10-point scale.

changes in my life", which scored an overall mean of 2.78 ± 0.34 on a 7-point scale. When examined according to their respective *R*, *NR* groups, it was determined that the *R* group scored themselves significantly higher than the *NR* group on both questions (*R* = 3.77 ± 0.7, *NR* = 2 ± 0.3, *P* = 0.001; *R* = 3.44 ± 0.6, *NR* = 2 ± 0.2, *P* = 0.001, respectively).

Two questions on the McGill Quality of Life questionnaire were also analyzed. Patients were asked to indicate on a scale of 1-10 the level of depression and anxiety they have experienced over the last 2 d. Figure 2 presents the results from these surveys. It was determined that individuals in the *R* group experienced significantly higher levels of depression (*R* = 5.25 ± 0.3, *NR* = 3 ± 0.4; *P* = 0.05) and anxiety (*R* = 5 ± 0.25, *NR* = 3 ± 0.6; *P* = 0.03) than their *NR* counterparts.

DISCUSSION

The purpose of this study was to examine the impact of spiritual fitness on overall physical fitness and feelings of depression and anxiety in individuals being treated for cancer. A major finding of this investigation was that health beliefs did not necessarily back up health practice. Although those who classified themselves as "religious" reported that their beliefs positively influenced their health behaviors, physiological and psychological data did not support this claim.

Physical fitness and religion

In the present investigation, religious individuals reported that their belief in God enabled them to make health-related behavior choices and changes in their life. However, when compared to the *NR* group, they had a higher percentage of body fat and a lower VO_{2max}. This finding is consistent with previous investigations, which report an inverse relationship between religious involvement and fat intake[24] and activity levels[25]. Because of their unique role in spiritual guidance, communication, and social support, churches can play an important part in health promotion efforts. Whitt-Glover *et al*[26] found that a faith-based physical activity intervention was successful at increasing physical activity among sedentary adults. Exercise programs that incorporate faith-based practices may appeal to religious individuals (*i.e.*, modest clothing, noncompetitive atmosphere), and provide an alternative strategy for increasing physical activity[27].

Coping

The present study found that religious individuals treated for cancer had higher rates of anxiety and depression than their non-religious counterparts. This finding is not in agreement with a considerable body of literature about the role of religion and coping with morbidity and mortality. Traditionally, research has showed that religious involvement is associated with a decrease in anxiety in both healthy populations[28], and in those battling cancer[29-33].

Appropriate coping techniques are important in combatting the anxiety associated with cancer. Treatment for anxiety typically begins with giving the patient adequate information and support, then developing coping strategies that suit the needs of each patient. Research on the role of religion in helping patient cope has traditionally focused on the behavioral variables of the individual, including church affiliation and attendance[34]. However, an investigation by Bowie *et al*[35] reported that it was the combination of attending church and accepting its teachings that led to lower levels of anxiety than simply church attendance alone. In other words, patients who fully accept their churches teachings on divine healing tend to report less anxiety than those who merely attended a church. Along those lines, a recent report indicated that individuals who claim to be "spiritual" but lack an allegiance to a specific religion may actually be more likely

to experience mental health problems[36]. Thus, certain forms of religious coping affect anxiety differently in cancer patients.

Three different ways religion is involved in coping with major life stressors have been identified: (1) "self directing" coping: where it is assumed that God has provided individuals with the skills and resources to handle their problems; (2) "deferring" coping: which involves the delegation of the responsibility to God, while individuals wait passively on the outcome; and (3) "collaborative" coping: whereby God is defined as a partner who shares in the responsibility with individuals for problem solving[37]. Research indicates that respondents who indicate that they adhere to a deferral-oriented coping style tend to be less anxious than those who cope using self-directing and collaborative means[37].

Practical applications

These findings point to a wide gulf that presently exists between the ideal cancer care and that which is received by most Americans[38], and support a 2005 report from the Institute of Medicine, which highlighted a need to allocate more health care resources for these patients' unique needs[39]. It is imperative that resources be made available to address palliative care, addressing the role of lifestyle and behavior change in improving the health and function of cancer survivors[40,41]. Research suggests that physical activity, nutrition, and emotional support are associated with decreases in feelings of depression, symptoms of late effects of treatment, and cancer relapse, as well as increased remission rates[40,41]. Therefore, efforts must be made to reach out to this unique group of individuals.

COMMENTS

Background

A cancer diagnosis can affect an individual's core assumptions regarding life trajectory, beliefs about the self, control, self-worth, and the existential. Oftentimes such a diagnosis leads an individual to a process of spiritual and emotional transformation. It is estimated that around 58% of cancer patients experience depression and approximately 23% suffer from anxiety. However, a positive correlation has been found between spirituality and emotional adjustment to cancer, indicating that spirituality plays a significant role in helping patients deal with their thoughts of mortality. Thus, the purpose of this study was to examine the relationship between spiritual fitness and overall physical fitness, and their resulting impact on feelings of depression and anxiety in individuals being treated for cancer.

Research frontiers

The important areas in the research field related to this article are any areas that would analyze the quality of life of an individual undergoing cancer treatment. A host of disciplines would be interested to read about how exercise and spirituality can impact anxiety and depression.

Innovations and breakthroughs

A major finding of this investigation was that health beliefs did not necessarily back up health practice. Although those who classified themselves as "religious" reported that their beliefs positively influenced their health behaviors, physiological and psychological data did not support this claim.

Applications

These findings point to a wide gulf that presently exists between the ideal cancer care and that which is received by most Americans, and support a 2005 report from the Institute of Medicine, which highlighted a need to allocate more health care resources for these patients' unique needs. It is imperative that resources be made available to address palliative care, addressing the role of lifestyle and behavior change in improving the health and function of cancer survivors. Research suggests that physical activity, nutrition, and emotional support are associated with decreases in feelings of depression, symptoms of late effects of treatment, and cancer relapse, as well as increased remission rates. Therefore, efforts must be made to reach out to this unique group of individuals.

Terminology

Religious: having or showing belief in and reverence for God; implies both belief and practice. Physical Fitness: good physical condition; being in shape or in condition; the state of good health. Anxiety: a feeling of worry, nervousness, or unease, typically about an imminent event or something with an uncertain outcome. Depression: severe despondency and dejection, accompanied by feelings of hopelessness and inadequacy.

Peer review

The peer reviewer read with great interest the manuscript, this manuscript is interesting and adds valuable information to this field.

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BRIEF ARTICLE

Evaluation of three methods for detection of methicillin-resistant *Staphylococcus aureus*

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Abstract

AIM: To evaluate GenoType methicillin-resistant *Staphylococcus aureus* (MRSA) Direct assay and cultivation for the identification of MRSA by using *mecA* polymerase chain reaction (PCR) as the "gold standard" assay.

METHODS: In total of 61 nasal specimens from patients at the intensive care unit were studied by GenoType MRSA Direct test, conventional culture method and automated bacterial identification system. The results of GenoType MRSA Direct assay were compared to conventional culture method the identification of MRSA and *mecA* gene PCR as the "gold standard" method. The sensitivity, specificity, positive predictive value and negative predictive value were calculated.

RESULTS: In total, 61 specimens were studied. Fifty-four specimens (88.5%) were negative by all three methods. Six swabs (9.8%) were found positive by GenoType MRSA Direct test, conventional culture method and automated bacterial identification system. The presence of *mecA* in these strains was confirmed by PCR. One swab sample was negative for culture methods but MRSA and *mecA* gene were detected by GenoType MRSA Direct test and *mecA* PCR respectively. GenoType MRSA Direct test had a sensitivity of 100% (6/6) and a specificity of 100% (55/55), with a positive predictive value of 100% and a negative predictive value of 98%. Culture method of MRSA had a sensitivity of 83.3% (5/6) and a specificity of 98.2% (55/56).

CONCLUSION: It was found that the GenoType MRSA Direct assay, which is a rapid and accurate test, is of the same sensitivity and specificity with mecA PCR. The GenoType MRSA Direct assay can be a better tool for rapid and accurate detection of MRSA in diagnostic laboratories.

Key words: Culture; Methicillin-resistant *Staphylococcus aureus*; Molecular assays

Core tip: For the identification of methicillin-resistant *Staphylococcus aureus* (MRSA), GenoType MRSA Direct assay and cultivation were evaluated by using mecA polymerase chain reaction (PCR) as the "gold standard" assay. Fifty-four specimens (88.5%) were negative by all three methods. Six swabs (9.8%) were found positive by GenoType MRSA Direct test, conventional culture method and automated bacterial identification system. The presence of *mecA* in these strains was confirmed by PCR. One swab sample was negative for culture methods but MRSA and *mecA* gene were detected by GenoType MRSA Direct test and *mecA* PCR respectively. It was found that the GenoType MRSA Direct assay, which is a rapid and accurate test, is of the same sensitivity and specificity with mecA PCR.

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INTRODUCTION

Methicillin-resistant *Staphylococcus aureus* (MRSA) has become increasingly prevalent worldwide. Since its discovery during the 1960s, MRSA has emerged as a common cause of nosocomial infection. Infections caused by MRSA is one of the major sources of morbidity and mortality nosocomial infections especially in the intensive care units (ICU). Prevention of nosocomial infections caused by MRSA in ICU has been recommended for several years[1,2]. The spread of MRSA can be controlled by effective preventive measures and to limit this spread, a rapid and sensitive test for detection of MRSA colonization is required. However, conventional tests for the identification of MRSA require at least 48 h to be completed[3]. In recent years, there has been a growing emphasis on the use of molecular methods to detect not only just infectious agents but also antimicrobial-resistance genes carried by microorganisms[4]. Several DNA based tests have been developed for the rapid detection of MRSA[3].

Methicillin resistance in *Staphylococcus aureus* (*S. aureus*) is mediated by the production of an altered penicillin-binding protein, PBP 2a[5]. The mec gene complex regulates the production of PBP 2a. The detection of the *mecA* gene or of PBP 2a provides much more accurate detection of methicillin resistance in *S. aureus*[5,6]. *MecA* gene detection tests based on polymerase chain reaction (PCR) are considered as the gold standard for methicillin resistance[5].

Screening of the patients with risk factors for MRSA carriage is important for a successful MRSA control policy. At our hospital, infection control precautions are taken immediately after a positive MRSA result becomes available from diagnostic and surveillance specimens. Since molecular methods are rapid, with turnaround times of 2 to 4 h, these tests are able to improve the utilization of infection control resources. We compared GenoType MRSA Direct assay and culture for identification of MRSA using PCR for mecA as the "gold standard" assay.

MATERIALS AND METHODS

A total of 61 consecutive patients were screened for MRSA. Of the patients, 32 (52.4%) were female and 29 (47.5%) were male. Ethical approval was received from Ataturk Training and Research Hospital Ethics Committee.

Specimen collection and processing

Nasal specimens were obtained from patients at ICU. Two concurrent specimens were obtained from each site swabbed. First swab was used for culture and second swab was used for molecular assays. Swabs were transported at room temperature and processed within 1 to 3 h of collection.

Bacteria isolation

The swabs were inoculated on blood agar plates directly on the day of receipt of the swab, incubated at 35 ℃ in O_2, and read after 24 and 48 h. A colony suggestive of Staphylococcus was confirmed as *S. aureus* by using a tube coagulase and DNase test, while methicillin resistance was confirmed with cefoxitin susceptibility testing according to the Clinical and Laboratory Standards Institute method[7]. The Phoenix (Becton Dickinson, Sparks, MD, United States) was used for confirmation of strains. Control strains, MRSA strain (ATCC 43300), and methicillin-susceptible *S. aureus* (ATCC 25923) were used in all tests.

GenoType MRSA direct assay

DNA extraction and amplification: The swabs were processed using the GenoType MRSA Direct (Hain Lifescience, Nehren, Germany) method. According to the manufacturers' recommendations, the swabs were washed in 300 μL of lysis buffer before DNA extraction. Bacterial DNA was released by incubation of the lysis buffer for 10 min at 95 ℃, followed by centrifugation for 5 min at 6000 *g*. Portions (5 μL) of the supernatant were used for amplification. In brief, 45 μL of primer nucleotide mix (provided with the kit), $MgCl_2$ to a final concentration of 2.5 mmol/L and 1 U of HotStart Taq polymerase (Qiagen, Hilden, Germany) were added, followed by amplification on a PE 9700 thermocycler (Applied Biosystems, Weiterstadt, Germany) for 15 min at 95 ℃, 35 cycles of 95 ℃ for 30 s, 55 ℃ for 40 s and 72 ℃ for 40 s, and a final extension at 70 ℃ for 8 min. Each run included a negative control sample to demonstrate the absence of contaminating DNA. The sensitivity of amplification and hybridisation was monitored using an internal control.

Hybridization protocol: Briefly, the assay uses a specific oligonucleotide probe, targeting the SCCmec chromosomal cassette of MRSA immobilized on membrane strips. During the detection process PCR amplicons hybridise with this probe. Hybridization and detection were performed in an automated washing and shaking device (Profiblot; Tecan, Maennedorf, Switzerland). PCR products (20 μL) were mixed for 5 min with 20 μL of denaturing reagent (provided with the kit) at room temperature in separate troughs of a plastic tray. After addition of 1 mL of pre-warmed hybridization buffer, the membrane strips in the kit were added to every trough. Hybridization was at 45 ℃ for 30 min, followed by two washing steps at 45 ℃ for 30 min with 1 mL of pre-warmed stringent wash solution. Streptavidin-conjugated alkaline phosphatase and the appropriate substrate were added for colourimetric detection of hybridised amplicons. After final washing, the strips were air-dried and fixed on a data sheet. DNA isolation, amplification and hybridisation, were monitored using an internal control to improve the reliability of the test.

MecA gene PCR

The following primers were used: M1 (TGGCTATCGTGTCACAATCG) and M2 (CTGGAACTTGTTGAGCAGAG) that amplify a 310-bp fragment of the *mecA*

gene, which codes for the PBP 2a protein. The mixture for PCR consisted of 5 μL of PCR buffer 10 (final concentration: 50 mmol/L KCl, 0.01% gelatin, 10 mmol/L Tris-HCl; pH 8.3), 1.5 mmol/L $MgCl_2$, 0.1 mmol/L dNTP (dATP, dCTP, dGTP and dTTP), 0.4 pmol/mL of each of the specific primers, 2 U of tag polymerase and 5 μL of the template to get a final reaction volume of 50 μL. All components were mixed in polystyrene tubes and subjected to amplification temperatures of the nucleic acid in a thermocycler. DNA from the methicillin resistant *S. aureus* reference strain (ATCC 43300) was used as positive control of the reaction and sterile bi-distilled water as negative control.

The mixture was initially denatured at 94 ℃ for 5 min and then underwent 35 cycles of: 30 s at 94 ℃, 30 s at 52 ℃ and 30 s at 72 ℃. The reaction was finished with 5 min at 72 ℃. The amplification products were detected with agarose gel electrophoresis (2% in TBE 0.5X buffer) at 100 V for 35 min.

Statistical analysis

The results of GenoType MRSA Direct assay were compared to conventional culture method the identification of MRSA and *mecA* gene PCR as the "gold standard" method. The sensitivity, specificity, positive predictive value and negative predictive value were calculated.

RESULTS

In total, 61 specimens were studied. Fifty-four specimens (88.5%) were negative by all three methods. Six swab samples (9.8%) were positive by conventional culture method and automated bacterial identification system (Table 1). The presence of *mecA* in these strains was confirmed by PCR and GenoType MRSA Direct test. Although one swab was negative by conventional culture method and automated bacterial identification system, it was positive for m*ecA* gene detected by GenoType MRSA Direct test and *mecA* PCR respectively. The results of 61 specimens studied were shown in Table 1. GenoType MRSA Direct test had a sensitivity of 100% (6/6) and a specificity of 100% (55/55), with a positive predictive value of 100% and a negative predictive value of 98%. Culture method of MRSA had a sensitivity of 83.3% (5/6) and a specificity of 98.2% (55/56). Images of *mecA* PCR and GenoType MRSA Direct test are shown in Figures 1 and 2.

DISCUSSION

The prevalence of MRSA carriage on hospital admission is important in determining the effect of implementing any screening policy. Standard culture methods require at least 24 to 48 h for the recovery and identification of *S. aureus* and additional confirmatory tests[8] or susceptibility testing methods to determine methicillin resistance. Genotype MRSA direct test has been completed in approximately 4 h for detecting MRSA in the present study. Early and specific diagnosis of MRSA infections is significant in preventing their spread. Delays in detection of MRSA lead to the increased transmission of MRSA among patients, higher numbers of MRSA infections, and increased hospital costs[3]. A rapid and reliable test for the identification of MRSA would be desirable so that effective therapy could be initiated immediately. In recent years, there has been a growing emphasis on the use of molecular methods to detect not just infectious agents but also antimicrobial-resistance genes carried by microorganisms[4]. A study investigating the value of rapid diagnostic tests for MRSA when used for admission screening to a critical care area reported a reduction in the incidence of transmission of MRSA from 13.89/1000 patient days to 4/1000 patient days[9].

PCR tests are valuable for the rapid detection of MRSA carriers[10]. Conventional culture based detection methods for MRSA are time-consuming which leads to delayed isolation. Rapid molecular detection assays such as conventional PCR, real-time PCR and gene probe hybridization assays. Real-time PCR, has improved the sensitivity, and specificity, enables detection of resistance in

Table 1 Results for the detection of methicillin-resistant *Staphylococcus aureus*

n	Genotype MRSA Direct test	Culture	MecA PCR
54	-	-	-
6	+	+	+
1	+	-	+
Total = 61			

MRSA: Methicillin-resistant *Staphylococcus aureus;* PCR: Polymerase chain reaction.

Figure 1 Agarose gel electrophoresis for mecA (310 bp) gene. Lanes 1 and 38: Molecular weight ladder; Lane 2: Negative control; Lanes 4, 10, 14, and 20: Positive clinical isolates; Lane 37: Positive control; Other lanes: Negative clinical isolates.

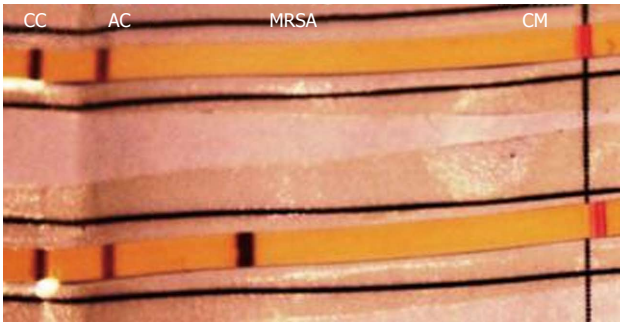

Figure 2 Image of positive and negative sample in GenoType methicillin-resistant *Staphylococcus aureus* Direct test. CC: Conjugate control; AC: Amplification control; MRSA: Methicillin-resistant *Staphylococcus aureus*; CM: Colored marker.

a shorter time and lower risk of contamination than conventional PCR[11,12]. IDI-MRSA and the genotype MRSA tests can detect MRSA within a few hours directly from screening swabs with good sensitivity and specificity of 81% to 92% and 93% to 98%, respectively[10]. GenoType MRSA Direct test was evaluated to detect for the rapid detection of MRSA from nasal specimens in the present study. We evaluated the results of GenoType MRSA Direct test with the results obtained from conventional culture assay and PCR as the gold standard. We found a sensitivity of 100% and a specificity of 100%, with a positive predictive value of 100% and a negative predictive value of 98% with three tests. Our results were similar previous studies[13-15]. Warren *et al*[13] used a commercially available real-time PCR kit to detect MRSA directly from nasal swabs of 288 patients. They reported a sensitivity of 91.7%, and a specificity of 93.5%, with a positive predictive value of 82.5% and a negative predictive value of 97.1%. Similar results were reported by Huletsky *et al*[14,15] with the same system from 331 nasal swab specimen, with a sensitivity of 100%, specificity of 96.5%, with a positive predictive value of 89.4% and a negative predictive value of 100%.

Rising colonization rates lead to increased infection rates in the community and in hospitals. It has also been reported that rapid detection of carriage has an important role to play in such a "search-and-destroy" strategy[16,17]. van Hal *et al*[18] compared the relative sensitivities and specificities of the IDI-MRSA and GenoType MRSA Direct assays and three selective MRSA agars, MRSA ID, MRSA*Select*, and CHROMagar MRSA, with swabs from the three most commonly screened sites, *i.e.*, the nose, groin and axilla. They informed that IDI-MRSA was the most sensitive method for the detection of MRSA with nasal swabs, with 90% sensitivity. GenoType MRSA Direct test had a sensitivity of 69%. However, Holfelder *et al*[3] found the sensitivity 94.5% of GenoType MRSA Direct test in their study. Swabs from 242 patients at risk for MRSA carriage were analysed by standard culture method and the PCR assay. They reported that the GenoType MRSA Direct assay provides a rapid, sensitive and specific method, in comparison with selective culture, for direct detection of MRSA in clinical swab specimens.

Tokue *et al*[6] tested *mecA* gene in 58 clinical isolates by the PCR and Southern blot analyses. Six PCR-positive strains were classified as methicillin susceptible by the conventional susceptibility test. They reported that the PCR assay appears to be more reliable than routine susceptibility testing. In the present study, one swab was negative for culture method but MRSA and *mecA* gene were detected by GenoType MRSA Direct assay and *mecA* PCR respectively. However, the broad use of MRSA PCR assays is hampered by high costs for PCR[19]. PCR tests are valuable for the rapid detection of MRSA, but high costs require the careful evaluation of their use. In patient populations with low MRSA endemicity, the broad use of PCR may not be cost-effective. But the rapid detection of MRSA carriers is important with low MRSA prevalence, since MRSA control is easiest when rates are still low, and maximal efforts should be made to maintain such epidemiology[10]. Metan *et al*[12] reported that the molecular assays would be appropriate for tertiary hospitals considering the upfront costs and requirement of expert laboratory staff.

Although conventional tests for identification of MRSA require at least 48 h, the GenoType MRSA Direct assay has rapid turnaround time of 4 h. This assay provides same day results and reduces the isolation time required for patients at risk of MRSA carriage. te Witt *et al*[20] emphasized that, nucleic acid-amplification techniques offer clear benefits over traditional culture-based assays, in particular, a reduced time to identification and an improved specificity and sensitivity. Luteijn *et al*[21] reported that it was a significantly higher sensitivity was found for the PCR in the recent article. Continual monitoring of clinical isolates is necessary to develop and maintain an effective strategy against *S. aureus* infection in the hospital setting[22].

As a conclusion, for the screening of MRSA in clinical swab specimens, it was found that the GenoType MRSA Direct assay, which is rapid and accurate test, is of the same sensitivity and specificity with mecA PCR in the present study. The GenoType MRSA Direct assay can be a better tool for the rapid and accurate detection of MRSA in diagnostic laboratories.

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Thanks to Hain Lifescience-Turkey for providing GenoType MRSA Direct test.

COMMENTS

Background

Methicillin-resistant *Staphylococcus aureus* (MRSA) has become increasingly prevalent worldwide. The spread of MRSA can be controlled by effective preventive measures and to limit this spread, a rapid and sensitive test for detection of MRSA colonization is required. Screening of the patients with risk factors for MRSA carriage is important for a successful MRSA control policy. Since molecular methods are rapid, with turnaround times of 2 to 4 h, these tests are able to improve the utilization of infection control resources. Authors compared GenoType MRSA Direct assay and culture for identification MRSA using polymerase chain reaction (PCR) for mecA as the "gold standard" assay.

Research frontiers

Infections caused by MRSA is one of the major sources of morbidity and mortality nosocomial infections especially in the intensive care units (ICU). Infection control precautions should taken immediately after a positive MRSA result becomes available from diagnostic and surveillance specimens. The article's significance originates from its emphasis on the area of hospital infections.

Innovations and breakthroughs

In recent years, there has been a growing emphasis on the use of molecular methods to detect not just infectious agents but also antimicrobial-resistance genes carried by microorganisms. A study investigating the value of rapid diagnostic tests for MRSA when used for admission screening to a critical care area reported a reduction in the incidence of transmission of MRSA from 13.89/1000 patient days to 4/1000 patient days. Warren *et al* used a commercially available real-time PCR kit to detect MRSA directly from nasal swabs of 288 patients. They reported a sensitivity of 91.7%, and a specificity of 93.5%, with a positive predictive value of 82.5% and a negative predictive value of 97.1%. Similar results were reported by Huletsky *et al*. The present study was performed in a tertiary hospital. Metan *et al* reported that the molecular assays would be appropriate for tertiary hospitals considering the upfront costs and requirement of expert laboratory staff.

Applications

Besides their advantages like high sensitivity and specificity, molecular methods require experienced staff and laboured work. Yet, automatized molecular methods, being effective after in-house PCR, provides standardization along with an ease of use. As more advanced molecular methods are introduced, these methods will be preferred routinely.

Peer review

This article is considered to be helpful for the clinicians about predicting MRSA infections among ICU patients. This consideration appears to be approved explicitly by the clinicians.

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15 Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis serial online, 1995-01-03, cited 1996-06-05;

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