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Pseudobezoars: Technology Progress and New Prospects as a Medical Platform

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ABSTRACT

In recent years, pseudobezoars have been a subject of research, mainly serving as a basis for a new non-invasive alternative to obesity treatment. A pill incorporating the technology has been proven to be successful as a weight loss therapy. It enables patients to sustain a diet longer, due to an increase in the level of satiety, resulting in a smaller amount of food intake. Utilization of the technology has recently found new prospects in another organ of the GI tract, the colon. Pseudobezoar technology can be utilized as an enhanced method for colon cancer screening and also as an alternative carrier for bacterial therapy.

Keywords: Pseudobezoars; Obesity; Colon Cancer Screening; Diagnostic Device; Therapeutic Device

1. Introduction

The pseudobezoar technology is relatively new and only recently has been granted a US patent [1]. However, early successes of utilizing the device as a dietary pill have already been reported [2-4]. The technology comprises a pill coated and targeted for the stomach, where the shell dissolves and the superabsorbent polymer granules within expanding due to the contact with and absorption of gastric liquid. The granules are kept in the stomach without an option to exit, since they are contained in a gauze that disintegrates only after a few days. Taking the pill in a prescribed regimen, demonstrated a significant weight loss in a double blind study [3]. These results confirmed the efficacy of the technology as a dietary pill targeted at the stomach.

We have recently described an additional possibility for usage of the technology, targeting the colon as the organ of choice. The method comprises use of the pseudobezoar as a colon cancer screening device when taken as a colon-targeted pill.

Section 2 will describe the current colon cancer screening options. Section 3 will describe the utilization of pseudobezoars as an alternative to current colon cancer screening technologies. Section 4 will briefly outline the prospects of the utilization of the device as a bacterial transplant and summarize this paper.

2. Current Colon Cancer Screening Options

Colon cancer is the most common gastrointestinal (GI) malignancy and the second leading cause of cancer deaths in the United States [5]. Of the many pre-neoplastic and neoplastic conditions in humans, nowhere is the ability to prevent disease as profound as it is in colon cancer [6]. Strategies for prevention have evolved over the past 15 years, now including the use of fecal occult blood test (FOBT), fecal immunology tests (FIT), fecal DNA tests, colonoscopy, video capsule endoscopy (VCE), and computed tomographic (CT) colonography, also known as Virtual Colonoscopy [7].

2.1. Fecal Occult Blood Tests

Although improved fecal occult blood tests have been utilized, the overall sensitivity of this approach is not impressive. In a 2005 study [8] Morikawa *et al* concluded that the sensitivity of 1-time immunochemical FOBT for detecting advanced neoplasia and invasive cancer was 27.1% and 65.8%, respectively. In addition, the sensitivity for invasive cancer detection according to Dukes' stages showed 50.0% for Dukes' stage A, 70.0% for Dukes' stage B, and 78.3% for Dukes' stages C or D [9]. The sensitivity for detecting advanced neoplasia in the proximal colon was significantly lower than that detected in the distal colon (16.3% vs 30.7%, $p < 0.00007$).

2.2. Fecal Immunology Tests

This testing method can be considered a refinement, extension and an additive improvement over the traditional fecal occult blood testing. It has been reported that when

a routine fecal occult blood test (*e.g.* a sensitive guaiac test) is combined with an immunological test for human haemoglobin, the sensitivity improves to 97% (only 3% false negative results) in patients and no false positives in controls [10]. Another far more comprehensive study [11] found that the sensitivity of the combined test was the highest among all occult blood tests (in the range of 80%), and its specificity for detecting cancer was above 97%. The problem of all fecal occult blood tests, however, is that they aim at discovering blood in the feces resulting from existing bleeding colorectal lesions, while adenomatous polyps in asymptomatic average-risk adults remain undetected. Therefore, by the time findings are obtained with the fecal tests, it is usually too late [12,13]. Nevertheless, the use of either annual or biennial fecal occult-blood testing significantly reduces the risk of colorectal cancer [14].

2.3. Fecal DNA Tests

Oncogene mutations that characterize colorectal neoplasia are detectable in exfoliated epithelial cells in the stool. Whereas neoplastic bleeding is intermittent making the detection of occult fecal blood more or less random, epithelial shedding is continual, potentially making fecal DNA testing more sensitive. Early 21st century reports indicated that a fecal DNA test had a sensitivity of 91 percent for the detection of colorectal cancer and 82 percent for the identification of adenomas[15]. However, one other report indicated that fecal DNA testing did not improve dramatically the preventive early detection of colon cancer compared to occult fecal blood testing [16].

2.4. Colonoscopy

Traditional colonoscopy has been considered the gold standard for assessing colonic abnormalities, offering sensitivity and specificity in detecting polyps exceeding 90%. Moreover, it also offers the ability to remove polyps during the procedure. Although classical colonoscopy can be considered safe, reliable, real-time and quick, recent population-based studies have demonstrated that the rate of protection against colorectal cancer that it offers was only 30% to 50% [17]. In addition, colonoscopy is an invasive procedure, performed in a hospital setting, requires extensive and expensive logistic preparations, carries substantial risks of harming patients (2-4/1000), is heavily operator-dependent, and requires post-procedural recovery [18,19].

2.5. Video Capsule Endoscopy

Orally administered video capsule endoscope(VCE) is a simple, safe, non-invasive, and non-sedation requiring procedure. VCE is well accepted and tolerated by the patients and allows complete exploration of the small bowel. Usually, it takes 24 to 48 hours for a VCE to pass through the entire GI tract as a result of its passive movement from mouth to anus [20]. In view of the fact that the movement of these capsules is controlled by spontaneous gut peristalsis, the application of VCE is currently limited to small-lumen organs [21]. In larger-lumen organs, such as the stomach or the colon, the capsules tend to tumble, which leads to incorrect recognition of a given organ segment by the capsule imaging system, thus rendering the images unsuitable for diagnostic purposes and a miss rate in the colon exceeding 30% [22].

In addition, rapid colonic motility could result in incomplete imaging considering that most of the commercial CEs are designed to acquire images at a pre-fixed frame rate, usually 2 frames per second (FPS) [23]. Moreover, tumbling movement by peristalsis also limits the visual field and causes failure to catch significant lesions or grossly distorts the perceived dimensions of polyps [24].

The Pill Cam Colon capsule (Given Imaging, Yoqneam, Israel) is the only VCE currently in use for colonic investigation. In the most recent study of 56 patients, colon capsule endoscopy (CCE) was followed by conventional colonoscopy (CSPY). Polyp detection rate (per patient) was 50% (n = 28) for CSPY and 62% (n = 35) for CCE. For relevant polyps (> 5 mm) there was a correspondence in the detection rates of both methods (p < 0.05). The mean sensitivity was 50% (p < 0.05), the mean specificity was 76% (p < 0.05), the positive predictive value (PPV) was 20% and the negative predictive value (NPV) was 93% [25]. These results indicate the general problem of VCE tumbling during its transit in the colon and the need for VCE stabilization [24]. A recent report on self-stabilizing capsule endoscopy systems seems to overcome this issue [26].

2.6. Computed Tomographic Colonography (Virtual Colonoscopy)

It has been suggested that virtual colonoscopy performed with a computed tomography is an accurate screening method for the detection of colorectal neoplasia in asymptomatic average-risk adults and compares favorably with optical colonoscopy in terms of the detection of clinically relevant lesions. In a 2003 study [27] Pickhardt et al. suggested that the sensitivity of virtual colonoscopy for adenomatous polyps was 93.8 percent for polyps at least 10 mm in diameter, 93.9 percent for polyps at least 8 mm in diameter, and 88.7 percent for polyps at least 6 mm in diameter. The sensitivity of optical colonoscopy for adenomatous polyps was 87.5 percent, 91.5 percent, and 92.3 percent for the three sizes of polyps, respectively. The specificity of virtual colonoscopy for adenomatous polyps was 96.0 percent for polyps at least 10 mm in diameter, 92.2 percent for polyps at least 8 mm in

diameter, and 79.6 percent for polyps at least 6 mm in diameter.

3. Utilization of the Pseudobezoar as a Diagnostic Screening Device

Recently proposed pseudobezoartechnology has been suggested for the treatment of obesity and for controlled drug delivery in the body (see e.g. [1]). Here we suggest to utilize these retaining devices as platforms for colon biopsy performed from the inside of the colon by a colon-targeted pseudobezoar which will be in contact with the colonic walls in a friction-like fashion severe enough to collect tissue samples, but moderate enough not to cause excessive or abnormal bleeding or mucosal damage. This "artificial stool" will enable generalized biopsy from the entire organ (without actually having the information from which exact location in the organ the tissue samples have been collected). The advantage of having it screen the entire organ is to overcome the miss of adenomas in the right side of the colon as attested by Schoenfeld in [28], who calls for improvements in colonoscopy.

A recent patent application close to what we propose has already been filed [29]. It discloses a colon-targeting ingestible device platform designed to recognize its entry to the colon and expand in the colon, ultimately aiming at improved imaging of the colon walls. On approaching the external anal sphincter muscle, the ingestible pill may contract or deform, for elimination. Colon recognition may be based on a structural image, based on the differences in diameters between the small intestine and the colon, and particularly, based on the semilunar fold structure, which is unique to the colon. Additionally or alternatively, colon recognition may be based on a functional image, based on the generally inflammatory state of the vermiform appendix. Additionally or alternatively, pH, flora, enzymes and/or chemical analyses may be used to recognize the colon. The imaging of the colon walls may be functional, by nuclear-radiation imaging of radionuclide-labeled antibodies, or by optical-fluorescence-spectroscopy imaging of fluorescence-labeled antibodies. Additionally or alternatively, it may be structural, for example, by visual, ultrasound or MRI means. Due to the proximity to the colon walls, the imaging is claimed to be advantageous to colonoscopy or virtual colonoscopy, as it is designed to distinguish malignant from benign tumors and detect tumors even at their incipient stage. Various sensors are envisioned to be embedded within the expandable colonic structure, including e.g. radioactive-emission detectors, fluorescence detectors, ultrasound detectors, MRI detectors, still and video cameras operating in the visible and/or infrared light ranges, temperature detectors, and impedance detectors.

Recently offered patent pending technology [30], also offers a colon-targeting expandable structure, but it has 4 distinct features: 1)Its expansion is facilitated by a permeable, mesh-like gauze structure which is in constant contact with the walls of the colon; 2) The expansion is provided by swellable granules of an appropriate biocompatible polymer (e.g. polyacrylic acid) which swell individually but do not fuse into each other, thus not forming a uniform mass non-permeable to gases and liquids causing colonic obstruction; 3) The design of the entire device is such that the mesh-like gauze structure can exert relatively constant pressure on the colonic walls from the moment it reaches its final dimensions, until it exits the organ, thus enabling abrasive contact (for scraping maximally well the colonic walls while retaining the scraped material within the structure, without, however, damaging the colonic walls); 4) This technology aims at collecting samples of tissue and bodily fluids, to be expelled from the body and analyzed later, rather than detecting colon pathologies in situ via detectors as disclosed in the cited US Patent Application 20050266074 [29];

The aim of the technology is creating a controllable, organ-targeting gastrointestinal pseudobezoar with the purpose to scrape the organ from inside in order to collect maximal diagnostic information for further processing. The implement can be self-administrable (in the case of humans) or administrable autonomously or unaided, meaning the implement is administrable in a non-invasive fashion, without the need of any external positioning or manipulating device functionally attached to it, such as an endoscope.

When the container has the first dimension, the implement can be retained in a capsule capable of being easily swallowed or administered autonomously. Once the capsule has dissolved and the container is released in the colon, the colonic fluids will enter the fluid-permeable, mesh-like, expandable container. When the fluid contacts the at least one swellable molecule cluster, the cluster will swell and the container will expand to the second dimension. When the container has expanded to the second dimension, it is sufficiently large so as to touch the colonic walls. The number of swellable molecule clusters in the container, their individual diameter, and their liquid-retaining and absorbing properties under various pressures, as well as the design of the container itself are made such that the swollen implement has an appropriate compliance to remain in constant touch with the colonic walls regardless of the lumen of the organ. For example, in a section of the colon where the lumen is large, the implement expands in a spherical shape to touch the walls of the organ. When the lumen of the colon is reduced, the implement elongates itself longitudinally in the organ, but it remains in contact with the colonic walls.

An initial implementation of such a pseudobezoar was administered inchronic dogs. Two dogs had been given 6 pills per day for a month. **Figure 1** depicts the pseudobezoar as it has left the colon. No intestinal obstructions have been reported during the entire duration of the tests. Further tests need to be carried to prove safety, but the initial testing had proven encouraging and we intend to continue to a second stage of chronic animal testing to demonstrate safety on a larger experimental sample.

Prospects include having this technology be competitive with current preferred screening technology of choice, which is assessed in [31] to be FOBT.

A recent debate was presented as to whethercolonoscopy is still the preferred screening method for colon cancer [28]. Indeed it seems that both physicians agree that that is the case for now. However it would be interesting to quote Dr. Schoenfield, "The "preferred" test for colorectal cancer (CRC) is not colonoscopy… in the future" [28].

4. Additional Prospects and Conclusion

We envision the utilization of the pseudobezoar technology for therapy as well. Fecal transplants are new therapy methods that are gaining more popularity although they involve the administration of feces from healthy subjects to the colons of patients suffering from a variety of disorders, such as infection with Clostridum Difficile bacteria [32]. The techniques used for administering such fecal transplants are invasive, and therefore, uncomfortable for patients. The futuristic prospect is to use the pseudobezoar platform for administering fecal transplants in a non-invasive way, via an ingestible pseudobezoar, impregnated with the bacteria to be served.

Figure 1. An image of thepseudobezoar as it has left the colon of a dog. All dimensions are in cm.

In conclusion, a new technology which can serve as an alternative to wide spread colon screening methods was described. Possibilities exist for a pseudobezoar-based medical device for colon cancer screening, early diagnosis of polyps, and even for bacterial transplant therapy. We have described early results pertaining to the safety of the implant in dogs. Efficacy over alternative screening methods and therapy is yet to be demonstrated. It appears that the pseudobezoar technology carries great promise both as medical diagnostic and therapeutic device and we look forward to describe new successes in this new area of medical device development in the near future.

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