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Arch Clin Exp Med Last issue - Link
Volume 2 - Issue 2 – Aug 2017

Original Research

- Primary splenic hydatidosis: Case series
  Pages 31 - 34
  Ayetullah Temiz, Yavuz Albayrak, Sadettin Er, Ayşe Albayrak, Onur Bora Aslan

- Laparoscopic sleeve gastrectomy versus endoscopical intra-gastric balloon placement: early results of morbidly obese patients
  Pages 35 - 38
  Hacı Çaycı, Umut Eren Erdogdu

- Diagnostic value of MR enterography for the assessment of small-bowel diseases
  Pages 39 - 44
  Mustafa Koplay, Hasan Erdogan, Emine Uysal, Hüseyin Korkmaz, Halil haldun Emiroglu, İlgar Allahverdiyev

Experimental Study

- Effects of Chlorine e6 mediated Photodynamic Therapy on MIA PaCa-2 and MRC-5 cells
  Pages 45 - 48
  Tuğba Kiriş Aydoğan, Saadet Akbulut, Bedia Çakmakoğlu, Elif Sinem Bireller, Haşim Özgür Tabakoğlu

Review

- Neural correlates of placebo effect: Review and future implications
  Pages 49 - 54
  Sezin Öner

Case Report

- Rarely seen left paraduodenal hernia case
  Pages 55 - 57
  Gülsen Atasoy, Yavuz Albayrak, Ayetullah Temiz, Ahmet Yalçın

- Giant splenic artery aneurysm: A case report
  Pages 58 - 59
  Tolga Canbak, Aylin Acar, Hüseyin Kerem Tolan, Fatih Başak

Letter to Editor

- MRI and Anesthesia & Sedation
  Pages 60 - 61
  Asst.Prof.Dr. Asim Esen, Muhittin Calim, Assoc.Prof.Dr. Huseyin Kadioglu

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Primary splenic hydatidosis: Case series

Primer dalak hidatik kist hastaliği: Olgu serisi

Ayetullah Temiz [1], Yavuz Albayrak [1], Sadettin Er [2], Ayşe Albayrak [3], Onur Bora Aslan [4]

Abstract

Aim: Primary hydatid cysts of the spleen are very rarely seen in endemic regions. We report here our experience with primary splenic hydatid cysts in adults.

Methods: We retrospectively analyzed eleven isolated spleen hydatid cyst cases that applied to our clinic and underwent surgery.

Results: Among 11 patients, who underwent operations for primary splenic hydatid cyst disease, six patients (54.5%) were male and five patients (45.5%) were female. The average spleen size was 14.2 cm (10–22 cm) in length. The average cyst diameter was 10.1 cm (5–20 cm). Nine (81%) patients underwent splenectomy as the surgical procedure and two (18%) patients underwent cystotomy, partial cystectomy, and tube drainage processes as a spleen protective surgery. Two patients could not undergo splenectomy because the cyst was localized in the lower pole of the spleen in one patient and in another patient, it was centrally localized.

Conclusion: Primary splenic hydatid cyst is a rare condition. Abdominal tomography is the best method for diagnosing splenic hydatid cyst. The treatment of splenic hydatid cysts is surgically. No exact consensus has been reached regarding the selection of an optimal surgical procedure.

Keywords: Splenic hydatidosis, Splenectomy, Splenomegaly

Öz

Amaç: Dalağın izole hidatik kist hastalığı endemik bölgelerde nadiren görülür. Biz bu çalışmada yetişkinlerde primer splenik hidatik kist hastalığı ile ilgili deneyimimizi sunuyoruz.

Yöntemler: Kliniğimize müracaat eden ve ameliyat edilen on bir izole dalak hidatik kist hastasını retrospektif olarak inceledik.

Bulgular: Primer splenik hidatik kist ameliyatı yapılan 11 hastanın altısı (%54,5) erkek, beşi (%45,5) kadın idi. Ortalama dalak büyüklüğü 14,2 cm (10-22 cm) uzunluğunda idi. Ortalama kist çapı 10,1 cm (5-20 cm) idi. Dokuz hastaya (%81) cerrahi girişim olarak splenektomi yapıldı. İki hastaya (%18) dalak koruyucu cerrahi olarak kistotomi, parsiyel kistektomi ve tüp drenaj işlemleri uygulandı. Splenektomi yapılmayan iki hastanın birinde kist dalak alt pol, diğerinde ise santral yerleşimli idi.

Sonuç: Dalağın izole hidatik kist hastalığı nadir görülebilen bir durumdur. Abdominal tomografi hastalığı saptamada en etkin yöntemdir. Dalağın hidatik kist hastalığının tedavisi cerrahidir. En uygun cerrahi yöntemin seçimi ile ilişkili bir uzlaşı sağlanamamıştır.

Anahtar kelimeler: Splenik kist hidatik hastalığı, Splenektomi, Splenomegali

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Introduction

Cystic hydatid disease, or cystic echinococcosis (CE), is an important parasitic zoonosis caused by the larval cyst stage of the dog tapeworm Echinococcus granulosus. This disease affects both healthy people and people who are involved in animal production in endemic regions such as South America, Mediterranean countries, and Middle Asia [1]. It is a significant disease problem in Turkey, particularly in the East and Southeast Anatolian Region [2]. Humans become infected by accidentally ingesting the eggs of the tapeworm [1].

Echinococcosis can be seen in almost every organ or tissue of the human body. Hydatid cysts are most frequently seen in the liver, followed by the lung. The brain, spleen, bile ducts, mesentery, and soft tissues are the organs where hydatid cyst is seen less frequently [3,4]. Hydatid cysts of the spleen are very rarely seen in endemic regions [5]. The prevalence of splenic hydatid cysts varies from series to series, ranging from 0.5–4%. The mean prevalence was reported as 3% [3-5].

We report here our experience with primary splenic hydatid cyst disease in adults.

Materials and methods

We retrospectively reviewed the case records of the patients attending our institution to identify those diagnosed as abdominal hydatidosis between July 2008 and March 2014 in the General Surgery Clinic of Erzurum Regional Education and Research Hospital. Details of the medical history and examination of these patients and results of relevant investigations were recorded. Of 193 patients with abdominal hydatid cysts, eleven (5.6%) had isolated splenic hydatid cysts. These patients form the basis of this report; patients with coexisting cysts in any other organ were excluded. The clinical findings, diagnostic methods, therapeutic measures undertaken, and histological data were retrospectively analyzed for all eleven patients. Abdominal computed tomography (CT) and abdominal ultrasound (US) were used as radiological diagnostic tools in the patients (Figure). After diagnosis, the patients underwent radical surgical resection of the splenic hydatid cyst, including elective splenectomy or spleen-preserving surgery (cystotomy, partial cystectomy, and omentoplasty), according to the number, location, and diameter of the cysts in each patient. All patients were routinely used with 20 % saline solution as a scolicidal agent into the cysts in the operation. Each specimen of the resected spleen and the cysts was histopathologically analyzed.

Results

Among 11 patients who underwent operations for primary splenic hydatid cyst disease, six patients (54.5%) were male and five patients (45.5%) were female. The average age was 45.1 years (23–80 years). Two patients complained of left upper quadrant pain, eight patients had nonspecific stomach ache, and one patient had dyspeptic complaints. Preoperative complete blood counts, renal and liver function tests, and chest X-rays were within normal limits.

A hydatid cyst serology test was performed on three patients: one showed positive and two showed negative responses. Abdominal CT and US were used as the radiological diagnostic tools in ten patients, and abdominal US alone was used in one patient. According to the Gharbi Classification, six of the cysts were type 2, and five of the cysts were type 3. No hydatid cyst disease in another organ was detected in any of the cases by radiological scanning, and none of the patients underwent operations due to hydatid cyst disease in another organ previously.

All patients were administered 15 mg/kg albendazole for five days in the preoperative period, and 15 mg/kg albendazole for 90 days in the postoperative period.

The average spleen size was 14.2 cm (10–22 cm) in length. Five patients had splenomegaly. The average cyst diameter was 10.1 cm (5–20 cm). Only one cyst was found in each case. Six patients (54%) had a cyst in the upper pole of the spleen, two patients (18%) had a cyst in the lower pole of the spleen and three patients (27%) had a cyst localized in the central part of the spleen. Nine (81%) patients underwent splenectomy as the surgical procedure. Two patients underwent cystotomy, partial cystectomy, and tube drainage processes as a spleen protective surgery. One of the patients who underwent spleen preservation surgery had a cyst at the lower pole and the other one had a cyst at the center (Table).

Diaphragm rupture and subsequent pneumothorax developed in one patient during the operation as the cyst in the spleen had adhered to the diaphragm. The patient underwent a left tube thoracostomy intra-operatively and the tube was drawn postoperatively on the 3rd day. One of the patients died due to pulmonary emboli on the 1st day postoperatively. The average postoperative hospitalization period was 3.9 days (1–7 days). All nine patients who underwent elective splenectomy received pneumococcal and meningococcal vaccines 2–3 weeks before the surgery to allow the development of protective antibodies.

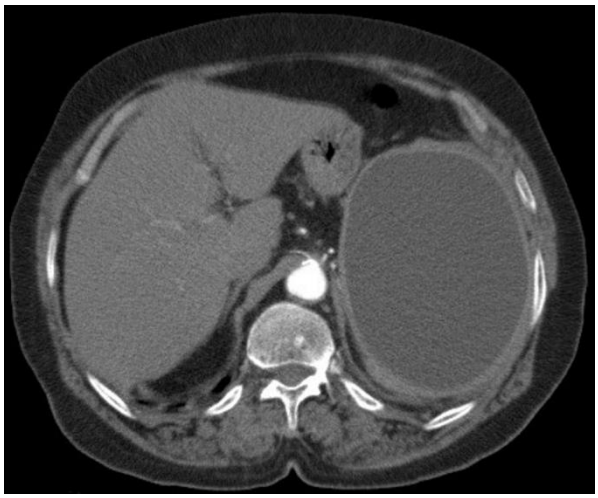

Figure: Hydatid cyst in the spleen

Table: Characteristics of the patients with splenic hydatid cyst disease. (M: Male, F: Female *: mm)

No	Sex	Age	Symptom	Spleen diameter*	Cyst diameter*	Operative procedure	Postoperative complications	Hospitalisation periods (day)
1	M	23	Abdominal pain	155	100x90	Splenectomy	-	4
2	F	27	Abdominal pain	140	70x55	Splenectomy	-	4
3	F	28	Abdominal pain	165	100x60	Splenectomy	Diaphragm rupture	4
4	M	60	Abdominal pain	120	60x40	Splenectomy	-	4
5	F	80	Abdominal pain	160	130x100	Splenectomy	-	3
6	M	25	Abdominal pain	220	200x150	Spleen-preserving surgery	-	3
7	M	52	Abdominal pain	160	130x80	Splenectomy	Pulmonary emboli	1
8	F	36	Abdominal pain	110	50x40	Splenectomy	-	3
9	M	35	Abdominal pain	100	100x80	Splenectomy	-	7
10	M	76	Abdominal pain	115	80x50	Spleen-preserving surgery	-	5
11	F	55	Abdominal pain	120	100x80	Splenectomy	-	5

Discussion

Hydatidosis is a disease caused by the larva belonging to the genus Echinococcus, with E. granulosus being the most commonly found [6]. Hydatid cyst disease has a wide prevalence in the world. The disease is frequently encountered in Turkey, particularly in Southeast and Eastern Anatolia regions involved in livestock breeding. The degree of prevalence of the infection depends on the multitude of herds raised in that region [7]. Although hydatid cyst disease can be found in almost all organs and tissues of the human body, it is most frequently seen in the liver (50–77%), the lungs (15–47%), the spleen (0.5–8%), and the kidneys (2–4%) [8,9]. In our experience, isolated splenic hydatid cysts constituted 5.6 % of our patients with abdominal hydatid disease.

The hydatid cyst factor, E. granulosis, can cause the disease by reaching the spleen via several means. The parasite can directly reach the spleen because the portal blood flow turns in the opposite direction in human beings with portal hypertension. Another possibility is that the parasite reaches the spleen by means of the lymphatics or blood flow, and a third is that it reaches the spleen as a result of reflux from the portal vein due to the increase in intra-abdominal pressure [10].

Clinically, nearly 30% of the patients with splenic hydatid cysts are asymptomatic. Splenomegaly is the most frequent finding, which is incidentally determined [11]. The clinical symptoms caused by splenic hydatid cyst mostly depend on the pressure effect of the cyst on the neighboring organs and the replacement of the neighboring organs. The symptoms are few, non-specific, and comprise mainly an abdominal mass mostly located in the left hypochondrium and less frequently in the epigastrium, pain that is usually a dull, dragging ache, dyspepsia, constipation due to pressure on the colon, and dyspnea due to pushing up of the left diaphragm [1,3,8]. A pain in the lumbar region constitutes a clinical sign in a few patients [12]. Hypertension induced by renal artery pressure is another clinical symptom that occurs due to the pressure of the cyst on the neighboring organs [4, 11]. In our study group, eight and two patients (totally 91%) had stomach ache and left upper quadrant pain, respectively, and while one case had dyspeptic complaints.

Several serological tests are specific to hydatidosis and are used to confirm the diagnosis. Enzyme-linked immunoelectrotransfer blotting, where available, is the test of choice. In some studies, it has greater than 95 percent of sensitivity and specificity [13,14]. In addition, ELISA has up to 84 percent sensitivity. The determination of specific IgG1 and IgG4 antibodies, which develop against Echinococcus in the human body might increase the specificity of ELISA test [15]. In our study, a hydatid cyst serology test was performed on three patients and one patient showed a positive response. We do not use serological tests routinely at our clinic. Özdoğan et al [16] emphasized that serological tests were not necessary for diagnosing hydatid cyst disease.

US and CT scans, alone or in combination, can establish a definite diagnosis of splenic hydatid cysts in almost all cases. Today, US is the primarily preferred monitoring method because it is inexpensive, easy, and has a high diagnostic value. It is diagnostic because it shows the cystic structure of the lesion, the presence of daughter vesicles, and hydatid sand [17]. CT is usually the next step after an US diagnosis has been made. The main purpose is to visualize the relation between the hydatid cyst and the surrounding tissue. Although CT scan is more sensitive than abdominal US, but non-calcified benign cysts without daughter cysts cannot be differentiated per se from other benign cysts either by CT or by US [15]. Direct imaging can also be exploited in diagnosing splenic hydatid cysts. The calcifications on the cyst wall are visible with direct imaging [18]. In our study, abdomen CT was used in ten patients and abdomen USG alone was used in one patient.

The primary nonparasitic cysts, pseudocysts of the spleen, spleenic abscesses, cystic neoplasia, and traumatic spleen cysts should be kept in mind in the differential diagnosis [19].

The treatment of splenic hydatid cysts is made conservatively or surgically. Small and asymptomatic splenic hydatid cysts require close follow-up, although they can be treated by anthelmintic medications [20]. Surgical operations vary from aspiration to total splenectomy [21]. No exact consensus has been reached regarding the selection of an optimal surgical procedure. Symptomatic or large cysts should be treated surgically because they can rupture spontaneously or traumatically [20]. Total splenectomy is preferred by most of the surgeons because of its very low or no recurrence rate [22]. It is the preferred approach undertaken in cases with larger, multiple, and symptomatic cysts of central or hilar location or in cases with simultaneous involvement of other organs [23]. However, sepsis-associated mortality rates of total splenectomy are 4% in children and 1.9% in adults and this is the greatest disadvantage of total splenectomy. For this reason, the number of surgeons in favor of spleen-saving surgery has increased. Spleen-saving approaches are preferred for small and single cysts that are settled in the periphery of the spleen. Spleen-saving approaches include partial splenectomy, enucleation, deroofing with omentoplasty, internal drainage with cystojejunostomy, or external drainage [24, 25]. In our study, nine patients (81%) underwent splenectomy as the surgical procedure and two patients (19%) underwent cystotomy, partial cystectomy, and tube drainage processes as a spleen-saving approach. No difference was found between total splenectomy and spleen-saving approaches in terms of the recurrence rate of the splenic hydatid cyst disease, postoperative hospitalization period, and complications [24]. Surgical treatment can also be made by laparoscopic or robotic methods [21,26,27]. However, the cyst can be torn during surgical treatments made by laparoscopic or robotic methods and this can result in anaphylactic shock, intra-abdominal dispersion, and recurrence of the cyst. Clinical experience and costs are also included among the significant problems [20,27,28]. If the splenic hydatid cyst is torn during the surgery, either spontaneously or traumatically, anaphylactic shock is a rare but severe condition that can occur. The patient can die if anaphylactic shock is not diagnosed, not immediately treated, or is resistant to treatment [29]. We did not observe any surgical operation-induced anaphylactic reactions in our patients.

In summary, splenic hydatid cyst is a rare condition that can be found in isolation or together with cysts that affect other organs. Abdominal CT is the best method for diagnosing splenic hydatid cyst. Although laparoscopic or robotic methods can be used in selected patients, the most prevalent treatment method is total splenectomy by open surgical methods. More spleen-protective methods should be preferred, particularly in children.

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Laparoscopic sleeve gastrectomy versus endoscopic intra-gastric balloon placement: Early results of morbidly obese patients

Laparoskopik sleeve gastrektomi ve endoskopik intragastrik balon uygulaması: Morbid obez hastalarda erken dönem sonuçlarımız

Haci Murat Cayci [1], Umut Eren Erdogdu [1]

Abstract

Aim: Endoscopic intra-gastric balloon (IGB) placement and laparoscopic sleeve gastrectomy (LSG) are widely used treatment modalities for weight loss in patients with morbid obesity. The aim of our study was to evaluate the results of these two methods in patients with morbid obesity.

Methods: The data of 119 patients who were treated during the same time period for morbid obesity (Body Mass Index (BMI) ≥40 kg/m2) and completed a 12-month follow-up period were evaluated retrospectively. The study comprised twenty patients who underwent IGB placement and 99 LSG patients. Patients from these two groups were compared according to their demographic data; rate of comorbidity; weight and BMI changes both preoperatively and postoperatively at the 12 months; excess weight loss (EWL); and excess BMI loss (EBL).

Results: Evaluation of postoperative 12th month weights showed a mean weight of 119.2 ±28.5 kg in the IGB group and 78.9 ±12.9 kg in the LSG group (p<0.001). The patients in the IGB group had lost 26.3 ±12.8 kg by the end of the 12th month, while patients in the LSG group had lost 45.35 ±12.2 kg (p<0.001). EWL recorded at the postoperative 12th month was 33.42 ±9.2 % in the IGB group and 67.68 ±14.9 % in the LSG group (p<0.001); EBL% at the postoperative 12th month was 41 ±17.3% in the IGB group and 81.48 ±18.8% in the LSG group (p<0.001).

Conclusion: In patients with morbid obesity, endoscopic IGB placement may still be preferred as an effective and safe alternative in patients who decline or are unsuitable for surgery.

Keywords: Morbid obesity, laparoscopic sleeve gastrectomy, intra-gastric balloon

Öz

Amaç: Morbid obes hastalarda kilo verilmesi için endoskopik intragastrik balon uygulaması (İGB) ve bariatrik cerrahi yöntemlerinden biri olan laparoskopik sleeve gastrektomi (LSG) yaygın olarak kullanılmaktadır. Çalışmamızda morbid obes hastalarda LSG ve İGB uygulanması sonuçlarımızın değerlendirilmesi amaçlanmıştır.

Yöntemler: Morbid Obesite (Vücut Kitle İndeksi-VKİ ≥40 kg/m^2) nedeniyle aynı dönemde tedavi edilen ve 12 aylık takip dönemini tamamlayan 119 hastanın verileri retrospektif olarak değerlendirildi. Çalışmada İGB uygulanan 20 hasta ve LSG yapılan 99 hasta yer aldı. Hastaların demografik verileri, yandaş hastalık, preoperatif ve postoperatif 12. ayda kilo ve VKİ verileri, verilen fazla kilo ve yüzdeleri, verilen fazla VKİ ve yüzdeleri kaydedilip gruplar karşılaştırıldı.

Bulgular: LSG ve İGB grupları arasında preoperatif kilo açısından istatiksel anlamlı farklılık olduğu görüldü (sırasıyla 124,3 ± 17 ve 145,5 ± 24,7; p<0,001). Postoperatif 12. ayda ölçülen kilo değerlendirildiğinde İGB grubunda ortalama 119,2 ±28,5 kg ve LSG grubunda 78,9 ± 12,9 kg saptandı (p<0,001). İGB grubundaki hastaların 12.ay sonunda ortalama 26,3 ±12,8 kg kilo verdiği, LSG grubundaki hastalarında 45,35 ±12,2 kg kilo verdiği görüldü (p<0,001). Postoperatif 12. ayda saptanan verilen fazla kilo yüzdesi İGB grubunda 33,42 ±9,2%, LSG grubunda 67,68 ±14,9% saptandı (p‹0,001). Postoperatif 12.ayda saptanan verilen fazla VKİ yüzdesi açısından İGB grubunda 41 ±17,3%, LSG grubunda 81,48 ±18,8% saptandı (p<0,001).

Sonuç: Morbid obes hastalarda endoskopik İGB uygulaması cerrahiye uygun olmayan veya cerrahi tedaviyi tercih etmeyen hastalarda etkin ve güvenli bir tedavi seçeneği olarak tercih edilebilir.

Anahtar kelimeler: Morbid obezite, laparoskopik sleeve gastrektomi, intragastik balon

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Introduction

Morbid obesity is an important cause of morbidity and mortality worldwide in itself, as well as leading to comorbidities associated with obesity (such as coronary artery disease, diabetes mellitus type 2, insulin resistance, non-alcoholic steatohepatitis and hypertension) [1,2]. In the non-surgical treatment of morbid obesity, a weight loss of between 3 and 9% can be achieved in a period of one year as a result of dietary changes, medical treatments and regular exercise although these percentages may differ in Europe and in Eastern communities [3]. Various bariatric surgical methods and endoscopic intra-gastric balloon (IGB) placement are now widely used in the treatment of morbid obesity [4-10].

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IGB placement is used in morbidly obese patients who do not choose surgery, with the aim of achieving efficient weight loss but also treating accompanying comorbid disease symptoms, while avoiding the risks of a primary bariatric surgical process [4, 5]. As IGB placement is relatively fast and easy, it is widely used in obese patients. The aim of IGB is to achieve weight loss by providing an early feeling of satiety due to abdominal distension, thereby reducing the desire for food consumption, delaying gastric emptying and consequently attaining weight-loss [6].

Bariatric surgical practices are indicated for cases of clinically severe obesity, where it is the most effective treatment option for achieving an efficient and sustainable weight control [7]. Although bariatric surgery brings with it an increased perioperative risk related to morbid obesity and its accompanying comorbid situations, surgery does provide treatment for obesity and comorbid diseases, and thus decreases long-term mortality [7,8]. Even though bariatric surgical practices are effective, it should be remembered that only 1% of morbidly obese patients can be admitted for bariatric surgery [7]. On the other hand, laparoscopic sleeve gastrectomy (LSG) is a relatively new, restrictive and hormonally efficient surgical practice that has been used more frequently in the last decade [9, 10].

In this retrospective study, we aimed to determine the efficiency and early results of IGB placement and LSG used to treat morbid obese patients.

Materials and methods

Patients

The data of 119 patients who were treated at Bursa Yuksek Ihtisas Teaching and Research Hospital, Department of General Surgery between January 2014 and June 2015 for morbid obesity (BMI ≥40 kg/m^2) and who completed 12 months of follow-up was retrospectively evaluated. 20 patients who underwent IGB and 99 patients who underwent LSG during the same period were included in the study. Morbidly obese patients were evaluated in the preoperative period by a team composed of endocrinology, psychiatry, general surgery and chest disease specialists. The patients were apprised before IGB placement and LSG, and their informed consent was obtained. Institutional review board approval was taken. Our study was performed in accordance with the World Medical Association Declaration of Helsinki. Written consent from the patients could not be taken due to the retrospective design of the study.

Study Design

Patients between the ages of 20-60 with BMI ≥40 kg/m^2, who had been advised to make changes in diet, exercise and lifestyle, however, did not achieved an efficient weight loss despite the recommendations for at least for 6 months were included. Within those patients, the ones who declined bariatric surgery were selected for IGB placement. Eleven patients that undergone previous bariatric surgery, patients that receive anticoagulant or steroid treatment and had alcohol or drug addiction in the time of surgery were excluded.

Demographic data, comorbidity, weight and BMI data preoperatively and postoperatively at the 12th month, excess weight loss (EWL) and percentages, excess BMI loss (EBL) and percentages of the patients in the IGB and LSG groups were recorded and compared.

Surgical and Endoscopic Techniques

IGB placement was performed in the endoscopy unit under the supervision of an anesthesiologist. An adjustable balloon (Spatz3 Adjustable Balloon, NY, USA) that can be remained in the stomach for 12 months was preferred for IGB. Sedation was provided with intravenous sedative agents (Propofol, Pfizer, New York, USA) in the lateral decubitus position. Following upper gastrointestinal system endoscopy, assessment of any obstructive pathology that would contradict the process was made. Subsequently, IGB was placed at the edge of the gastroscope and brought to the fundus of the stomach. A solution of methylene blue (10 ml) and saline (540 ml) was released into IGB under direct vision. Methylene blue was used, as it would provide a change in urine color (green color) in case of rupture of the balloon. After the procedure, patients were hospitalized to evaluate IGB toleration. Patients who had no significant vomiting or abdominal pain were started on a liquid diet on the day after the procedure and were discharged from the hospital on the second day if they tolerated this diet. For the first week, the patients were restricted to a liquid diet only. After the first week, a low calorie diet, prepared by a dietician, was applied. If a patient's weight loss stopped during the follow-up period, a further 50 ml saline was added to IGB in the endoscopy unit under sedation. After 12 months, the IGB was extracted from the patients in the endoscopy unit, under intravenous sedation.

All LSG procedures were performed by the same surgeon; the operations were performed in the Lloyd Davies position and a 34 F bougie was standard. The gastrectomy removed approximately 80% of the stomach, with the remnant stomach capacity of <100 ml, and none of the cases required conversion to open surgery. All patients were given a liquid diet before the operation. In addition, the night before the operation, all patients were administered low molecular weight heparin (Enoxaparine, Sanofi, Paris, France) subcutaneously for deep venous thrombosis prophylaxis and were dressed with pneumatic compression stockings. A liquid diet was started following flatus discharge from the anus in the postoperative period. The patients who tolerated oral intake and had no morbidity development were discharged from the hospital on the fourth postoperative day.

All patients who underwent IGB placement and LSG had weight follow-ups in the 1st, 3rd, 6th and 12th postoperative months.

Statistical Analysis

Statistical analysis was performed with IBM Statistical Package for Social Sciences (SPSS) for Windows, version 21.0 (SPSS. Inc., Chicago, IL). Distribution of continuous numerical variables was assessed with histograms and the Shapiro-Wilk test. Continuous numerical variables were reported as mean, standard deviation and minimum-maximum, and categorical variables as case number and percentage (%). Related samples Wilcoxon Test and Paired and Independent Samples T test were used for the comparison of preoperative and postoperative parameter averages. The results were accepted as statistically meaningful when the p value was < 0.05.

Results

Demographic features of the patients who underwent IGB placement or LSG and the data on comorbidity, morbidity and mortality were given in Table 1. In the study, there were 20 (16.8%) patients in the IGB group and 99 (83.2%) in the LSG group. The rate of accompanying comorbidity was 11 (55%) in the IGB group and 30 (30.3%) in the LSG group. The comorbidities in the IGB group were coronary artery disease in one (5%) patient; hypertension in three (15%) patients; type 2 diabetes mellitus in four (20%) patients; and both type 2 diabetes mellitus and hypertension in three (15%) patients. In the LSG group, coronary artery disease was detected in two (2.02%) patients, hypertension in nine (9.09%) patients, type 2 diabetes mellitus in 11 (11.1%) patients, and both type 2 diabetes mellitus and hypertension in eight (8.08%) patients. Therefore, the presence of comorbidity was higher and statistically significant in the IGB group ($p=0.034$).

Table 1: Demographic data, comorbidity, morbidity and mortality data of the patients who underwent IGB placement and LSG.

	IGB (n=20)	LSG (n=99)	p value
Age (year)	39.8 ± 9.6	36.6 ± 9.9	0.188
Gender M/F	3 / 17	10 / 89	0.457
Comorbidity n(%)	11 (55%)	30 (30.3%)	0.034
Morbidity n (%)	-	3 (3.03%)	-
Mortality n (%)	-	-	-

M: Male, F: Female, IGB: Intra-Gastric Balloon, LSG: Laparoscopic Sleeve Gastrectomy

While morbidity was not seen in the IGB group, it was seen in three (3.03%) patients in the LSG group. Postoperative hemorrhage occurred in these three (3.03%) patients, while the patients who were hemodynamically stable were followed-up conservatively. Nausea and vomiting and abdominal pain were seen in 11 (55%) and 5 (25%) patients in the IGB group, respectively. But no significant lesion such as gastric ulcer or mucosal erosion was detected. As three (15%) IGB patients could not lose sufficient weight during their follow-up period; the volume of their balloons was increased by 50 ml in the endoscopy unit. There was no mortality in any of the groups.

Weight and BMI values recorded preoperatively and at the postoperative 12th month; excess weight loss-EWL and percentage; excess BMI loss-EBL change and percentage data for both the IGB and LSG groups were given in Table 2.

Table 2: The values of weight and BMI preoperatively and at the postoperative 12th month, EWL and EBL change and their percentage changes.

	IGB (n=20)	LSG (n=99)	p value
Preoperative weight (kg)	145.5 ± 24.7	124.3 ± 17	<0.001
Preoperative BMI (kg/m^2)	53.7 ± 11.3	50.9 ± 4.9	0.078
12th month weight (kg)	119.2 ± 28.5	78.9 ± 12.9	<0.001
12th month BMI (kg/m^2)	43.29 ± 11.1	29.35 ± 4.7	<0.001
Weight loss (kg)	26.3 ± 12.8	45.35 ± 12.2	<0.001
Weight loss (%)	18.07 ± 10.5	36.32 ± 11.3	<0.001
EWL (%)	33.42 ± 9.2	67.68 ± 14.9	<0.001
EBL (%)	41 ± 17.3	81.48 ± 18.8	<0.001

BMI: Body Mass Index, EWL: Excess Weight Loss, EBL: Excess Body Mass Index Loss, IGB: Intra-Gastric Balloon, LSG: Laparoscopic Sleeve Gastrectomy

Discussion

Nowadays, following a world-wide trend, the prevalence of morbid obesity in Turkey is on the increase. The search for an efficient, safe treatment method with low complication rates and easy to apply still continues. IGB placement has been developed for this purpose and is used in tandem with advanced technology to provide weight control in morbidly obese patients [11]. IGB placement can deliver weight loss and also reduce comorbidity [12].

IGB placement is performed in patients who cannot lose enough weight with conservative treatment, who are not candidates for surgery or who do not wish to have surgical intervention [13]. In this procedure, balloons of different size and stability are used and can be inflated with air or liquid [11]; in our clinic, adjustable balloons that can be remained in the stomach for up to 12 months are used and inflated with saline. Accordingly, in our study, IGB content was increased by 50 ml in 3 cases as sufficient weight loss had not been achieved. Using an IGB rather than bariatric surgery in morbidly obese patients means that there is no risk of decreasing the volume of the left hepatic lobe, but also that the general risks of definitive surgical intervention and anesthesia can be avoided [14]. None of our IGB patients were further been operated for obesity disease, thus they all are selected between the patients that declined bariatric procedure.

IGB placement is considered less efficient than definitive bariatric surgical interventions in terms of weight loss; but more effective than diet, exercise and lifestyle changes [15]. Moreover, initial BMI and the patient's motivation and compliance with the diet program significantly affect weight loss after IGB placement. Although IGB placement is efficient in the short term, its long-term effectiveness has not yet been well-defined [16].

Bariatric surgical interventions provide efficient weight loss and permanent weight control in morbidly obese patients [17]. When bariatric surgery is compared with IGB placement, it is more efficient but it has a higher risk ratio [4]. LSG was performed in our study and is reported to be an increasingly common method; it provides effective weight loss and comorbidity resolution in the management of obesity and has restrictive and hormonal effects [9, 10]. Some of its advantages are the absence of diarrhea or dumping syndrome as the pylorus and duodenum are protected; avoidance of serious malabsorption; the absence of anastomosis; and simplicity of the technique.

In our study, we also observed that the patients who underwent LSG achieved better weight loss during the one-year follow-up period compared to patients who received IGB (45.35 ± 12.1 and 26.3 ± 12.84, respectively) (p<0.001). When the EWL% was evaluated after one postoperative year, the LSG group recorded better results than the IGB group (67.68 ± 14.9%; 33.42 ± 9.2 % respectively) (p<0.001). The EBL% of the LSG group in the first postoperative year was also significantly different from the IGB group (81.48 ± 18.8% and 41 ± 17.3%, respectively) (p<0.001). Overall our study shows that LSG is more efficient than IGB placement in treating morbidly obese patients, a result which is compatible with the literature [15, 17].

According to the literature, following IGB placement, the mean weight loss is 17.8-24.4 kg, and the EWL ratio is 48% [18,19]. After IGB placement, 33.7% and 29% of the patients report abdominal pain and nausea, respectively [20]. Certain complications after IGB placement are also reported, such as small bowel obstruction (0.3%), spontaneous balloon deflation (6%), balloon migration (1.4%), gastric mucosal injury (2%) and mortality at a rate of 0.08% [20]. In our study, there was no morbidity or mortality among our IGB cases. All patients have not seen problem to keep balloon for 1 year in IGB application.
LSG provides efficient weight loss in morbidly obese patients. Although a considerable decline in mortality is achieved after LSG, reported rates of early and late period morbidity vary between 9% and 23%, leakage is recorded at 1%-6% and hemorrhage as 2% and 7.3% [21, 22]. Leakage development after LSG is an important cause of morbidity and mortality [23]. Patients with BMI> 50, use of a dilator with a diameter less than 40F, and revision surgery were defined as independent risk factors for development of leakage [24, 25].

In our study, hemorrhage developed in the postoperative period at a rate of 3.03% and was treated conservatively. Studies report a EWL% that ranges from 49% to 81% after LSG; and a postoperative BMI that varies between 24.4 and 32 kg/m^2 [26-28]. In our study, in the first year after LSG, the EWL% was recorded as 67.68 ± 14.9% and the EBL as 81.48 ± 18.8%. Therefore, our results following LSG were consistent with the literature.

There are some limitations to our study; namely, the relatively low number of cases and the single-centered, retrospective nature of the study.

In conclusion, in morbid obesity treatment, LSG and IGB provide efficacy to different degrees. The most efficient treatment option for morbidly obese patients to achieve and maintain weight loss is a bariatric intervention, such as LSG. However, IGB placement may be preferred as an efficient and safe treatment method for morbidly obese patients who do not prefer surgical treatment or whose general health conditions do not allow surgical intervention. In order to clarify the role of IGB placement in morbid obesity treatment, we believe that further studies, with larger cohorts of patients and including short and long term results, are needed.

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İnce bağırsak hastalıklarının değerlendirilmesinde MR enterografinin tanısal değeri

Diagnostic value of MR enterography in evaluation of small bowel diseases

Ilgar Allahverdiyev [1], Mustafa Koplay [1], Hasan Erdoğan [2], Emine Uysal [1], Hüseyin Korkmaz [3], Halil Haldun Emiroğlu [4]

Öz

Amaç: Bu çalışmamızda kolay elde edilebilen ve iyi bir bağırsak distansiyonu sağlayan %3 mannitol ile manyetik rezonans (MR) enterografi yönteminin tanısal etkinliğinin değerlendirilmesini amaçlıyoruz.

Yöntemler: Yaşları 7-71 yıl arasında değişen 42 hasta çalışmaya dahil edildi. MR enterografi protokolü 1.5 Tesla MRG (Magnetom Aera; SiemensMedical Solutions, Erlangen, Germany) cihazı ile yapıldı. Bulgular cerrahi-fiberoptik kolonoskopiden elde edilen histopatolojik sonuçlarla karşılaştırıldı. Duyarlılık, özgüllük, pozitif ve negatif öngörü değerleri, tanısal doğruluk oranı istatiksel olarak hesaplandı.

Bulgular: Duyarlılık %83, özgüllük %93, pozitif öngörü değeri %83, negatif öngörü değeri %93 ve tanısal doğruluk oranı %90 olarak saptanmıştır. Yalancı negatif olan iki hasta radyolojik olarak normal değerlendirildi, ancak patolojik inceleme nonspesifik inflamasyon olarak geldi. Yalancı pozitif olan bir hastada patolojik inceleme ülseratif kolit olarak, bir hastada ise invajinasyona neden olan ektopik pankreas dokusuna ait polipoid kitle saptandı. Gerçek pozitif olan dokuz hastada patoloji sonucu Crohn hastalığı, diğer hastada ise tipik olmamakla birlikte Crohn hastalığı lehine değerlendirildi. Ayrıca Crohn hastalığ ile takip edilen bir hastada iki yerde ince bağırsak segment tutulumu, diğer bir hastada da ileoileal fistül izlendi.

Sonuç: MR enterografi, Crohn hastalığının takibinde, hastalığın aktif sürecindeki inflamasyonun, fibrostenoz evredeki striktürlerin, obstrüksiyonların, komplikasyonların belirlenmesinde ve tedavi seçeneğinin değerlendirilmesinde önemlidir. Gelecekte, mevcut MR sekansları ve yeni geliştirilen sekans teknikleriyle yapılacak geniş hasta katılımlı karşılaştırmalı çalışmalara ihtiyaç vardır. MR, ince bağırsağın diğer hastalıklarının değerlendirilmesinde de umut vericidir.

Anahtar Kelimeler: MR enterografi, Crohn hastalığı, Mannitol

Abstract

Aim: We aim to evaluate the diagnostic efficiency of magnetic resonance (MR) enterography and mannitol %3 which have been gathered easily and provide good intestine distension.

Methods: 42 patients whose ages are between 7 and 71 have been included in the project. MR enterography protocol has been done by 1.5 Tesla MRG (Magnetom Aera, Siemens Medical Solutions, Erlangen, Germany) device. Findings were compared to histopathological results obtained by surgery and fiberoptic endoscopy. Sensitivity, specificity, positive and negative predictive values, and diagnostic accuracy rate have been calculated statistically.

Results: Sensitivity, specificity, positive predictive value, negative predictive value and diagnostic accuracy rate were calculated as 83%, 93%, 83%, 93% and 90%, respectively. Two patients with false negative results were evaluated as normal in the radiologic manner but pathologic investigation came as nonspecific inflammation. Pathologic investigation was recognized as ulcerative colitis for a patient with false positive result and in another patient with false positive result, invagination caused by a polypoid bulky mass due to the ectopic pancreas tissue was detected. Nine real positive patients were evaluated as having Crohn's disease according to the pathologic investigation and other patient was evaluated as having Crohn's disease though it was atypical. Additionally involvement of two small intestinal segments was seen for a patient with Crohn's disease and ileoileal fistula was seen for another patient.

Conclusion: MR enterography is important for tracking of Crohn's disease, inflammation in active process of the disease, strictures in fibro-stenotic phase, obstructions, determination of complications and evaluation of treatment options. There will be a need for comparative studies which have been done by current MR sequences and recently developing sequence techniques with inclusion of large number of patients. MR enterography is promising for evaluation of other diseases in the small intestine too.

Keywords: MR enterography, Crohn's disease, Mannitol

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Giriş

Gastrointestinal sistemin radyolojik olarak değerlendirilmesinde ince bağırsaklar, anatomik ve fizyolojik özellikleri nedeniyle tanıda en çok sorun yaratan bölümdür. İnce bağırsaklar lokalizasyonu, uzunluğu ve birbirleri üzerinde sıkışık yerleşimleri nedeniyle radyolojik olarak iyi görüntülenemedikleri gibi tam ve optimal bir endoskopik eksplorasyona da izin vermemektedir. İnce bağırsak patolojileri genel popülasyonda sıklıkla karşımıza çıkmakta ve ayırımının yapılmasında endoskopik ve radyolojik teknikler gerektirmektedir.

İnce bağırsak non-invaziv görüntüleme yöntemlerine ultrasonografi, enteroklizis, konvansiyonel pasaj grafisi, bilgisayarlı tomografi (BT) veya manyetik rezonans (MR) enterografi, kapsül endoskopi; invaziv yöntemlere ise balonlu enteroskopi ve spiral enteroskopi örnek olarak gösterilebilir. Geleneksel olarak ince bağırsak hastalığından şüphelenilmesi halinde baryumlu enteroklizis ve endoskopi kullanılır. Ancak bu inceleme yöntemleri, lümen bütünlüğünü ve ekstralüminal uzanımları eş zamanlı değerlendirmede yetersiz kalmaktadır. İnvaziv olmaları ve radyasyona maruz kalma da bir diğer dezavantajıdır. Ayrıca ince bağırsak hastalıklarının birçoğunun kronik hastalık olması nedeniyle sık sık takiplerinin yapılmasına gerek duyulmaktadır. Hasta popülasyonunun çoğunluğunu gençlerin oluşturması radyasyon riskini daha ön plana çıkarmaktadır.

Bağırsak patolojilerinin değerlendirilmesinde invaziv olmayan kesitsel görüntülemeler endoskopik tetkiklerin yerini almaktadır. Son yıllarda hem BT, hem de MR görüntüleme teknolojilerindeki yeniliklerle beraber, kısa sürelerde yüksek çözünürlüklü görüntüler elde edilebilmesi ve elde edilen görüntülerin multi-planar olarak değerlendirilebilmesi mümkün olmuştur. Bunun neticesinde, bu görüntüleme yöntemleri eşliğinde uygulanan enteroklizis ve enterografi teknikleri geliştirilmiş, ince bağırsak hastalıklarının tanısında giderek artan biçimde kullanılmaya başlanmıştır. MR enterografi yeni bir yöntemdir ve ince bağırsak lümenini, duvarını ve etrafındaki yapıları değerlendirebilir. MR enterografi ile yapılan çalışmalarda infeksiyon, tümör, polip, yapışıklık, vasküler malformasyon ve inflamatuvar bağırsak hastalıklarının (İBH) saptanmasında anlamlı sonuçlar elde edilmiştir [1-3]. Ayrıca süperpozisyon ve radyasyon maruziyetinin olmaması, yumuşak doku kontrastının yüksek olması, hamilelerde ve iyot alerjisi öyküsü olan hastalarda kullanılabilir olması da yeni bir yöntem olarak dikkatleri MR enterografiye çekmiştir. Diyagnostik kalitede MR görüntüleri elde etmek için hızlı MR sekansları gerekmektedir. Ayrıca bağırsak distansiyonu için de çeşitli enterik kontrast ajanlar (mannitol, su, baryum sülfat, polietilen glikol ve diğerleri) kullanılmaktadır.

Bizim bu çalışmada amacımız, ince bağırsakların radyolojik görüntüleme yöntemlerini gözden geçirmek ve MR enterografi yöntemi kullanılarak elde edilen görüntülerde lüminal distansiyonu ve duvar görüntüleme yeterliliğini değerlendirmektir. Ayrıca bu çalışmamızda kolay elde edilebilen ve iyi bir bağırsak distansiyonu sağlayan %3 mannitol ile MR enterografi yönteminin etkinliğinin değerlendirilmesini amaçlıyoruz.

Gereç ve Yöntemler

Hastalar

Çalışma grubumuza Nisan 2013 – Ekim 2014 tarihleri arasında İBH tanısı veya ön tanısı olan (klinik olarak karın ağrısı, ishal, kilo kaybı şikayetleri ile başvuran) 42 hasta dahil edildi. Hastaların 35'i erkek, 7'si kadındı ve yaşları 7 ile 71 yıl arasında değişmekteydi (yaş ortalaması 37,8 yıl). İBH tanısı önceden bilinen 4 hasta mevcuttu. Diğerleri IBH ön tanısı ile incelemeye alındı. Çalışmaya dahil edilen hastaların hiçbirinde BT ya da MR tetkikleri için kontrendikasyon oluşturan; akut ya da kronik böbrek yetmezliği, allerji öyküsü, gebelik, hemodinamik instabilite gibi klinik bir durum bulunmamaktaydı. Hastalara, şikayetleri nedeni ile poliklinik veya acil servise başvurmalarından sonraki en geç 1 hafta içerisinde, uygulanacak prosedür konusunda bilgi verilerek MR enterografi çekildi.

Çalışma Helsinki Bildirgesinde yer alan kriterlere uygun olarak gerçekleştirildi. Hastalardan yazılı onam, çalışmanın retrospektif özelliğinden dolayı alınmadı.

MR Enterografi Protokolü

Tüm hastalara tetkik öncesi en az 6 saat açlık önerildi. Çalışmamızda enteral kontrast madde olarak kolay elde edilebilen ve iyi bir bağırsak distansiyonu sağlayan %3 mannitol kullanıldı. Oral yoldan %3'lük mannitol 50 kg altındaki hastalarda tetkikten 1 saat önce 10 ml/kg dozda, tetkikten 30 dk önce 5ml/kg dozda ve MR ünitesine alınmadan hemen önce 5ml/kg dozda olacak şekilde verildi. 50 kg üzerindeki hastalarda ise, tetkikten 1 saat önce 500 ml, tetkikten 30 dakika önce yine 500 ml, MR ünitesine alınmadan önce ise 300-500 ml verildi. Hastalara antispazmolitik olarak intravenöz (IV) yoldan manuel yavaş infüzyonla Hyoscine-N-butylbromide (Buskopan) 50 kg altındaki hastalarda 0,3 mg/kg dozda, 50 kg üzerindeki hastalara ise 20 mg (1 ampul) olarak çekimden 20 dakika önce ve MR ünitesine alınmadan hemen önce olmak üzere 2 kez kullanıldı. IV kontrast madde olarak gadolinium 0,2 ml/kg dozda, otomatik pompa enjektörle 2-3 ml/sn hızda çekime 45 saniye kala verildi. Çekim öncesi hazırlık amacıyla kullanılan prosedür esnasında hastalar tarafından, hafif bulantı dışında ciddi intolerans şikayeti bildirilmedi.

MR Enterografide Kullanılan Sekanslar

İnceleme 1.5 Tesla MR cihazı (Magnetom Aera, Siemens, Erlangen, Germany) ile yapıldı. Optimum MR enterografi görüntüleme protokolü ile ilgili kesin bir fikir birliği yoktur. Genel olarak kabul görmüş yöntemde, T2 ağırlıklı sekans ile enterik kontrast maddenin terminal ileum ve/veya sağ kolona ulaşmasına bakılır. Enterik kontrast madde, bu alanlara ulaşmamışsa 500 ml daha verilerek 15-30 dakika sonra çekim tekrarlanır. Çalışma protokolünde kullanılan sekanslar; aksiyel ve koronal planlarda yağ baskılı ve yağ baskısız olarak yapılmış olup tablo 1'de gösterilmiştir.

Tablo 1: MR enterografide kullanılan sekanslar ve parametreler.

Parametreler	Kesit Kalınlığı (mm)	Gap (mm)	FOV	TR	TE
T2 HASTE	5	1	380	2000	92
T2 TRUFI	5	1	380	3,69	1,85
T1 VIBE	3	0	400	4,36	1,1
DİFFÜZYON	5	5	380	6900	60

Görüntü Analizi

Tüm görüntü veri setleri, post-proçes değerlendirme için iş istasyonuna (Syngo.via, Siemens Healthcare, Forchheim, Germany) aktarıldı. Görüntüleme sonuçları, Crohn hastalığı semptomları ya da ön tanısı dışında tüm bilgilerden habersiz olan iki radyolog tarafından görüş birliğiyle değerlendirildi.

Crohn hastalığının varlığı, lokalizasyonu, yaygınlığı ve aktif Crohn hastalığı için tipik bulgular olan duvar kalınlaşması (> 4 mm), lümen stenozu (komşu normal bağırsak lümen çapına kıyasla % 50 azalma), pre-stenotik distansiyon (ortalama proksimal bağırsak lümenine kıyasla en az % 150 artış), skip lezyon, mukoza veya duvarda kontrastlanma, T2 ağırlıklı sekanslarda duvar sinyal artışı, artmış mezenterik vaskülarite

(tarak işareti), büyümüş mezenterik lenf nodlarının varlığı (kısa eksende çapı 5 mm'yi aşan, kontrastlanan) ya da apse gibi parametreler değerlendirildi.

İstatistiksel Analiz

Tüm istatistiksel analizler SPSS 18.0 yazılımı (Chicago, IL, ABD) kullanılarak yapıldı. Demografik veriler, ortalama ± standart sapma olarak özetlendi. Tüm hastaların duyarlılık, özgüllük, gerçek pozitif, gerçek negatif, yalancı pozitif ve yalancı negatif değerler, pozitif ve negatif öngörü değerleri ve test geçerliliği değerleri hesaplandı.

Bulgular

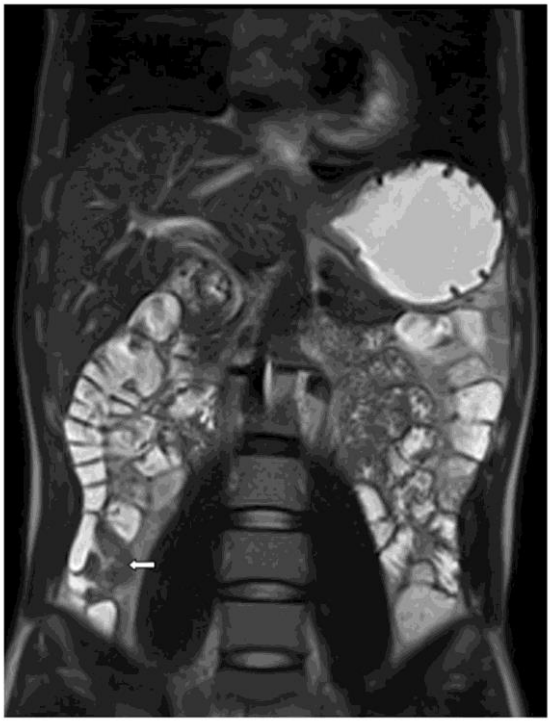
Çalışmaya toplam 42 hasta (7 kadın, 35 erkek) dahil edilmiştir. Yaş aralığı 7-71 yıl (ortalama 37,8 yıl) arasında dağılım göstermekteydi. 3 hastada cerrahi spesmenden, diğerlerinde terminal ileum düzeyinden fiberotik endoskopi ile alınan histopatolojik sonuçlarla karşılaştırılma yapıldı. Crohn hastalığı olan tüm hastalarımızda terminal ileum tutulumu mevcuttu. Hastaların gerçek pozitif, gerçek negatif, yalancı pozitif ve yalancı negatif değerler, duyarlılık, özgüllük, pozitif öngörü değeri, negatif öngörü değeri ve test geçerliliği değerleri tablo 2'de verilmiştir.

Tablo 2: Gerçek pozitif, gerçek negatif, yalancı pozitif, yalancı negatif, duyarlılık, özgüllük, pozitif öngörü değeri negatif öngörü değeri ve test geçerliliği değerleri

	değer
Gerçek Pozitif (n)	10
Gerçek Negatif (n)	28
Yalancı Pozitif (n)	2
Yalancı Negatif (n)	2
Duyarlılık (%)	83,33
Özgüllük (%)	93,33
Pozitif öngörü değeri (%)	83,33
Negatif öngörü değeri (%)	93,33
Test geçerliliği (%)	90,47

Yalancı negatif olan iki hasta radyolojik olarak normal değerlendirildi, ancak patolojik inceleme sonucu nonspesifik inflamasyon olarak geldi. Yalancı pozitif olan 2 hastanın birinde radyolojik olarak CH düşünüldü, ancak patolojik inceleme ülseratif kolit olarak geldi. Diğer hastada ise radyolojik bulgular nonspesifik terminal ileum inflamasyonu lehine değerlendirildi, ancak patolojisi tipik olmamakla birlikte Crohn hastalığı lehine değerlendirildi. Gerçek pozitif olan dokuz hastada patoloji sonucu Crohn hastalığı, bir hastada ise invajinasyona neden olan ektopik pankreas dokusuna ait polipoid kitle olarak geldi.

Crohn hastalığı tanısı ile takip edilen bir hastada 2 ayrı ince bağırsak segment tutulumu, diğer bir hastada da ileoileal fistül izlendi. Ayrıca rastlantısal olarak bir hastada rektal polip, 18 hastada böbrek kisti, bir hastada plevral efüzyon, altı hastada karaciğer kisti saptandı. Ultrasonografi ile ileal invajinasyon lehine değerlendirilen 7 yaşındaki bir kız hastada ise, MR enterografi incelemesinde invajinasyon olmadığı ve Crohn hastalığı lehine ileal duvar kalınlaşması olduğu gösterilmiş olup, patoloji sonucu da Crohn hastalığı olarak gelmiştir. Crohn hastalığı olan hastaların MR enterografi bulguları Resim 1-4'de izlenmektedir.



Resim 1:Crohn hastalığı tanısı olan hastanın koronal HASTE sekansında terminal ileum düzeyinde kısa segment duvar kalınlık artışı (ok) izlenmektedir.

Genel görüntü kalitesini, distansiyon ve duvar vizualizasyonunu değerlendirmede, yapılan benzer çalışmalar örnek alınarak ve çalışmamıza uyarlanarak 1-5 arasında skorlama yapıldı (4, 5). Görüntü kalitesi skorlaması tablo 3'te verilmiştir.

Tablo 3: Genel görüntü kalitesi, distansiyon ve duvar vizualizasyonunu değerlendirme skorları.

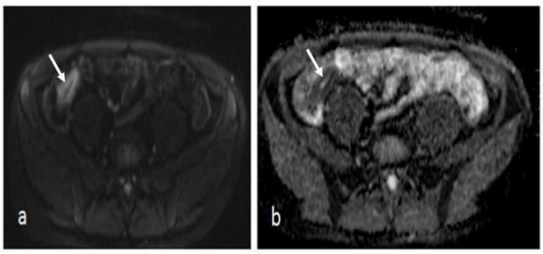
Skor	Değerlendirme Düzeyi	Tetkik Sayısı
1	Teknik yetersizlik	-
2	Suboptimal	2
3	Suboptimal ancak değerlendirme yapılabiliyor	7
4	Optimal	18
5	Çok iyi	15

Tartışma

İnce bağırsak hastalıklarının tanısı, geliştirilen görüntüleme yöntemlerine karşın zordur. İnceleme yöntemlerinin avantajları ve dezavantajları vardır. Endoskopik yöntemlerden konvansiyonel olanlar teknik yetersizlikler nedeniyle sadece belirli bölgeleri görüntülemeye imkan sağlamaktadır.

Enteroklizis, bütünüyle görüntülenmesi teknik olarak zor olan ince bağırsakların hastalıklarının tanısında kullanılan primer görüntüleme yöntemidir. Mukozal detayın değerlendirilmesi, ayrıca ince bağırsak boyunca patolojinin lokalizasyonunun gösterilmesi bakımından BT'den üstün olduğu gösterilmiştir. Hem lüminal (mukoza, morfoloji), hem de fonksiyonel (motilite) değerlendirmede faydalıdır [6]. Röntgenografik tetkikler patolojilerin ekstramural yayılımını ve eşlik edebilecek komplikasyonları direkt olarak gösterememesi yanında, alınan X-ışın dozunun yüksek olması gibi dezavantajları mevcuttur. Ayrıca bu yöntemde lümen distansiyonunu sağlamak

için uygulanan nazojejunal kateterizasyon, hasta konforunu azaltan bir zorunluluk olmasının yanı sıra yöntemi minimal invazif prosedürler arasına sokmakta ve pratiklikten uzaklaştırmaktadır.



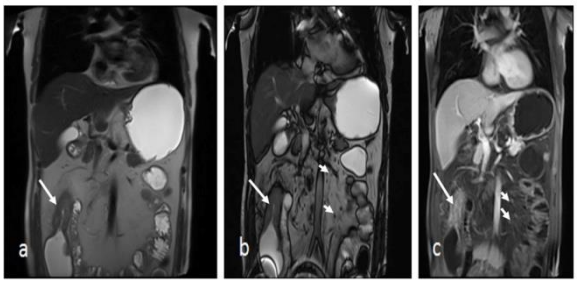
Resim 2: Diffüzyon ağırlıklı görüntülemede (a) ve ADC haritalamasında (b) akut evre Crohn hastalığı ile uyumlu difüzyon kısıtlanması izlenmektedir.

Video (kapsül) yöntemler mukozal değişiklikleri göstermede üstündür. Ancak striktür ve obstrüksiyonlarda sınırlı bilgiler verir. Fazla sayılacak kadar kontrendikasyonları vardır [7-9].

Son yıllarda kesitsel görüntüleme yöntemlerinden BT hem lümen içi, hem lümen dışı patolojileri göstermedeki üstünlüğü nedeniyle ince bağırsak hastalıkları tanısında kullanılan birincil tanısal yöntem haline gelmiştir. İnce bağırsak lezyonlarının tanısında kullanılan kesitsel görüntüleme yöntemlerinin; lezyonun transmural yayılımı, intraperitoneal-ekstraintestinal komplikasyonları ve geniş görüntü alanına giren diğer sistemik bulguları gösterebilme, ek olarak IV kontrast madde kullanımı ile vasküler patolojiler ile ilgili bilgi sağlayabilme imkanı non-invaziv ve pratik olan bu tekniği günümüzde oldukça popüler kılmıştır. Ancak yine alınan X ışın dozu BT'nin dezavantajıdır. BT'de effektif doz ortalama 16,1 mSv dir. 10 mSv üzeri effektif dozda ölümcül kanser riski 1/2000 dir [10-12].

Radyasyon dozu, hasta populasyonunu genellikle genç vakaların oluşturduğu İBH gibi durumlarda özellikle önem kazanmaktadır. Bu amaçla mukozal yapıları, bağırsak duvarını, ekstraluminal oluşumları görüntüleyebilecek ve radyasyon riski taşımayan yeni tetkiklere ihtiyaç duyulmaktadır. Bağırsak hareketleri ve solunum hareketlerine bağlı artefaktlar nedeniyle önceleri ince bağırsak hastalıkları tanısında kullanılması hiç tercih edilmeyen MR'da hızlı görüntüleme yöntemlerinin gelişmesi, nefes tutmalı sekansların kullanılması ince bağırsakların görüntülenmesinde büyük kolaylık sağlamıştır. İnce bağırsakların görüntülenmesinde MR yöntemlerinden MR enterografi ve MR enteroklizis kullanılmaktadır. BT görüntülemede olduğu gibi bu incelemenin ikisi arasındaki temel fark, MR enteroklizisde bir enterik tüp yolu ile kontrast maddenin verilmesidir. Ana avantajı daha iyi bağırsak distansiyonu sağlaması ve mukozal yapıları daha iyi değerlendirmeye olanak vermesidir.

MR enterografi uygulaması kolay ve non-invaziv bir tetkiktir. Hastalar tarafından daha iyi tolere edilir. İyonizan radyasyon riski taşımaz. Bunun yanında, peritoneal kavite anatomisini koronal kesitlerde görüntüleyebilmesi ve özellikle küçük intraperitoneal sıvı koleksiyonlarını değerlendirebilmesi MR enterografiye BT'ye oranla avantaj sağlamaktadır [5]. Biz koronal görüntülerin, sıvı tespiti konusundaki başarısı haricinde, sıvı sensitivitesi yüksek olan HASTE sekansı ile "ince bağırsak pasaj grafisi" imajı oluşturduğu, obstruksiyon durumlarında ya da cerrahi ve endoskopik girişim öncesi anatomik oryantasyona yardımcı olduğunu gördük. Yine IV kontrastlı inceleme mukoza ve duvar kontrastlanması sağlayarak akut inflamasyon olan segmentler hakkında bilgi vermektedir. Bağırsak motilite değerlendirilmesi için kullanılan CINE görüntüler geçici ve sabit darlıkların ayırmada bilgiler vermektedir [13-15]. Oral olarak Buscopan kullanmakta amacımız yeterli ve etkin bir lüminal distansiyon sağlamaktır.

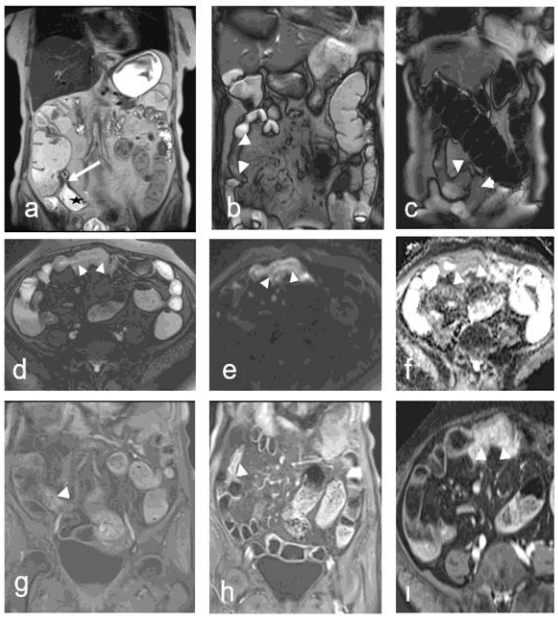


Resim 3: Crohn hastalığı tanısı olan hastada bağırsak duvarında konsantrik kalınlık artışı (uzun oklar) izlenmektedir. HASTE sekansında (a) mezenterik alanda belirgin patoloji seçilemezken TRUFI sekansı (b) ve kontrastlı T1 ağırlıklı VIBE sekansında (c) "comb sign" (tarak işareti) oluşturan mezenterik vaskülarite artışı (kısa oklar) izlenmektedir.

MR görüntülememizde ultra hızlı MR çekim sekansları kullandık. Yatış pozisyonu "prone" veya "supine" tercih edilebilir. Bununla ilgili yapılan çalışmalarda nefes hareketine bağlı artefaktların azalması nedeniyle genellikle "prone" pozisyon tercih edilmiştir. Maccioni ve ark. [16] yaptığı bir çalışmada, duyarlığın "prone" pozisyonunda % 66,8, "supine" pozisyonunda ise %63 olduğu gösterilmiştir. Biz ise çalışmamızda alışılagelmiş olan "supine" pozisyonu tercih ettik.

İnce bağırsak hastalıklarında MR enterografi, hastalıkların tanısı ve özellikle tedavi seçeneğinin değerlendirilmesinde kullanılabilir. Ancak asıl yararlı olduğu ve sıkça kullanıldığı alan İBH ve özellikle Crohn hastalığının takibidir. Hastalığın etkilediği segmentler, mural ya da ekstramural etkilenim, ayrıca hastalık aktivasyonu değerlendirilir. Komplikasyonlar olan apse, fistül, obstrüksiyon gibi bulgulara tanı konulur. Biz Crohn Hastalığında duvar kalınlaşmasının önemli bir bulgu olduğunu gördük ve 3 mm'den fazla olan kalınlaşmalar genellikle patolojik olarak sonuçlandı. Bunun yanında 10 mm'nin üzerindeki duvar kalınlaşması durumlarında, örneğin lenfoma gibi başka patolojilerin de araştırılması gerekmektedir. Bizim çalışmamızda ileum düzeyinde bağırsak duvar kalınlığını 10 mm'nin üzerinde olarak saptadığımız bir hastanın patoloji sonucu ektopik pankreas olarak geldi.

Crohn hastalığı tanısı olan bazı hastalarımızda lenf bezleri aktif ve kronik süreçlerde görüldü. Ancak takipte lenf bezlerinde büyüme ve kontrast tutulumu aktif inflamasyon lehine değerlendirildi. Bu bulguyu destekleyen çalışmalar mevcuttur [14, 17].Yapılan çalışmalar MR enterografide mukozal ülserasyonlar ve nodülaritelerin çok iyi ortaya konamayabileceğini fakat derin ülserlerin görüntülenebildiğini göstermiştir [18].



Resim 4: Akut ve kronik Crohn hastalığı bulguları. Koronal T2 ağırlıklı HASTE sekansında (a) fibrotik stenoz (ok) ve proksimalde bağırsak luminal dilatasyonu (yıldız) izlenmektedir. Koronal T2 ağırlıklı TRUFI (b,c) ve aksiyel yağ baskılı T2 ağırlıklı TRUFI (d) sekanslarında ileum segmentlerinde bağırsak duvar kalınlık artışı izlenmektedir. Difüzyon ağırlıklı görüntü (e) ve ADC haritasında (f) kısıtlanmış difüzyon görülmektedir. Koronal yağ baskılı kontrastlı T1 ağırlıklı VIBE sekansı terminal ileumda (g) ve distal ileumda (h) mukozal kontrastlanmayı, aksiyel yağ baskılı T1 ağırlıklı VIBE sekans (i) ise farklı bir ileum segmentinde (ok başları) transmural kontrast tutulumunu göstermektedir.

Striktür ve fibrozis, ince bağırsak anslarında 3 cm üzerinde distansiyon ya da obstrüksiyon saptandığında düşünülmelidir. Fibrozis tespitinde CINE imajları, fibrotik striktürlerde duvar kalınlaşması ayrıca striktür duvarında T2A imajlarında sinyal artımının görülmemesi önemlidir. Striktür aramada koronal imajlar idealdir. Kronik ve subakut süreçlerde yağ birikimi önemlidir.

Fistüller komşu ince bağırsak ansları, ince bağırsaklar ile kolon, mide ve mesane arasında görülebilir. Biz fistülleri, sinüs traktları ve apselerin duvarlarının kontrast tutmaya meyilinden dolayı en iyi kontrastlı yağ baskılı T1 ağırlıklı imajlarda görüntüledik. Yapılan çalışmalarda Crohn hastalığında fistülleri göstermede MR enterografinin önemli rolü olduğu gösterilmiştir [19]. Kontrastlı yağ baskılı T1 ağırlıklı imajlarda komşu bağırsak segmentleri arasındaki adezyonlar, fistüllerden daha geç parlaklaşmaları ile ayırt edilebilir. Nitekim bizde de endoskopi ile ulaşılamayan bir hastada ekstraintestinal patoloji düşünüldüğü için MR enterografi yapıldı ve ileoileal fistül saptandı.

Bizim çalışmamızın retrospektif çalışılması, ADC haritalarında değerler hesaplanmaması, sadece kısıtlanmış difüzyona göre inflamasyon tanısı konması ve hasta sayısının az olması gibi kısıtlılıkları mevcuttur.

Crohn hastalığında radyolojik yöntemlerin duyarlılık ve özgüllüğü ile ilgili birçok çalışmalar yapılmıştır. Konvansiyonel enteroklizistе duyarlılık %92, özgüllük %100 [14], BT enterografide duyarlılık %89-%95, özgüllük %80-%89 [20, 21] olarak bildirilmiştir. BT enterografi ile konvansiyonel enteroklizisin birbirine yakın pozitif öngörü değeri gösterdiği ifade edilmektedir [22]. MR enterografide duyarlılık %88-%89, özgüllük %78-%100 [15], ultrasonografide özgüllük %89-%100, duyarlılık %67-%83 [23] olarak saptanmıştır [24]. Bizim çalışmamızda ise MR enterografideki özgüllük %83, duyarlılık %93, pozitif öngörü değeri %83, negatif öngörü değeri %93 ve tanısal doğruluk oranı %90 olarak bulunmuştur.

Sonuç olarak, MR enterografi; çocuk, gebe, sık nükseden İBH, bilinen hastalığın rutin kontrolü gibi seçilmiş vakalarda radyasyon riskinden kaçınmak için, yeterli lümen genişliğini sağlayıp uygun sekanslar ile görüntüler elde edildiğinde etkin şekilde kullanılabilecek önemli bir yöntemdir. İBH takibinde, hastalığın aktif sürecindeki inflamasyonun, fibrostenoz evresindeki striktürlerin, obstrüksiyonların ve diğer komplikasyonların belirlenmesinde ve tedavi seçeneklerinin değerlendirilmesinde önemlidir. Gelecekte, mevcut MR sekansları ve yeni geliştirilen sekans teknikleriyle yapılan geniş hasta katılımlı karşılaştırmalı çalışmalara ihtiyaç vardır. Böylelikle MR enterografi, İBH'nın yanı sıra ince bağırsağın diğer hastalıklarında da umut verici şekilde kullanılabilir.

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Chlorine e6 tabanlı Fotodinamik Terapinin MiaPaCa-2 ve MRC-5 hücreleri üzerindeki etkisi

Effects of Chlorine e6 mediated Photodynamic Therapy on MiaPaCa-2 and MRC-5 cells

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Öz

Amaç: Pankreas kanseri, güncel tedavi yöntemlerine karşın halen yüksek mortalitesi olan önemli bir sağlık sorunudur. Bu yüzden yeni tedavi metotlarının geliştirilmesine ihtiyaç duyulmaktadır. Fotodinamik terapi (PDT), ışığa duyarlı (PS) bir ajanın önceden verilmesi ve lokal olarak tümör dokusunda birikmesi sonrasında ajanın absorpsiyon yapacağı dalga boyunda bir ışık kaynağı ile uyarılması esasına dayanır. Bu çalışmanın amacı MIAPaCa-2 pankreas epitelyal kanser hücreleri ile MRC-5 normal akciğer (kanserli olmayan) epitelyal hücreler üzerinde chlorine e-6 tabanlı fotodinamik terapinin sitotoksik etkisini belirlemektedir.

Yöntemler: MIAPaCa-2 pankreas epitelyal kanser hücreleri ile MRC-5 normal epitelyal hücreleri 10μM Ce6 ile 60 dakika boyunca inkübe edildikten sonra 670 nm dalgaboyuna sahip bir diyot lazer ile 5 J/cm^2 ile uyarılmıştır. Tedaviden 4 – 24- 48 ve 72 saat sonra WST-1 ile hücre proliferasyonu testi yapılmıştır.

Bulgular: Ce6 tabanlı fotodinamik terapinin MIAPaCa-2 grubunda diğer tedavi gruplarına kıyasla hücre canlılığını anlamlı bir oranda azalttığı bulunmuştur ($p<0.05$). Diğer yandan Ce6 tabanlı PDT'nin MRC-5 hücreleri üzerinde %33 sitotoksik olduğu belirlenmiştir.

Sonuç: Işığa duyarlı ajan Ce6 konsantrasyonu, inkübasyon süresi ve lazer parametresi her hücre hattı için ayrı ayrı belirlenmelidir. Ce6 tabanlı fotodinamik tedavi pankreas kanserinde tümörü küçültmede ve/veya palyatif bir tedavi seçeneği olarak umut vaat etmektedir.

Anahtar Kelimeler: PDT, Ce6, pankreas kanseri, MIA PaCa-2, MRC-5

Abstract

Aim: Pancreatic cancer is an important health problem with high mortality despite current treatment methods. Therefore, new methods for treatment are needed to be developed. Photodynamic therapy (PDT) is based on firstly pre-treatment of tumor region with a light-sensitive (PS) agent, following local accumulation in tumor loci irradiation with appropriate wavelength light source. The aim of this study is to determine the cytotoxic effects of chlorine e-6 based photodynamic therapy on MIA PaCa-2 pancreatic epithelial cancer cells and MRC-5 normal lung (non-cancerous) epithelial cells.

Methods: MIA PaCa-2 pancreatic epithelial cancer cells and MRC-5 normal epithelial cells were incubated with 10 μM Ce6 during 60 min and followed by irradiated with a diode laser (λ =670nm) at 5 J/cm^2. Cell proliferation test was performed with WST-1 assay 4 - 24- 48 and 72 hours after post treatment.

Results: Ce6-based photodynamic therapy significantly reduced cell viability in the MIAPaCa-2 group compared to other treatment groups ($p <0.05$). On the other hand, it was determined that Ce6-based PDT was 33% cytotoxic on MRC-5 cells.

Conclusion: Ce6 concentration, incubation time and laser parameters should be determined separately for each cancer cell line. Ce6 based photodynamic therapy is promising as a palliative treatment option and / or minimizing tumor in pancreatic cancer.

Keywords: PDT, Ce6, pancreatic cancer; MIA PaCa-2, MRC-5

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Giriş

Pankreas kanseri, hastalığa yakalananların %7'sinden azında 5 yıllık sağ kalım oranına sahiptir. Özelikle pankreas başı yerleşimli tümörlerde uygulanan pankreatikoduodenektomi (whipple prosedürü) etkili olan tek tedavi yaklaşımı olarak görülmektedir [1). Bununla birlikte rezeksiyon sonrası ortalama sağ kalım oranı sadece 10- 20 ay arasındadır. Cerrahi tedavi uygulanan hastaların sadece %12-35'inde 5 yıllık sağ kalım oranı görülmüştür [2). Fakat hastaların büyük bir çoğunluğuna, cerrahi tedavi yapma imkanı bulunmamaktadır. Pankreasın retroperitoneal yerleşimli olması, pankreas kanserinde erken tanı belirtilerinin olmaması ve erken dönemde teşhisinde etkili olacak bir görüntüleme yönteminin olmaması nedeniyle hastalık ancak ileri evrelerinde teşhis edilebilmektedir. Palyatif tedavi seçenekleri cerrahi, kemoterapi ve radyasyon tedavisidir fakat başarı oranı düşüktür ve yaşam süresini arttırmada yeterince etkili değildirler [3].

Bu durum göstermektedir ki, minimal girişimsel bir tedavi yöntemi ile tümör dokusunun lokal olarak yok edilmesi ve/veya küçültülmesi tedavi edilemez olarak görülen pankreas kanserinde uygulanabilir bir yöntem olacaktır.

Fotodinamik terapi (PDT), bir ışığa duyarlı (PS) ajanın önceden verilmesi ve lokal olarak tümör dokusunda birikmesi sonrasında ajanın absorpsiyon yapacağı dalga boyunda bir ışık kaynağı ile uyarılması esasına dayanır. Serbest oksijenin varlığında dokuda hücre ölümü meydana gelir. PDT ile gerçekleştirilen etki fotokimyasaldır [4]. Başarılı klinik uygulamalar için PS'in taşıması gereken belirli özellikler vardır. Bunlar, PS'in dokuya daha derin nüfuz etmesi için görünür ve yakın kızılötesi spektrumda absorpsiyon yapması ve serbest oksijen oluşturma kapasitesinin yüksek olması, düşük sitotoksititesi olması, seçici olarak tümör dokuda birikmesi ve vücuttan hızlı temizlenmesidir [5].

BPD, NPe6, Ce6, SnET2 ve CASPc gibi 2. kuşak PS'lar 660-690nm arasında ışık aktivasyonu, porfimer sodyuma göre daha fazla kırmızı ışık absorbsiyonu, tedavi sonrası fotosensitivitesinin sıklıkla bir haftadan az sürmesi gibi özelliklere sahiptirler. Bu çalışmada MIA PaCa-2 pankreas epitelyal kanser hücreler ile MRC-5 normal akciğer epitelyal hücreleri üzerinde chlorine e6 tabanlı PDT uygulamasının sitotoksik etkileri araştırılmıştır.

Gereç ve Yöntemler

Hücre Kültürü

Çalışmada kullanılan MIA PaCa-2 pankreas epitelyal tümör ve MRC-5 normal akciğer epitelyal hücre hattı Amerikan Tür Kültür Koleksiyonundan (ATCC) temin edilmiştir. MIA PaCa-2 tümör hücreleri %10 fetal bovin serum (FCS), 100 u/ml penisilin ve 100 µg/ml streptomisin içeren $NaHCO_3$ solüsyonu, 2 µM L-glutamin ile desteklenmiş Roswell Park Memorial Institute 1640 (RPMI) besiyerinde, %5 CO_2'li inkübatörde 37°C'de çoğaltılmıştır.

MRC-5 sağlıklı epitelyal hücreler %10 FCS, 100 u/ml penisilin ve 100 µg/ml streptomisin içeren $NaHCO^3$ solüsyonu, 2 µM L-glutamin ile desteklenmiş Dulbecco tarafından modifiye edilen MEM (DMEM) besiyerinde, %5 CO_2'li inkübatörde 37°C'de çoğaltılmıştır. Hücrelerin 2 gün ara ile besi ortamı yenilenmiştir. Yeterli hücre yoğunluğuna ulaşan kültürler tripsin ile kaldırılarak 96'lık hücre plakalarına (10.000 hücre/kuyu) ekilip 24 saat inkübe edilmiştir

Fotodinamik Terapi Uygulaması

Öncelikle sadece Ce6 nın MIA PaCa-2 tümör hücreleri üzerinde farklı dozlardaki etkisi araştırılmıştır. Hücre plakalarındaki tümör hücrelerine 9 farklı konsantrasyonda Ce6 uygulanmıştır. Uygulanan konsantrasyonlar; 100µM, 50µM, 25µM, 20µM, 12,5µM, 10µM, 6,25µM, 5µM ve 2,5 mikromolardır.

96'lık hücre kültür plakalarındaki hücreler 4 gruba ayırılmıştır (Tablo 1). 2 ve 4 no'lu gruplardaki hücreler 10µM konsantrasyonda Ce6 ile, 1 ve 3 no'lu gruplar ise sadece besiyer ile 60 dakika inkübe edilmiştir.

İnkübasyon süresinin bitimini takiben tüm kuyulardaki besiyer çekilip, taze besiyer verilmiştir. 3 ve 4 no'lu gruplar 5 j/cm^2 ile 670 nm dalgaboyunda sürekli (cw) modda diyot lazer kaynağı ile uyarılmıştır.1 ve 2 no'lu gruplar ışıma süresince karanlıkta bekletilmiştir.

Tablo 1: Çalışmadaki deney grupları.

Grup Numarası	Grup Adı	Açıklama
1	Kontrol	Sadece Hücre
2	Ce6	Hücre + Ce6
3	Lazer	Hücre + Lazer
4	PDT	Hücre + Ce6 + Lazer

Hücre Canlılık Analizi

Ce6'nın yalnız başına farklı konsantrasyonlardaki etkisi (doz optimizasyonu) WST-1 testi ile değerlendirilmiştir.

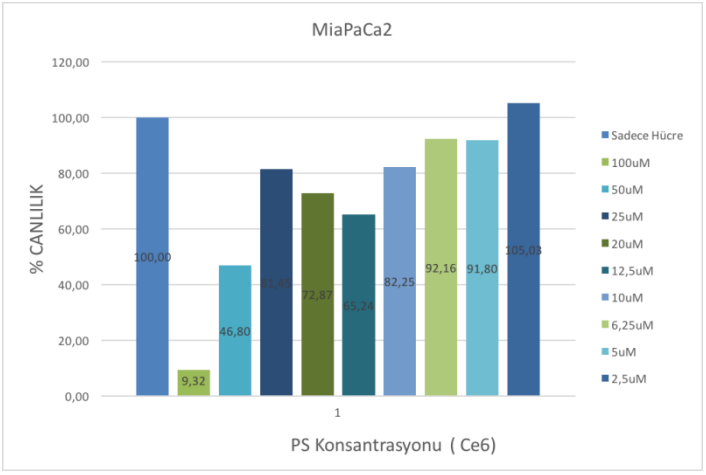
Tedavi gruplarının uygulanması sonrası metabolik aktivite temelli proliferasyon testlerinden olan 2-(4-iyodofenil)-3-(4-nitrofenil)-5-(2,4-disulfofenil)- 2H-tetrazolyum (WST-1) testi ile 4 saat, 24 saat, 48 Saat ve 72 saat olmak üzere dört farklı sürede yapılmıştır. İlgili tedavilerin uygulanmasının ardından her kuyucuğa 10 µl WST-1 çözeltisi ilave edilmiştir. 37ºC'de 4 saat inkübasyondan sonra hücre canlılığının tespiti için 96 kuyucuklu platelerin absorbans yoğunluk değerleri ELİSA plate okuyucuda 440 nm'de okunmuştur. Canlı hücreler sarı renk oluştururken, ölü hücrelerde renk oluşumu gözlenmemiştir. Kontrol grubu baz alınarak yüzde canlılık hesaplanmıştır.

İstatistik Analizi

Veriler ortalama± standart sapma şeklinde sunulmuştur. Gruplar arasındaki istatistik farklılık ANOVA ve Student's t test ile SPSS programında değerlendirilmiştir. Tüm deneyler 3 kez tekrarlanmıştır (n = 3). P değeri <0.05 istatistiksel olarak anlamlı kabul edilmiştir.

Bulgular

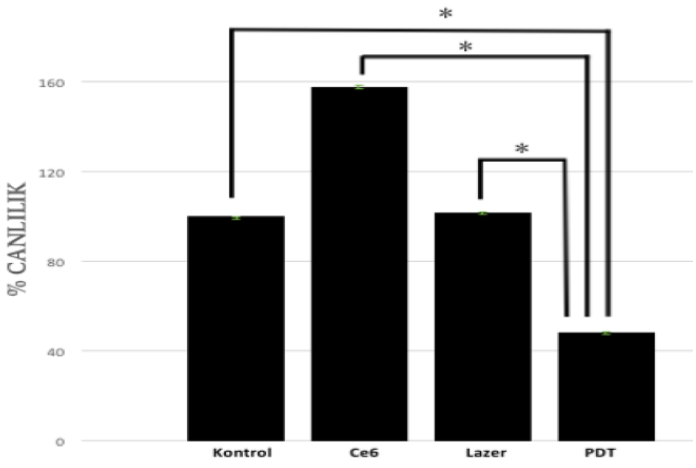
Ce6'nın yüksek dozda uygulandığında (100- 50µM) hücreler üzerinde toksik etkiye sahip olduğu ölçülmüştür. Dozdaki azalmayı takiben canlılık üzerine etkisinin azaldığı grafikten (Şekil 1) anlaşılmaktadır. Çok düşük dozlarda uygulandığında (2,5µM) ise hücrede proliferasyona neden olduğu ölçülmüştür.



Şekil 1: 100µM, 50µM, 25µM, 20µM, 12,5µM, 10µM, 6,25µM, 5µM ve 2,5µM olmak üzere 9 farklı konsantrasyonda Ce6'nın tümör hücrelerine verildikten 24 saat sonra yapılan WST-1 analizi grafikte verilmiştir.

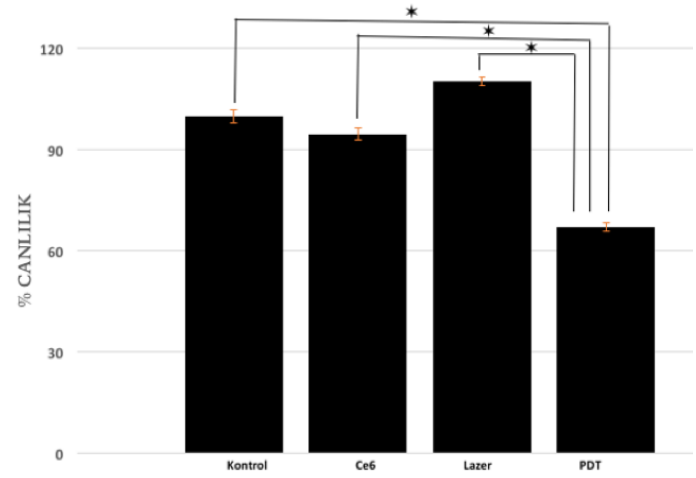
MIA PaCa-2 pankreas epitelyal karsinoma hücre hattına ait tedaviden 4 saat sonra yapılan WST-1 testi sonuçları Şekil-2 de gösterilmiştir.

MIA PaCa-2 pankreas epitelyal karsinoma hücrelerinin sadece 10µM konsantrasyonda Ce6 ile 60 dakika boyunca inkübasyonu sonucunda hücre canlılığı %158 olarak ölçülmüştür. Uygulanan Ce6 dozunun hücreler üzerinde toksik etki oluşturmadığı aksine proliferatif bir etkiye sebep olduğu görülmüştür. Sadece lazer uygulanan grupta canlılığın %102 olduğu ve fototoksik bir etki oluşturmadığı gözlemlenmiştir (Şekil 2). PDT grubunda ise tedavi sonrası canlılığın %48,5'a düştüğü görülmüştür.



Şekil 2: Tedaviden 4 saat sonra MIA PaCa-2 tümör hücrelerinin canlılık analizi. Kontrol; Sadece Hücre, Ce6; Hücre+Chlorine e6, Lazer; Hücre+Lazer, PDT; Hücre+Ce6+Lazer. PDT tedavi grubu ile diğer gruplar arasında istatistiksel anlamlı fark bulunmuştur (*P<0.05).

MRC-5 normal akciğer epitelyal hücre hattına ait tedaviden 4 saat sonra yapılan WST-1 testi sonuçları Şekil-3 de gösterilmiştir.



Şekil 3: Tedaviden 4 saat sonra MRC-5 epitelyel hücrelerinin canlılık analizi. Kontrol; Sadece Hücre, Ce6; Hücre+Ce6, Lazer; Hücre+Lazer, PDT; Hücre+Ce6+Lazer. PDT tedavi grubu ile diğer gruplar arasında istatistiksel anlamlı fark bulunmuştur (*P<0.05).

MRC-5 akciğer epitelyal hücrelerinin 10µM konsantrasyonda Ce6 ile 60 dakika boyunca inkübasyonu sonucunda canlılık %94 olarak ölçülmüştür. Sadece lazer uygulanan grupta hücre canlılığının %110 olup herhangi bir fototoksik bir etki oluşturmadığı gibi proliferatif bir etkisi olduğu belirlenmiş olup kontrol grubuyla arasında anlamlı fark olmadığı belirlenmiştir. PDT grubunda ise canlılık %67 olarak ölçülmüştür (Şekil 3).

Tartışma

Bu çalışmada PDT'nin MIA PaCa-2 pankreas epitelyal karsinoma ve MRC-5 akciğer epitelyal hücre hattı üzerindeki sitotoksik etkisi WST-1 testi kullanılarak araştırılmıştır. Çalışmada MRC-5 akciğer epitelyal hücre hattının seçilmesinin amacı, reaktif oksijen türleri tarafından oluşturulan hasarın normal hücreler üzerindeki etkisinin gösterilmesidir. MRC-5 akciğer epitelyal hücre hattı kültür çalışmalarında diğer normal hücrelere kıyasla iyi üreme yeteneğine sahip olması sayesinde tedaviden sonra proliferasyon kapasitesi ölçülebilmektedir [6].

Öncelikle Ce6'nın MIA PaCa-2 pankreas epitelyal karsinoma hücreleri üzerindeki yalnız uygulanmasının etkisinin tespiti için doz optimizasyonu yapılmıştır. 9 farklı dozda yapılan sonuçlara göre Ce6 yalnız başına uygulandığında toksik etki göstermediği 10µM PS konsantrasyonu tedavide kullanılacak doz olarak seçilmiştir (Şekil 1). MIA PaCa-2 hücre hattına ait tedaviden 4 saat sonra yapılan WST-1 testi sonuçları Şekil-2 de gösterilmiştir. MIA PaCa-2 pankreas epitelyal karsinoma hücrelerinin sadece 10µM konsantrasyonda Ce6 ile 60 dakika boyunca inkübasyonu sonucunda canlılığın %158 lere arttığı ve hücreler üzerinde toksik etki oluşturmadığı gözlemlenmiş aksine proliferatif bir etkiye sebep olduğu görülmüştür. Üçüncü tedavi grubunda uygulanan sadece 5 J/cm^2 lazer kaynağı ile uyarılması sonucunda MIA PaCa-2 pankreas epitelyal karsinoma hücrelerinin canlılığının %102 olduğu ve fototoksik bir etki oluşturmadığı gözlemlenmiştir (Şekil 2). Ana deney grubu olan 4. grupta (PDT) ise tedavi sonrası canlılığın %48,5'a düştüğü görülmüştür. PDT'nin hücre canlılığını büyük oranda azalttığı tespit edilmiştir ve tüm gruplarla arasında istatistiksel anlamlı fark olduğu belirlenmiştir (P<0.05).

MRC-5 hücre hattına ait tedaviden 4 saat sonra yapılan WST-1 testi sonuçları Şekil-3 de gösterilmiştir. Elde edilen sonuçlara göre; MRC-5 akciğer epitelyal hücrelerinin 10µM konsantrasyonda Ce6 ile 60 dakika boyunca inkübasyonu sonucunda canlılığın %94 olduğu ve hücreler üzerinde toksik etki oluşturmadığı gözlemlenmiştir. Bununla birlikte üçüncü tedavi grubunda uygulanan 5 J/cm^2 lazer ışınlaması sonucunda MRC-5 akciğer epitelyal hücre canlılığının % 110 lara çıktığı ve herhangi bir fototoksik bir etki oluşturmadığı, aksine proliferatif bir etkisi olduğu belirlenmiş olup kontrol grubuyla arasında anlamlı fark olmadığı belirlenmiştir. Ana tedavi gurubu olan PDT (4. Grup)'nin MRC-5 akciğer epitelyal hücre hattı üzerindeki etkisi tüm gruplarla karşılaştırıldığında canlılığın %67 olduğu ve tüm gruplarla arasında istatistiksel anlamlı fark olduğu belirlenmiştir (P<0.05).

Sara Abdel Hamid ve arkadaşlarının glioma hücrelerinde Ce6 tabanlı PDT uygulaması yaptığı bir çalışmada Ce6'nın LD_{50} dozunu 10µM bulmuşlardır. Yine aynı çalışmada 4 saatlik 10µM Ce6 inkübasyonunun ardından glioma hücrelerine 665 nm diyot lazer uygulaması yaptıklarında glioma hücrelerinde tedavinin %100 hücre ölümüne sebeb olduğunu göstermişlerdir [7]. İnsan kolon kanseri hücresi olan SW480 üzerinde yapılan bir çalışmada Ce6'nın endoplazmik retikulum ve lizozomda birkimi tespit edilmiştir. Yine aynı çalışmada 650 nm dalgaboyunda [6 J/cm$^{2)}$ lazer uygulaması ile yapılan Ce6 tabanlı PDT'nin uygulanan 1 µg/ml ve üzerindeki konsantrasyonlarda hücre canlılığını inhibe ettiği, reaktif oksijen türlerinin üretimine ve apoptoza sebeb olduğu gösterilmiştir. Düşük dozlarda uygulanan Ce6'nın (0.125 ve 0.25 µg/ml) koloni oluşumu ve hücre proliferasyonunu arttırdığı tespit edilmiştir [8]. Fare kolerektal kanser hücresi olan C26 ile yapılan çalışmada 0.5 µg/mL konsantrasyonda Ce6 ile 662 nm dalgaboyunda ışık kaynağı ile farklı güç değerleri uygulanarak PDT uygulması yapılmıştır. PDT uygulamasının CLIC4 (chloride intracellular channel 4) ve MMP9 (matrix metalloproteinase) ekpresyon seviyelerini azaltarak tümör hücrelerinin migrasyonunu baskıladığı gösterilmiştir [9]. Fareler üzerinde yapılan bir çalışmada denek başına intraperitonel 7,5 mg/kg Ce6 ve 652 nm dalgaboyunda100 J/cm ^{2} lazer uygulanarak yapılan PDT'nin malign melanomların yok edilmesinde etkili olduğu tespit edilmiştir [10].

Yapılan bu çalışma ve literatür verileri uygun PS konsantrasyonu ve inkübasyon süresi ile uygulanan lazer parametrelerinin her hücre tipinde farklılık gösterdiği sonucunu desteklemektedir.

MRC-5 akciğer epitelyal ve MIAPaCa-2 pankreas epitelyal karsinoma hücre hatları üzerinde yaptığımız çalışmanın sonuçları değerlendirildiğinde Ce6 tabanlı PDT'nin MIA PaCa-2 pankreas epitelyal karsinoma hücreleri üzerindeki sitotoksik etkisinin MRC-5 akciğer epitelyal hücrelerinden daha fazla olduğu gözlemlenmiştir. Buradan yola çıkarak *in vivo* olarak

uygulanacak PDT'nin tümör doku üzerinde oluşturduğu sitotoksik etkinin tümör çevresindeki sağlıklı bölgedeki hücrelere kıyasla daha fazla olacağı söylenebilir. Böylece PDT sayesinde geleneksel kanser tedavilerinin en önemli dezavantajı olan sağlıklı doku harabiyetinin de önüne geçilebilir.

Bu çalışmanın devamı niteliğinde PDT'nin tümör hücreleri üzerinde meydana getirdiği sitotoksik etkinin kaynağının belirlenmesi için Annexin-V ve Kaspaz/BCA protein aktivitesinin incelenmesi gerektiği sonucuna varılmıştır. Özellikle caspase 3, 9 ve BCA protein seviyeleri ile apoptoz ve/ veya nekroz tayini ile PDT'nin sebep olduğu hücresel ölüm tipinin araştırılması gereklidir.

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Neural correlates of placebo effect: Review and future implications

Plasebo etkisinin nöral temelleri: Geçmiş bulguların gözden geçirilmesi ve çıkarsamalar

Sezin Öner [1]

Abstract

Experimental and clinical research has documented expectancy related symptom improvement in a variety of conditions, leading to a growing interest in the placebo effect. Despite significant treatment outcomes, placebo-induced effects have been regarded as nonspecific psychological factors associated with the subjective experience of healing that operates different than the actual drug agent . However, neuroimaging research revealed more complex regulation of the placebo response, which indicates a top-down regulation of the symptom improvement enhanced by the expectancy effects. It appears that, placebo response is not solely function of higher order control processes, but also involves diverse disease-specific neurobiological mechanisms. In the current review, neural mechanisms underlying placebo effect have been addressed focusing on the analgesia, Parkinson's disease and major depression. Along with the opiate system, dopaminergic and serotonergic functions in the brain are discussed in relation with the three target conditions. Last, potential implications of the placebo research are discussed with respect to experimental and clinical practice.

Keywords: placebo effect, pain, antidepressants, Parkinson's disease, treatment expectancy

Öz

İyileşme beklentisi ile ilişkili hastalığa-özgü semptomlardaki iyileşme literatürde sıkça gösterildiğinden plasebo etkisine olan ilgi giderek artmaktadır. Her ne kadar tedavi etkinliği plasebo gruplarında belirgin olsa da, bu etkinin asıl maddeden ziyade, hastanın iyileşme beklentisi ve öznel iyilik değerlendirmesinin bir sonucu olarak düşünülmektedir. Öte yandan, beyin görüntüleme çalışmaları daha karmaşık bir sürecin var olduğuna işaret etmektedir. Denetimli kontrol mekanizmalarının yönettiği plasebo etkisinin iyileşme beklentisi ile güçlendiği görüşü giderek ağırlık kazanmaktadır. Bu bağlamda görünen odur ki, plasebo etkisi tek bir sistem üzerinden değil, hastalık temelli mekanizmalar aracılığı ile ortaya çıkmaktadır. Bu derleme çalışmasında da, plasebo etkisinin nöral boyutlarının sıkça incelendiği ağrı, Parkinson ve depresyon olgularına ilişkin bulgulara odaklanılmış ve opiat sistemi ile dopaminerjik ve serotonerjik işlevler incelenmiştir. Bu doğrultuda da, geçmiş bulguların gözden geçirilmesinin ardından plasebo etkisinin gelecek çalışmalardaki rolü tartışılmıştır.

Anahtar sözcükler: Plasebo etkisi, ağrı, antidepresanlar, Parkinson, tedavi beklentisi

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Introduction

The notion of *placebo effect* refers to the positive outcome of a treatment that is known to have no particular effect for the condition being treated; but the resulting treatment response acts as if the patients have received an active, effective treatment for the particular condition [1]. A number of studies have addressed the mechanisms underlying placebo effect and current evidence highlight the learning and expectancy related outcomes [2,3], yet there is still much to be uncovered. A number of confounding factors have been implicated both in the methodology and design employed in empirical studies [4-6]. Individual differences in placebo responsiveness, disease-specific outcomes and difficulty of testing nonspecific psychological factors further blur the conclusions drawn from the symptom improvement. On the other hand, use of neuroimaging techniques, such as functional magnetic resonance imaging (fMRI), positron emission tomography (PET), allowed researchers to objectively examine the course of placebo-induced 'healing' when it exists. But more importantly, this line of research revealed the neural mechanisms through the course of placebo effect and how the outcome is modulated by the higher-order cognitive processes. Accordingly, current review outlined the major evidence on the neurobiology of the placebo effect. Although clinical trials on any clinical conditions consider placebo effect, neuroimaging data mostly comes from analgesia, Parkinson's disease and depression, thus, here the focus is limited to these particular conditions.

Pain and Placebo Analgesia

In general terms, pain is the natural physical response of the organism, placebo analgesia is the voluntary modulation of pain, either consciously or nonconciously [1]. Converging evidence demonstrated that central nervous system, through its diverse connections to internal body parts and sense organs. Recent brain imaging research has revealed that sensory intensity and subjective experience associated with pain are processed by separate mechanisms such that somatosensory cortex and mainly the insula lead the sensory experience whereas affective experience of pain is modulated by anterior cingulate cortex [7,8].

The mechanism for placebo analgesia was first shown by injection of naloxone to patients after the administration of active and placebo treatments[1].They found that naloxone impaired the analgesic affects of placebo that subjects who in that group experienced increased post-operative pain. As naloxone being an opioid antagonist, the very early explanations of the placebo effect focused on the opioid receptors. Subsequent studies pointed out the role of specific brain regions and neurochemicals underlying placebo analgesia. For example, Petrovic et al. [9] compared healthy adults for their responses to thermal pain in saline (placebo) and remifentanil, a short acting opioid analgesic drug. Verbal instructions were exactly the same in order to eliminate expectancy-related outcomes. They found increased opioid related activity in right ACC (anterior cingulate cortex) and OFC (orbitofrontal cortex) for both conditions In addition to this, overlapping activity was observed in regions of right ACC, periaqueductal gray matter (PAG) and pons in both groups, suggesting for the comparable opioid mechanisms activated to reduce pain in response to active and placebo treatments that placebo analgesia involves the same opioid activations with the active drug effects to decrease pain experience. However, different from the active drug condition, for the placebo group, higher opiate activity observed in right ventrolateral prefrontal cortex (VLPFC) underlined the top-down control of placebo-induced analgesia. Zubieta et al.[10] provided confirming evidence using a PET scan in a group of participants under sustained pain. Specifically, they examined changes associated with carfentanil, a potent opioid analgesic competing with endogenous opioid receptors. Changes in the opioid release were tested in relation with placebo analgesia. Placebo treatment resulted in the down-regulation of opioid receptors in both cortical and subcortical structures such as dorsal ACC, lateral PFC, insula, nucleus accumbens (NAcc), thalamus and amygdala. Sustained pain paradigm was tested also using a different experimental design in which subjects were delivered pain alone or with the simultaneous placebo treatment. Findings supported the previous evidence, in that, placebo analgesia was mediated by the opioid receptors' activation in right ACC, dorsolateral PFC (DLPFC), anterior insula and NAcc. Time course of activation, however, was notable, such that increased opioid receptor activation in DLPFC before placebo administration was associated with decreased subjective pain experience, pointing out the top down control of pain experience. Expectancy of pain reduction triggers activation of opioid system in DLPFC, which then results in the attenuation of pain experience through other subcortical functions.

Regulation of the subjective pain experience appeared to be regulated by cognitive control mechanisms. In their disruption theory, Liebarmann et al.[11] suggested that automatic negative affective processes generates subsequent reflective conscious processes that results in the inhibition of very same negative affective processes by the hardwired biofeedback mechanism. The role of ventrolateral PFC, especially lateralized to right, in modulating the negative affect by its projections to dorsal ACC and amygdala. In order to test their hypothesis, they examined the PET scans of patients with IBS (irritable bowel syndrome) during rectal stimulation under either placebo given or active drug conditions. Increased activation was found in right ventrolateral PFC associated with expectancies for the analgesic effects of the treatment. More specifically, increased right ventrolateral PFC activity was followed by the decreased dorsal ACC activity, leading to symptom improvement. Such findings are also important in terms of demonstrating the independence of placebo effect from health improvements due to time course, because, the effects of habituation to rectal stimulation were associated with a different region of ACC from where the placebo effects were observed.

Modality of the pain was also investigated to test whether distinct neural mechanisms are involved in the analgesic effects for thermal pain and shocks [12] however, consistent with previous findings, decreased activity in right ACC, insula; thalamus was associated with decreased subjective reports for both groups. However, brain regions activated during pain anticipation were found to be different from that pain experience. Increased activity in right ACC, OFC, PAG and DLPFC during pain anticipation was associated with subsequent symptom improvement. Findings indicated the role of cognitive control such that top-down regulation of pain initiated by the expectancy of pain reduction that is reflected on the activation of frontal cortices, specifically, ventrolateral PFC and ACC. These regions trigger the functions of the midbrain regions modulating actual pain experience. Pain experience is further monitored by the right ACC through the feedback mechanisms, supporting for the role of cognition in analgesia. Such evidence is also in line with the view arguing for the interactions between prefrontal and cingulate systems mediating the cognitive reappraisal of the meaning of the evocative stimuli [13,14].

Converging evidence has been reported recently by Nemoto and colleagues (2007) in a study examining analgesic responses to thermal pain in healthy subjects who responded to placebo or not [15]. They found similar pattern of activation before the placebo administration such that placebo-responder group showed increased activation of medial PFC and ACC, whereas right ACC activity gradually decreased subsequent to pain stimulation. Placebo-nonresponders showed activations in the same regions with the placebo-responders during preadministration and pain, however, the decreased right ACC activation was not observed, supporting for the role of the neural changes in the anticipation phase in organizing the placebo analgesia.

Overall, such findings point out the role of top-down regulation of placebo analgesia in which expectation-induced changes in prefrontal structures influence the subcortical opioid releasing regions such as PAG and midbrain. This is important in the sense that placebo analgesia is not simply the subjective reports of change, but rather reflected on the objective neural responses involved in the pain experience.

Opioid-related placebo analgesia has been discussed, non-opioid based placebo analgesia has been implicated so far [16]. For example, in their study, Amanzio and Benedetti [17] administered a non-opioid analgesic drug ketolorac for 2 days and on the third day, they replaced the drug with the placebo (saline). On that replacement day, they told subjects that the drug was either an analgesic or just an antibiotic. They found that following administration of naloxone blocked the analgesic effect of placebo only when the subjects were told the drug was an analgesic but not the drug was an antibiotic. In that sense, findings were in line with learning accounts of placebo effect [18]. When contextual cues signaling analgesia were made salient, analgesia could be blocked by the opioid antagonist naloxone, however when the analgesia expectancies were

eliminated, naloxone could not impair the analgesic effects of placebo.

Placebo analgesia has been discussed in relation with dopaminergic functioning. PET results revealed that higher dopamine release in NAcc during analgesic anticipation was associated with more analgesia expectations in placebo-responders group than non-responders group [19]. Increased dopaminergic activity was shown to be associated with the anticipation of the reward that is the analgesic outcome which, has been proposed as the core mechanism accounting for the attenuation of the pain experience associated with increased dopamine release. In the next section, the role of dopaminergic functions in mesolimbic pathway is addressed in the context of placebo responses.

Dopaminergic Pathways Involved in Placebo Effect

The role of dopaminergic activity has been demonstrated in placebo analgesia, however, most of the evidence comes from the placebo research on Parkinson's disease (PD) and psychoactive drugs [20] both of which are characterized by changes in dopamine functions. Parkinson's disease is a motor disorder characterized by the resting tremors, bradykinesia, akinesia, and postural instability. Symptoms are associated with the abnormalities in striatal dopamine functioning, specifically in caudate and putamen significantly less than usual.

A number of studies have demonstrated the placebo effect in a group of PD patients. For example, in a double blind trial of pergolide, a dopamine agonist commonly prescribed for PD, patients in placebo group did improve as much as active-drug pergolide group [21]. Goetz et al.[22] reported consistent evidence for another dopamine agonist drug, ropinirole, in a randomized placebo-controlled study. When groups given placebo and ropinirole were compared, placebo group was found to show 50% improvement in motor functioning, mostly in bradykinesia and rigidity that are the dopamine-related impairments. Such findings are in line with that placebo-induced symptom improvement in PD is mediated by the dopaminergic functioning. It is important to note that objective versus subjective improvement can be discriminated more precisely in PD compared to conditions of pain or depression, which further indicates concrete mechanisms other than the expectancy-driven experience of well-being [23].

Increased striatal dopamine release was demonstrated in PD patients who expected to receive apomorphine, a DA agonist. PET scans revealed that, compared to control condition, placebo treatment resulted in increased dopamine release specifically in caudate and putamen and placebo group also reported significant objective clinical benefits associated with higher dopamine release in motor striatum [24]. The same research group provided further evidence supporting the clinical improvement associated with increased dopamine release in dorsal striatum. In addition, expectancies for the treatment response were found to be associated with increased dopamine release in ventral striatum [25].

Striatal dopamine function was also demonstrated in a transcranial magnetic stimulation (TMS) study. Patients with PD were told that they had 50% chance to have real or sham (placebo) treatment, but actually all the patients received the sham treatment. Placebo group showed higher dopamine release in both dorsal and ventral striatum, however, not all of the patients showed symptom improvement. Only the patients with high dopamine concentration in dorsal striatum showed symptom improvement whereas dopamine in ventral striatum was not related to any clinical benefit [26].

Such differentiation in dopaminergic functions of dorsal and ventral striatum is in line with their functional differentiation. Specifically, dorsal striatum is especially involved in voluntary movement whereas ventral striatum modulates functions related to expectancy, motivation and reward anticipation [27]. Accordingly, although placebos act as a reward due to the positive treatment expectancies of patients [23], it is not directly related to symptom improvement [26]. In that sense, placebo induces objective improvements in clinical symptoms through its disease specific effect on dorsal striatum whereas expectancies of healing operate on the reward circuit regulated by the ventral striatum [25,28].

Reward Expectation and Placebo Outcome

Reward expectation is one way to explain placebo effect observed not only in Parkinson's disease but also in the placebo analgesia [19,29,30]. Martikainen et al. [31] found that the striatal dopamine receptor binding potential six years before predicted analgesia responses of healthy subjects. In the more recent fMRI study, Scott et al. [19] measured the brain activity during reward anticipation and a control task. Also, emotional and behavioral responses to the placebo analgesic and expectancies regarding the drug efficacy were examined. Subjects who showed more NAcc activation during reward anticipation task had also higher expectancy for analgesic outcome. Moreover, the subjects who had more analgesic responses reported the placebo to be more effective than they expected.

Findings are in line with the dopaminergic activity in the brain's reward pathway. The midbrain dopamine cells are grouped in to form three major pathways and the reward circuitry is one of these characterized as originating from the medial parts of ventral tegmental area (VTA) and projecting to mesolimbic cortex [32]. The most important region in terms of reward processing is the ventral striatum, especially the NAcc, where the dopamine cells play critical role in reward expectancy and goal-directed motivated behaviors. Phasic (fastly changing) and tonic (stable or relatively slow changes) dopamine cell firings in ventral striatum are important determinants of reward processing as well.

Dopaminergic activity in ventral striatum represents the anticipation or the prediction of the reward, rather than actual rewards to optimize the organism's goals [32,33]. If there is no actual reward, then, how do the placebo drugs trigger the activity of the reward pathway as if actual rewarding stimuli? In clinical cases, healing is the main goal of the treatment, the situational cues in the treatment setting, suggestions for healing, having prior experience with the treatment, (learning experience), even only being the treatment recipient forms a treatment expectancy that signals the reward that is healing. Ventral striatal mechanisms modulate not only such anticipatory mechanisms but also the saliency of the reward [16].

This functional framework was supported in a PET study with healthy participants [34]. Initially, amphetamine was administered in a particular context and then tested how subjects responded to placebo in that particular context. As amphetamine and context were paired, placebo drug was expected to act as the active drug, making the 'reward' salient and activating the stimulus-response chains learned

in that context. Similar to the expectancy-induced placebo outcomes, dopamine release in NAcc for the placebo condition was found to be no different than it was for the active drug administration.

On the other hand, it has been also argued that reward-related expectancies driven by top-down processes were better predictors of drug effects than simply the conditioning [35]. They provided supporting evidence by simply manipulating the expectancy effects. In their study, healthy subjects were told that they would receive either methylphenidate or placebo. When subjects did expect to receive methylphenidate, they showed lower dopamine release in ventral striatum in response to methylphenidate compared to when they did not expect to receive. More importantly, even naive subjects who had no prior experience of methylphenidate, showed increased dopamine release in NAcc and decreased activity in thalamus and cerebellum, when they expected to receive methylphenidate but they were given the placebo, suggesting for the role of higher-order cortical processes in the regulation of placebo response.

As most of the studies target the link between dopaminergic activity and placebo response in PD, placebos seem to induce disease-specific effects. However, midbrain dopaminergic pathway is involved in the processing of reward in general and its role is not limited to PD but also demonstrated in depression as reviewed in the following section.

Placebo Effect in Depression

Major depression is another field which placebo effect has been studied extensively. An early metaanalysis [36] on the effectiveness of antidepressants proposed the 75% effectiveness of the antidepressants is due to the placebo effect, which has further encouraged the placebo controls in antidepressant research. Current findings are exciting because significant placebo-related symptom improvement has been observed in depression, even in severe cases [37,38]. Although such findings underline the ethical and practical questions arise in relation with the prevalent use of antidepressants, however, it is important to understand the dynamics of the placebo effect before discussing it in the context of active drug effects.

Serotonergic system has been implicated as the major mechanism underlying the placebo effect [39-41]. As in cases of pain analgesia and Parkinson's disease, placebos, in depression, result in responses matched with antidepressant effects of serotonin reuptake inhibitors [42] (SSRIs). It is important to note that clinical improvements are significantly different in placebo or antidepressant treatments, there appears to be anatomical differences in regions involved in producing such improvements.

Placebo effect seemed to result from the top-down modulation of treatment expectancies. Prefrontal cortex activity, especially in the cingulate cortex, has been found to determine the treatment response [43] in both placebo and antidepressant treatments, however, in placebo treatments increase in the frontal cortex activity was observed in the very beginning whereas antidepressant-related frontal activation occurs much later throughout the treatment course [33].

Mayberg et al. [40] demonstrated the common and distinguishing mechanisms through the course of 6-week placebo and fluoxetine treatment in a double-blind PET study. Clinical improvement, for both types of treatments, was found to be related to, decreases in subgenual cingulate and thalamus, and also increases in posterior cingulate, and prefrontal cortex. Despite comparable improvement, fluoxetine resulted in decreased activity in hippocampus and striatum, increased activity of brainstem/pons, especially which the latter suggested for the bottom-up regulation of the autonomic nervous system activity. Changes in neural activity induced by fluoxetine were widespread, however, no significant differences were found with respect to changes in depressive symptomology. One explanation may be related to the longevity of the treatment response. In other words, differences in neural activity may determine further improvement in the symptoms or the maintenance of the remission [43]

Functional differences in brain activity were more specifically examined demonstrated in an electroencephalography (EEG) study [44]. Subjects' prefrontal EEG cordance were measured at three time points, at the placebo lead-in phase (1 week pretreatment period), at the beginning of the medication (either antidepressant or placebo) and at the end of the treatment. No clear differences in clinical improvement for placebo and active treatment groups. More importantly, treatment response was determined by the decreases in the EEG cordance at PFC during the placebo lead-in phase, which represents the regulatory activity of anterior cingulate cortex. Such findings were in line with previous evidence demonstrating the role of ACC in cognitive modulation of treatment outcomes [10,11,42].

It is also likely that personal expectations formed during the pretreatment phase, the positive interpersonal relations with the medical team might be critical determinants of the improvement [44]. Since medication (either antidepressant or placebo) effects are not apparent in the first week of the treatment, regional neural changes observed during that first week of treatment might reflect the expectancy component of treatment. At the first week, different from the active-drug condition increased ACC activity was observed in the placebo group. On the other hand, activational changes in hippocampus, striatum and brain stem are unique to active-drug condition, which may reflect the long term outcome such as remission. In that sense, especially striatal changes may reflect the reward-related changes before the beginning of the actual treatment. However, despite supporting evidence for PD and analgesia [10,24,35], the role of dopaminergic activity has not been demonstrated so far.

Existing evidence support the comparable effectiveness of placebos as antidepressants along with the associated neural changes. However, there are some important issues that need to be addressed regarding the placebo 'antidepressants'. One of them is the *active placebos* Kirsch and Sapirstein [36], the drugs that have no specific antidepressant effect but produce certain side effects, such as dry mouth, sedation, as these antidepressants. It has been argued that patients receiving placebos with the expectation of antidepressant may not hold strong positive beliefs regarding the effectiveness of the medication. However, if such patients also experience the specific side effects which they think that the antidepressant drug produce, their positive expectations about the treatment outcome result in greater improvements in depressive symptoms, which in turn increases their use in research and clinical practice. However, it is also likely that use of active placebos may reduce the blindness of the subjects as well as experimenters. Depending on the type or intensity of the side-effects, subjects may guess the condition in which they are assigned and as blindness is a must especially in placebo research, this may interfere their treatment outcome. Another point is the variability in patients' disease or medication/ treatment histories. Clinical trials on depression rarely include first-episode patients or patients who are naïve to treatment. Prior conditioning or experience with the antidepressants influence the expectancies and inevitably bias the results regarding the treatment efficacy [43].

Despite certain limitations, neuroimaging studies have revealed the placebo effect as comparable to active antidepressants [45-47]. Overall, it appears that placebo antidepressants have comparable efficacy to active antidepressants in terms of clinical improvement in depressive symptoms. Similar to the antidepressant functions, placebo treatments act on the serotonergic functions in frontal cortex and the resulting disease specific improvements tend to be modulated by the expectancies of the treatment outcome.

Stress Response in Placebo Effect

Expectancies of well-being might provide individuals feelings of comfort and drive them to experience less anxiety and stress throughout the treatment. Studies that had stress-related measures have found evidence accordingly. Studies employing measures of affect or stress provided empirical support. For example, when subjects were given placebo, they were told that either drug does work or not. Expectancies for the drug efficacy were found to be associated with decreased levels of cortisol and less negative thoughts regarding the treatment. Although symptom reduction was no different in two groups, the former group expecting the drug would work experienced less stress during the treatment.

It has also been suggested that perceived stress in treatment setting and placebo responsiveness may be related. Involvement of mesolimbic structures and also reward mechanisms may explain individual differences in placebo responses and the responses of these structures, to a certain extent, are related to individuals' perceptions during the treatment course. Minimal stress experience in the environment and also high treatment expectancies facilitate responsiveness to placebo [45]. However, research in this area is still limited and anxiolytic effect of placebo and its underlying mechanisms are needed to be explored.

Conclusion and Implications for the Future

Neurological mechanisms underlying placebo effect is relatively a newborn area of research, and there is still much to explore for the future. First of all, the mechanisms underlying individual differences in the placebo response are needed to be explored in more controlled designs. Genetic differences may operate via the higher-order cortical functions, but it is also possible such differences may be a function of the genotypic variation in the neurotransmitter functions. Personality characteristics, such as openness to experience, suggestibility, may moderate placebo responsiveness. Addressing this, future research will not only reveal the traits that enhance or reduce placebo effect but also broaden our understanding regarding the mechanisms underlying placebo response. Last, disease-specific outcomes may be coordinated by different neural mechanisms although treatment expectancy accounts for most of the placebo effect. More specifically, an analgesic drug is expected to show its effect in the short run whereas the effect of antidepressants appears weeks later. Thus, commonalities and distinctions in the neural mechanisms underlying placebo effect need to be specifically examined in the future research.

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A rare case of left paraduodenal hernia: A case report

Nadir görülen sol paraduodenal herni vakası: Bir olgu sunumu

Gülsen Atasoy [1], Ayetullah Temiz [1], Yavuz Albayrak [1], Ahmet Yalcin [2]

Abstract

The paraduodenal hernia, is formed by a potential cavity next to the ligament of Treitz and malrotation of the midgut. These hernias, which are the most frequently seen type of internal hernia, are responsible for approximately 1% of small intestine obstructions.

A patient was admitted to the emergency room with complaints of abdominal pain and the inability to defecate. A computed tomography cross section that passed through the abdominal right upper quadrant, adjacently to the duodenal intestinal ansae within a hernia sac, showed a portion of the transverse colon and dilated mesenteric vascular structures. The patient underwent an exploratory operation that showed an orifice of approximately 3 cm in the ligament of Treitz and a shifting of almost all the small intestines and a portion of the transverse colon to the paraduodenal surface. The herniated structures were reduced at that point and the defect from the ligament of Treitz was sutured with non-absorbable suture material and closed.

The paraduodenal hernia is a rare cause of intestinal obstruction but may result in late diagnosis and life threatening conditions such as intestinal gangrene. A patient with an intestinal obstruction who has not undergone a previous abdominal procedure should be considered as potentially having a paraduodenal hernia and should be immediately diagnosed in order to undergo surgical treatment.

Keywords: Hernia, intestinal obstruction, internal hernia

Öz

İnternal herninin bir tipi olan paraduodenal herniler Treitz ligamentinin yakınındaki potansiyel bir boşluktan ve ortabarsağın malrotasyonundan dolayı oluşur. Paraduodenal herniler, internal hernilerin en sık görülen formudur ve ince barsak obstrüksiyonlarının yaklaşık %1'inden sorumludur.

Bir hasta acil kliniğine karın ağrısı ve gaz gaita çıkaramama şikayetleriyle müracaat etti. Batın sağ üst kadran seviyesinden geçen bilgisayarlı tomografi kesitinde, duodenum komşuluğunda bir herni kesesi içerisinde intestinal anslar, transvers kolonun bir kısmı ve dilate mezenterik vasküler yapılar izlendi. Hastaya tanısal laparatomi yapıldı. Yapılan eksplorasyonda Treitz ligamentinde yaklaşık 3 cm'lik bir açıklık olduğu ve buradan ince barsakların tamamına yakınının ve transvers kolonun bir kısmının paraduodenal bölgeye geçmiş olduğu görüldü. Bunun üzerine herniye olan yapılar redükte edildi. Daha sonra Treitz ligamentindeki defekt emilmeyen sütür materyali ile sütüre edilerek kapatıldı.

Paraduodenal herni intestinal obstrüksiyonun nadir bir nedenidir. Bundan dolayı tanıda geç kalınarak barsak gangreni gibi hayati tehlike yaratabilecek durumlara yol açabilir. Bu durumu engellemek için daha önceden karın ameliyatı geçirmemiş intestinal obstrüksiyonlu hastalarda paraduodenal herni olabileceği düşünülmeli ve gecikmeden tanısı konularak hastaya cerrahi tedavi uygulanmalıdır.

Anahtar Kelimeler: Paraduodenal herni, intestinal obstrüksiyon, internal herni

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Introduction

An internal hernia result from protrusion of one or more abdominal viscera through an intraparietal opening with the herniated viscera remaining inside the peritoneal cavity [1].It is one of the rare causes of an acute abdomen and can result in intestinal obstruction and ischemia if not treated in a timely manner [2,3]. One type of internal hernia, the paraduodenal hernia, is formed by a potential cavity next to the ligament of Treitz and malrotation of the midgut [4]. These hernias, which are the most frequently seen type of internal hernia, are responsible for approximately 1% of small intestine obstructions [5].

Our aim in this study is to present a left paraduodenal hernia case who was admitted with intestinal obstruction and to describe our approach to therapy.

Case Report

A 25-year-old male patient was admitted to the emergency room with complaints of abdominal pain and the inability to defecate. The patient had experienced this abdominal pain occasionally for nearly 2 years. The patient had no disease or operative history. His white blood cell count was 12500/mm^3. The other laboratory findings were normal. A physical examination of the patient revealed moderate abdominal sensitivity. No defense or rebound was noted. Air-liquid levels were evident during a direct abdominal radiography in the standing position. A computed tomography scan showed adjacently to the duodenal intestinal ansae within a hernia sac, showed a portion of the transverse colon and dilated mesenteric vascular structures (arrows) (Figure 1).

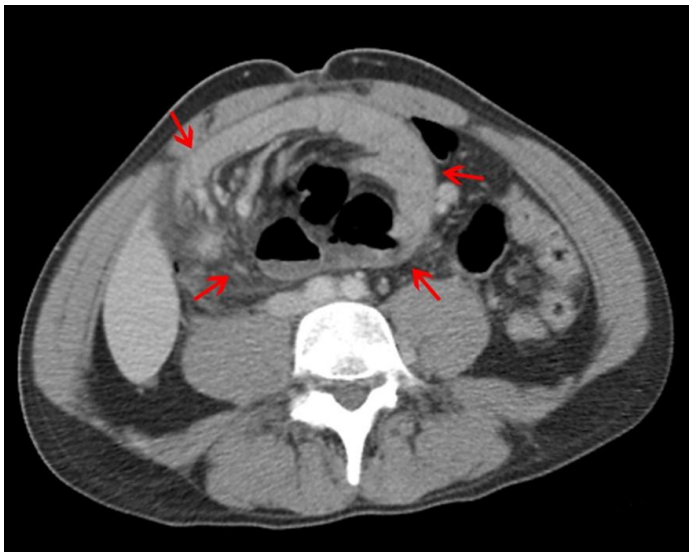

Figure 1: A computed tomography section showed a portion of the transverse colon and dilated mesenteric vascular structures (arrows).

The patient underwent an exploratory operation at about 12 hour post hospitalization. The exploration showed an orifice of approximately 3 cm in the ligament of Treitz and a shifting of almost all the small intestines and a portion of the transverse colon to the paraduodenal surface (Figure 2).

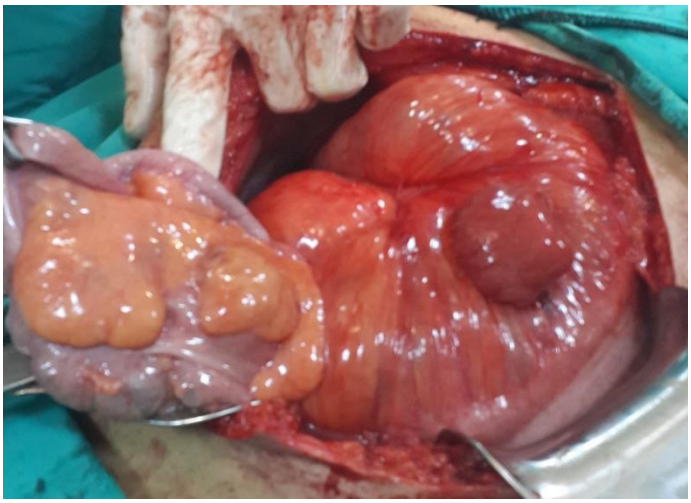

Figure 2: The picture showed beginning of exploration.

The herniated structures were reduced at that point and the defect from the ligament of Treitz was sutured with non-absorbable suture material and closed. A color alteration initially noted in the proximal small intestinal segments became normal within about 15 minutes (Figure 3). The patient was discharged as healthy on the 6th post operative day.

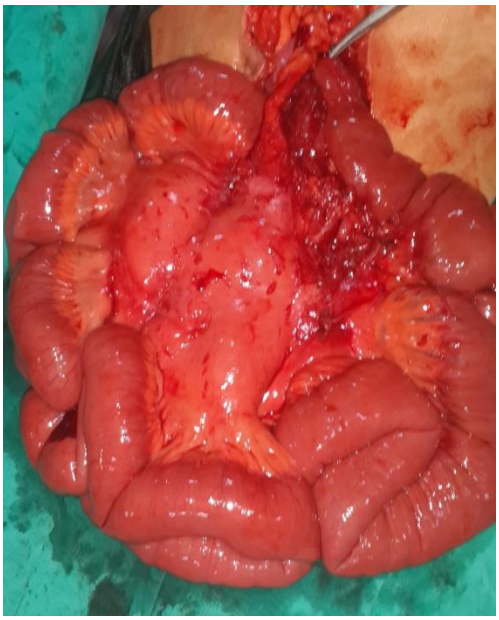

Figure 3: The small intestine after it is taken out from hernia sac.

Discussion

Internal hernias are rare pathologies that account for fewer than 2% of small intestine obstructions [6,7]. The paraduodenal hernias, the most frequent reason for congenital internal hernias, are responsible for approximately 1% of the small intestine obstructions [7]. These paraduodenal hernias are divided into right and left types, according to their intraabdominal location. The left paraduodenal hernia is defined as a herniation of the intestines from the Landzert fossa, which is an orifice found in almost 2% of the population [8].

The clinical symptoms are recurring cramp-like pains, intestinal obstruction due to torsion, sickness, vomiting, and abdominal distension [3,9]. Almost 50% of paraduodenal hernia patients experience intestinal obstruction attacks periodically during their lifetimes. The remaining 50% are asymptomatic and are diagnosed incidentally [9]. Our patient had intestinal obstruction findings and had experienced abdominal pains occasionally for the previous 2 years.

Radiologic viewing methods are necessary for the early diagnostic and planning of the surgical treatment. The intestinal obstruction is diagnosed with direct abdominal radiography with the patient in a standing position. The ultrasonography may show the presence of intraabdominal liquid, internal tubular cysts, or abdominal masses. Celiac and superior mesenteric arteriography may show a shift of the jejunal or splenic arteries to the left [10]. Gastrointestinal graphics with barium may show dilated small intestine loops from the upper abdominal quadrant, obstruction points, or slowing down of the contrast substance flow [8,11]. Computed tomography is very important for the diagnosis of the paraduodenal hernias [3].

Frequently observed radiologic findings of the left paraduodenal hernia include the clustering of the small intestine loops, the ligament of Treitz, a mass in the form of a sac with no capsule, depression of the duodenojejunal junction site, a mass effect on the posterior wall of the stomach, dislocation of the main mesenteric veins, and depression of the transverse colon [6]. The direct abdominal radiography of our patient in a standing position revealed small intestinal type of air-liquid levels. The patient's computed tomography images revealed intestinal ansae in a hernia sac adjacent to the duodenum, a portion of the transverse colon, and dilated

mesenteric vascular structures.The surgical procedure should reduce the herniated intestine segments and the hernia orifice should be closed. Care should be taken to avoid injury to the left colic artery and inferior mesenteric arteries [12]. Left paraduodenal hernias have a 50% risk of lifelong incarceration [3,5,13,14]. The mortality rates associated with paraduodenal hernias are not well established, although rates around 20-50% are reported [14].

Left paraduodenal hernias should be treated surgically as soon as they are diagnosed since they have the risk of intestinal ischemia associated with obstruction and strangulation.

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Dev splenik arter anevrizması: Bir olgu Sunumu

Giant splenic artery aneurysm: A case report

Tolga Canbak , Aylin Acar , Hüseyin Kerem Tolan , Fatih Başak

Öz

Splenik arter anevrizması, nadir görülmektedir. Dev splenik arter anevrizması olan olgu literatürde oldukça az sayıda belirtilmiştir. Bu yazıda, dev splenik arter anevrizması saptanan bir olgunun sunulması amaçlandı.

Altmış yaşında kadın hasta, karın ağrısı şikayeti ile başvurdu. Fizik muayenede, sol subkostal bölgede ele gelen sertlik vardı. Laboratuar inceleme normaldi. Manyetik rezonans görüntülemede, 10 cm çapında splenik arter anevrizması ile uyumlu bir görünüm saptandı. Splenektomi yapıldı. Peroperatif ve postoperatif dönemde kan replasmanı yapılmadı. Postoperatif 2. gün taburcu edildi. Takiplerinde komplikasyon gelişmedi.

Semptomatik ve 2 cm'den daha büyük splenik arter anevrizmaları tedavi edilmelidir.

Anahtar kelimeler: Splenik arter, anevrizma, splenektomi

Abstract

Splenic artery aneurysm is rare. Only a few cases with giant splenic artery aneurysm has been reported in the literature. In this article, we aimed to present a case with giant splenic artery aneurysm.

A 60-year-old female patient presented with a complaint of abdominal pain. On physical examination, there was stiffness on the left subcostal area. Laboratory examinations were normal. Magnetic resonance imaging revealed an appearance in compatible with splenic artery aneurysm with a diameter of 10 cm. Splenectomy was done. Blood replacement was not performed in the peroperative and postoperative period. She was discharged on the second postoperative day. No complication occurred in the patient.

Symptomatic and splenic artery aneurysms over 2 cm should be treated.

Key words: Splenic artery, aneurysm, splenectomy

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Giriş

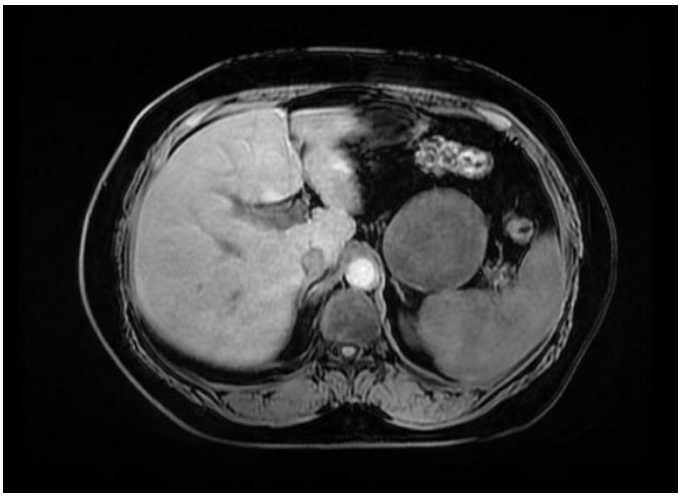
Splenik arter anevrizması nadir görülmektedir. Dev splenik arter anevrizması olan olgu literatürde oldukça az sayıda belirtilmiştir. Asemptomatik olması ve rüptür olasılığı nedeniyle önem arz etmektedir. Yaklaşık % 25 rüptür ve % 8,5'lik bir mortalite ile sonuçlandığı için erken tanı ve tedavi önemlidir [1, 2].

Splenik arter anevrizmaları, tüm visseral anevrizmaların %60'ını oluşturan nadir bir lezyondur ve toplumda ortalama % 0,8 oranında görülmektedir. Genellikle asemptomatiktir ve insidansı kadınlarda erkeklerden dört kat daha fazladır. Çoğu anevrizma, 2 cm'den daha küçük ve sakkülerdir. Sıklıkla dalak arterinin orta kesiminde veya distal segmentinde dallanmanın olduğu lokalizasyonda bulunur [1, 2].

Bu yazıda, dev splenik arter anevrizması saptanan ve splenektomi ile tedavi edilen bir olgunun sunulması amaçlandı.

Olgu sunumu

Hastadan olgu sunumunun hazırlanması ile ilgili yazılı onam alınmıştır. Altmış yaşında bir kadın hasta, karın ağrısı şikayeti ile başvurdu. Fizik muayenede, sol subkostal bölgede ele gelen sertlik vardı. Özgeçmişinde hipertansiyon öyküsü mevcuttu. Laboratuar inceleme normaldi. Ultrasonografide, pankreas ile dalak arasında 9 cm'lik düzgün sınırlı kistik bir lezyon saptandı. Manyetik rezonans görüntülemede, 10 cm çapında splenik arter anevrizması ile uyumlu bir görünüm saptandı (Resim). İki cm'den büyük olması ve rüptür riski taşıması nedeniyle cerrahi tedavi planlandı. Eksplorasyonda, splenik arter distalinde 10 cm'lik bir anevrizma saptandı. Splenik arter anevrizma proksimalinden klipslendi, anevrizma disseksiyonlarla pankreas kuyruğundan ayrıldı. Splenektomi yapıldı. Peroperatif ve postoperatif dönemde kan replasmanı yapılmadı. Postoperatif 2. gün taburcu edildi. Takiplerinde komplikasyon gelişmedi.



Resim: Manyetik rezonans görüntülemede dalak komşuluğunda splenik arterde dev anevrizmatik dilatasyon.

Tartışma

Splenik arter anevrizmaları, arteriyel visseral anevrizmaların en sık görülen tipidir ve tüm vakaların% 60'ını oluşturmaktadır. Kadınlarda 4 kat daha fazla oranda görülmektedir. Sunulan olgu literatür bilgisi ile uyumlu olarak kadın idi. Etiyoloji kesin olarak bilinmemekle birlikte, en yaygın patolojik bulgu tunika mediada elastik lif ve düz kas kaybı kusurudur [3]. Splenik arterde artmış kan akımı anevrizma gelişimi ile ilgili bir faktör gibi görünmektedir; bu nedenle bu anevrizmalar fibromüsküler displazi, portal hipertansiyon, enfeksiyon, konjenital anomaliler, karaciğer nakilli ve pankreas maligniteli hastalarda daha sık görülmektedir [2]. Kadınlarda, özellikle multiparlarda prevalansı daha yüksek olup, gebelikte tipik olan hormonal ve hemodinamik değişikliklerle arter duvarında oluşan intimal hiperplazi, anevrizma gelişimini kolaylaştırmaktadır. Başka bir hasta sınıfı, poliarteritis nodoza, bakteriyel endokardit veya pankreatit atağı gibi arteryel duvarın enflamatuar değişikliklerinin olduğu durumlardır [2]. Sunulan olgumuzda, hastanın özgeçmişinde hipertansiyon dışında bir özellik yoktu.

Splenik arter anevrizmaları genellikle asemptomatiktir ancak nadiren, hastalar rüptür sonucu periton boşluğuna, gastrointestinal kanala veya pankreatik kanala kanamaya neden olan yüksek hacimli kanamalar ile başvurabilir. Çoğu olguda klinik bulguların ve belirtilerin bulunmaması tanıyı zorlaştırır ve genellikle rutin testler sırasında rastlantısal olarak saptanır [3]. Sunulan olgumuzda rastlantısal olarak görüntüleme yöntemleri ile saptanmıştır.

Sol üst kadran ve sırtta epigastrik ağrı, doğurgan yaştaki kadınlar, eşlik eden portal hipertansiyon varlığı, karaciğer transplantasyonu, herhangi bir boyuttaki psödoanevrizmalar ve anevrizmanın 2 cm'den büyük olması tedavi endikasyonları olarak kabul edilmektedir.

Rüptür gelişme riski en fazla 2 cm'den büyük, semptomatik, daha önce transplantasyon gerçekleştirilen, enflamatuar süreçlerle ilişkili splenik arter anecrizması gelişen, doğurgan yaştaki ve hamile kadınlarda olmaktadır [2-4].

Tedavi seçenekleri, açık veya laparoskopik vasküler ligasyon veya dalak ile anevrizmanın yakın ilişki gösterdiği olgularda splenektomidir [5-7]. Arter embolizasyonu gibi endovasküler işlemler veya stent yerleşimi de kullanılmaktadır. Bu yaklaşımlar cerrahi riskleri en aza indirmekte ve hastanın hastanede kalış süresini kısaltmaktadır.

Sonuç olarak semptomatik ve 2 cm üzerindeki splenik arter anevrizmalarının cerrahi olarak tedavi edilmesi, ilerde gelişmesi muhtemel komplikasyonların önlenmesi açısından yararlı olabilir.

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MRI and Anesthesia & Sedation

MRG ve Anestezi & Sedasyon

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Key words: MRI, anesthesia, sedation
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In 1945, Broch & Purcell described the term "Nuclear Magnetic Resonance" [1]. It has been used for chemical and biochemical analyses for the long years. It was widely used in medical applications after Lauterburg's study in 1973 [2].

The primary screening method for the breast cancer is mammography as known. It is the only method that positively affects survival. But its sensitivity and specificity is not absolute and it can be an inadequate method especially at some ages. Studies showed that magnetic resonance imaging (MRI) as a complimentary test to mammography increases success rates, but increased false positivity rates can cause some unnecessary invasive procedures. However, breast MRI is widely used for screening, diagnosis and staging [3].

More than 80 million MRI is worldwide applied yearly. Claustrophobia rates are between 1-15% and more than 2 million breast MRI application is interrupted for the necessitation of sedation [4]. Melendez et al. [5] noticed that the rate around 30%. Also 3-5% of these cases were interrupted due to the sedation necessitation. Anxiety and claustrophobia can cause sequence repeating, procedure cancellation and important time and labor loss.

Besides sedation and anesthesia, some methods such as information/education, different patient positions, manipulation of the environment, lighting levels, installation of panic buttons, music, open MRI design, psychological preparation and hypnosis have been used to decrease anxiety and claustrophobia. But, these methods do not have absolute success to resolve for reduction of anxiety and distress [6].

Most of anxious and claustrophobic patients necessitate sedation or anesthesia. These problems can be totally solved by these procedures. However, these procedures have some limitations and need some arrangements. Sedation and anesthesia must be performed by an anesthesiologist; also both procedures necessitate some equipment and additional room for patient-doctor communication, preparation and recovery of the patients.

Some national and international institutions have prepared detailed guidelines for non-operating room anesthesia practice [7]. Non-operating room anesthesia practice are risky than the operating room practice. The cause of this risk is the lack of some facilities that are present in the operating rooms. Data obtained from the American Society of Anesthesiologists Closed Claims database showed that unfavorable events at non-operating room practice are resulted in worse outcomes [8].

Patients' evaluation and preparation at non-operating room procedures should be the same with the operating room practice. Equipment about monitoring and airway management should be complete, and devices for difficult airway management and defibrillator should be attended. Ferromagnetic tools and equipment should not be in the MRI unit, so the monitors and other equipments should be MRI compatible.

The narrow bore shape of MRI can cause some problems at the patients' management. Patients routinely lie down at the prone position at breast MRI scanning, therefore airway management may be much more difficult. Due to this situation, preoperative airway management decision should be done more detailed.

Follow up at the recovery room should be done as carefully as in the operating room.

These equipments, preparation, requirements for staff and extra room can be thought as extra cost and time. But, anesthesia should be in the same quality as in the operating room or out of the operating room. By the way, we can minimize the risk for the patients.

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