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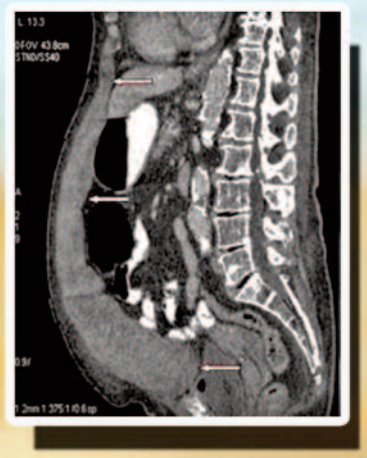

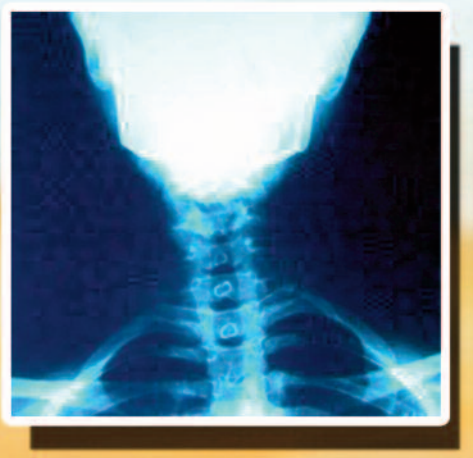

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Table of Contents

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Review

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Early graft failure after coronary artery bypass grafting: diagnosis and treatment

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ABSTRACT

Early postoperative graft failure after coronary artery bypass grafting (CABG) is still a significant problem that results in high morbidity and mortality. Different therapeutic options are available to manage this complication which include reoperation, balloon angioplasty, angioplasty along with stenting and conservative medical management. Herein, we review the existing literature in diagnosis and treatment options for overcoming early graft failure immediately following CABG.

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Keywords: Coronary artery bypass grafting; graft failure; percutaneous coronary intervention

Introduction

The success of coronary artery bypass grafting (CABG) depends on constructing quality anastomoses with durable conduits on to appropriate target coronary arteries. Despite its highly favorable outcomes, a significant number of patients suffer early graft failure after CABG. Several angiographic studies have demonstrated that up to 15% of saphenous vein grafts and 8% of left internal thoracic artery grafts are occluded in the very early postoperative period of CABG [1-6]. If identified, this problem may be repaired shortly after or at the time of the operation because it is thought to be mainly a result of a surgical or technical problem. Besides poor graft patency has been clearly correlated with markedly increased 30-day and late mortality [4].

Patency rates after CABG

The gold standard for detecting the patency of the bypass grafts is coronary angiography. Regarding the type of bypass grafts, the left internal thoracic artery grafts achieve improved long term patency when compared with the saphenous vein grafts that have a 10-12% incidence of failure within the early postoperative period after CABG [1, 6]. There are several studies in the literature that demonstrated up to 12 % early graft failure especially in the saphenous vein grafts by using coronary angiography. Fittzgibbon *et al.* [1] showed 565 (12%) occlusions in 4592 vein grafts and 25 (5%) occlusions in 456 arterial grafts in the early postoperative period.

Wiklund *et al.* [7] performed coronary angiography in the first five days of the postoperative

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period in eighty-four consecutive patients undergoing CABG without the use of cardiopulmonary bypass. The mean number of grafts (n=113 grafts) was 1.4±0.1. One hundred and two arterial grafts and 11 saphenous vein grafts were used in their study and they showed occlusion of the internal thoracic artery in four patients and occlusion of a vein graft to the right coronary artery in one patient. These results meant a 96% overall graft patency. In their recent study Kim *et al.* [5] performed early postoperative angiography to assess anastomosis accuracy and patency after off-pump coronary artery bypass grafting in 1345 patients between 1998 and 2007. Of the 1345 patients, 1278 patients (95.0%) underwent early postoperative angiography on postoperative 1.6±1.2 days. A total of 3857 distal anastomoses were evaluated and they found arterial graft patency as 98.9%, and saphenous vein graft patency as 88.2%. Similar to aforementioned studies Jokinen *et al.* [8] found a 5% failure in the left internal thoracic artery and 17% failure (26/149) in the saphenous veins.

Detection of graft failure

Graft failure during or following CABG results in acute myocardial ischemia/infarction which is an important clinical problem because it is closely associated with increased morbidity and mortality. The development of myocardial infarction is often preceded by a period of myocardial ischemia. Therefore early detection of perioperative myocardial ischemia and an emergent secondary revascularization procedure may relieve the ischemia and decrease the incidence and the size of myocardial injury that will preserve ventricular function and improve the patients' outcome.

The pathogenesis of myocardial cell damage during the postoperative course of CABG has been the subject of intensive clinical research and it is shown by several studies that ischemia appearing shortly after CABG could either be graft-related or non-graft related [1, 9, 10]. The most common graft-related reasons for peroperative myocardial infarction are graft occlusion due to acute graft thrombosis, kinking or overstretching of the graft, subtotal anastomotic stenosis, injury of the graft during harvesting and graft spasm [4, 11]. Non-graft-related peroperative myocardial infarction might be induced by different mechanisms during surgery, including inadequate cardioplegic perfusion and myocardial protection, incomplete revascularization, and distal coronary microembolization due to surgical manipulation [6, 12]. These graft-related or non-graft-related etiologies induce myocardial hypo or malperfusion with regional myocardial dysfunction, leading to myocardial cell damage extending from the subendocardium to the subepicardium in a time-dependent fashion which may all lead to myocardial necrosis with elevations of cardiac biomarkers and enzymes.

In the early postoperative period, patients are usually monitored with frequent biochemical analysis and routine ECG recordings. Myocardial infarction diagnosed by these two methods is associated with adverse outcome. Several studies have been reported the issue of diagnosing myocardial infarction by serial blood sampling for determination of CK-MB troponin I, and troponin T, and various cut-off limits have been suggested [9, 10, 12, 13]. The diagnostic performance of these markers in the nonsurgical setting is very well described in numerous studies [14]. Holmvang *et al.* [12] reported their study in 103 patients with a conclusion that serial postoperative biochemical data, preferably CK-MB mass and troponin T can identify a subgroup of patients with a high rate (20 to 27%) of early graft occlusion. However, diagnosis of peroperative myocardial infarction is associated with several problems. Due to the surgical trauma and cardiopulmonary bypass, the usual non-invasive indicators of myocardial infarction such as pain, ECG changes, and elevated biochemical markers have less diagnostic value than in nonsurgical patients [11, 12]. Transesophageal echocardiography will be able to identify an area with reduced contractility, but will be unable to provide the detailed information about the underlying cause.

Recently observations with cardiac troponin I showed promising results in detecting peroperative myocardial infarction. Thielman *et al.* [10] in their prospective study, performed acute re-angiography in 94 of 3308 consecutive CABG patients because of evidence of peroperative myocardial infarction and found that perioperative cardiac troponin I elevation after CABG was significantly higher in patients with graft-related peroperative myocardial infarction than in patients with non-graft- related myocardial infarction. This finding might be due to the fact that the size of myocardial infarction induced by graft failure was potentially greater than myocardial infarction induced by non-graft-related mechanisms.

The major limitation of this was that cardiac troponin I reach to a prognostic value at least 12 to 24 hours after the surgical procedure which leads to a delay in reintervention time. But the possible benefit of re revascularization for preserving the ventricular function is time dependent.

This brought out an interest for detecting the early graft failure intraoperatively which led to the use of new tools for intraoperative patency assessment which were described in literature. Indocyanine green fluoroscopy and transit-time ultrasound flowmetry are validated and easy to use means of identifying graft errors and surgical correction intraoperatively [8, 15-19]. However, they pose potential risks to the patient by prolonging cross-clamp and cardiopulmonary bypass times, and they may theoretically could lead to poorer anastomosis quality and patency by inappropriate revision.

Early graft occlusion is frequently responsible for peroperative myocardial infarction when it is manifested by acute ST-segment changes, rise in cardiac biomarkers (especially cardiac troponin I), hemodynamic instability, or sustained ventricular arrhythmia. Most of the cardiac surgeons experience addressing this problem was that occlusion of a graft was a constant finding in patients that suffers circulatory collapse early after CABG and survival after immediate re-operation is possible. This may lead one to the hypothesis, that if early graft failure and/or incomplete revascularization are the most common causes of myocardial ischaemia early after CABG, this should be diagnosed by angiography and treated by a re-intervention either re-CABG or PCI [11, 20, 21].

Rasmussen *et al.* [11] reported their study including 71 patients among 2003 isolated CABGs that underwent acute re-angiography or immediate reoperation (Table 1). In this study, their objective was to study causes of perioperative ischaemia and infarction by acute re-angiography and to treat incomplete revascularization caused by graft failure or any other cause. Of the 71 patients 59 underwent acute re-angiography and 12 underwent reoperation due to circulatory collapse. In the acute re-angiography group graft failure/incomplete revascularization was demonstrated in 43 patients (73%). Their angiographic findings were: occluded vein graft in 19 (32%); poor distal run-off to the grafted coronary artery in 10 (17%); internal thoracic artery stenoses in 4 (7%); internal thoracic artery occlusion in 3 (5%); vein graft stenoses in 3 (5%); left internal thoracic artery to subclavian artery steal in 2 (3%); and the wrong coronary artery grafted in 1 (2%). According to these findings, 27 patients were re-operated and re-grafted with a 30-day mortality of 3 (7%) patients. In the immediate reoperation group, graft occlusions were found in 11 patients (92%) and

Table 1. Angiographically controlled study results from literature

Authors	Patients with graft failure	Angiographically evaluated graft failure	Treatment (number of patients)	Effected Graft
Thielman *et al.* [6]	67	84 failure -70 occlusion -5 kinking graft -9 stenosis)	PCI (25) Re-operation (15) Medical (27)	LITA=35 RITA=1 SVG=48
Price *et al.* [24]	14	9 failure -2 occlusion -6 stenosis -1 poor runoff	PCI (10) Medical (4)	LITA=2 SVG=6
Rasmussen *et al.* [11]	55	41 failure -22 occlusion -6 stenosis -10 poor runoff -2 subclavian steal -1 wrong coronary	Reoperation(27) Emergent op (12) Medical (16)	LITA=7 SVG=22
Fabricius *et al.* [4]	86	70 failure -41 occlusion -29 stenosis	PCI (9) Reoperation (34) Emergent surgery (23) Medical (20)	Not available

PCI=percutaneous coronary intervention, LITA=left internal thoracic artery, RITA=right internal thoracic artery; SVG=saphenous vein graft

the 30-day mortality was 6 (50%) patients. As a conclusion they recommended that acute re-angiography demonstrates graft failure or incomplete revascularization in the majority of patients with myocardial ischemia early after CABG and reoperation for re-revascularization can be performed with low risk besides a few patients with circulatory collapse can be saved by an immediate reoperation without preceding angiography.

In another study Fabricius *et al.* [4] studied 131 (6.4%) patients among 2052 isolated CABGs those met the criteria of perioperative myocardial ischemia/infarction, which was defined as: increase in the isoenzyme ratio of CK/CK-MB above 10%; ischemic electrocardiographic findings (defined as a new onset of elevated ST-segment change lasting at least 1 min and involving a shift from baseline of greater than or equal to 0.1 mV of ST-depression and a new association of a postoperative Q wave; recurrent episodes of sustained ventricular tachyarrhythmia as well as ventricular fibrillation; hemodynamic deterioration despite adequate inotropic support). Angiography was performed in 108 (5.3%) of 131 patients whereas other 23 patients (1.1%) were immediately re-operated due to severely compromised hemodynamics. Results of the angiographic group showed regular grafts in 45 patients; in 63 patients there were 41 occluded grafts, 29 incorrect anastomoses, 14 graft stenosis, 6 graft spasm, 6 displaced grafts, 5 poor distal run-off and 2 incomplete revascularizations. Of these 45 patients, 43 underwent a re-operation (34 patients) or an early angioplasty (9 patients). Due to poor coronary artery status no intervention was performed in the remaining 20 patients with angiographic findings (Table 1).

Operative findings in immediately operated 23 patients showed graft occlusion in 10 patients (43.5%), incorrect anastomoses in 5 patients (21.7%), bleeding, stretched graft, venous graft spasm and displaced graft in one patient (4.3%) each, and no patho-morphological finding in 4 patients (17.4%). Thirty-day mortality rate was 10 patients (9.3%) with angiographic findings opposed to 9 patients (39.1%) in immediately operated group without performing angiography. They also concluded that the combination of ST segment change and CK/CK-MB ratio is effective in detecting graft failure and acute re-angiography should be performed in stable patients with the event of perioperative ischemia after CABG which allows safe and precise diagnosis and enables early re-intervention.

In their recent study, Thielman *et al.* [6] tried to identify the source of peroperative myocardial infarction and to pursue the appropriate re-revascularization strategy, coronary re-angiography was performed in 118 among 5427 consecutive isolated CABG patients with evidence of peroperative myocardial infarction. As a result, patients immediately underwent acute PCI, emergency reoperation, or were treated conservatively. Re-angiography revealed early graft failure in 67 of 118 patients and 84 of 214 bypass grafts after CABG (see Table 1). Acute PCI was applied in 25 patients, redo-CABG in 15 patients, and conservative treatment in 27 patients. Global left ventricular ejection fraction was reduced during the acute ischemic event when compared with preoperative values ($p<0.01$). Left ventricular ejection fraction improved during follow-up within each group ($p<0.001$), but did not differ between the three groups. In-hospital and 1-year mortality rates were 12.0% and 20.0% in PCI group, 20.0% and 27% in reoperation group, and 14.8% and 18.5% in the conservatively treated group, respectively (p=NS). In this prospectively designed but not a randomized trial to compare the three treatment groups, they concluded that emergency re-revascularization with PCI may limit the extent of myocardial cellular damage when compared with the surgical-based treatment strategy in patients with acute perioperative myocardial ischemia due to early graft failure following CABG because it seems be quicker and less invasive.

Hanratty *et al.* [22] reported their experience with 5 patients those underwent PCI to the distal anastomosis early after CABG. In all of the patients PCI was preferred over reoperation because the vessel was initially difficult to graft or because of excessive risks of reoperation due to co-morbidity. There was no mortality and no procedural complication. In a similar study, Laflamme *et al.* [23] reported 32 patients suffering from early postoperative graft failure. Fifteen of the patients were treated with PCI, four of the patients underwent reoperation and thirteen of the patients were treated conservatively. The authors concluded that acute reintervention either PCI or reoperation was superior to conservative management in terms of myocardial cellular damage.

Price *et al.* [24] reported their recent study in which they examined the angiographic and clinical outcomes of ten patients who underwent percutaneous

coronary intervention for myocardial infarction or ischemia soon after CABG. In this study, they analyzed 14 (4.3%) of 321 patients in a two years period whom underwent unplanned cardiac catheterization after the procedure was analyzed of these four patients were treated medically (3 without a culprit lesion and 1 with an atretic free right internal mammary artery graft that led to an obtuse marginal that was believed to be suitable to PCI). The remaining 10 patients underwent emergency PCI and 6 received drug-eluting stents. The etiology of myocardial ischemia/infarction was venous graft occlusion in 2 patients, venous graft stenosis in 4 patients, left internal mammary artery stenosis in 2 patients, incomplete revascularization in 2 patients, and poor distal run-off in one patient (1 patient had a venous graft stenosis and occlusion). Mortality rate was 20% with 2 patients, major bleeding occurred in 40 % (4 patients; one patient with sirolimus-eluting stent, one patient with a heparin-coated stent, and 2 patients with standalone balloon angioplasty). The site of bleeding was cardiac tamponade within 24 hours after PCI in 2 patients, gastrointestinal in one patient, and significant chest tube drainage in one patient. As a major finding they stated that rescue PCI for perioperative myocardial ischemia is feasible, but that angiographic complications are not uncommon and postprocedural bleeding is frequent, especially in patients who undergo intervention acutely after CABG and added that their findings support the contention that PCI of freshly sutured anastomosis may pose a significant risk of graft/native coronary rupture ,especially if high-pressure stent deployment is involved which means that the use of drug-eluting stents in this patient group should be carefully considered.

Treatment options

In the light of the whole aforementioned studies postoperative myocardial ischemia following CABG adversely affects both short- and long-term prognosis. Early graft failure is the major cause of ischemia or

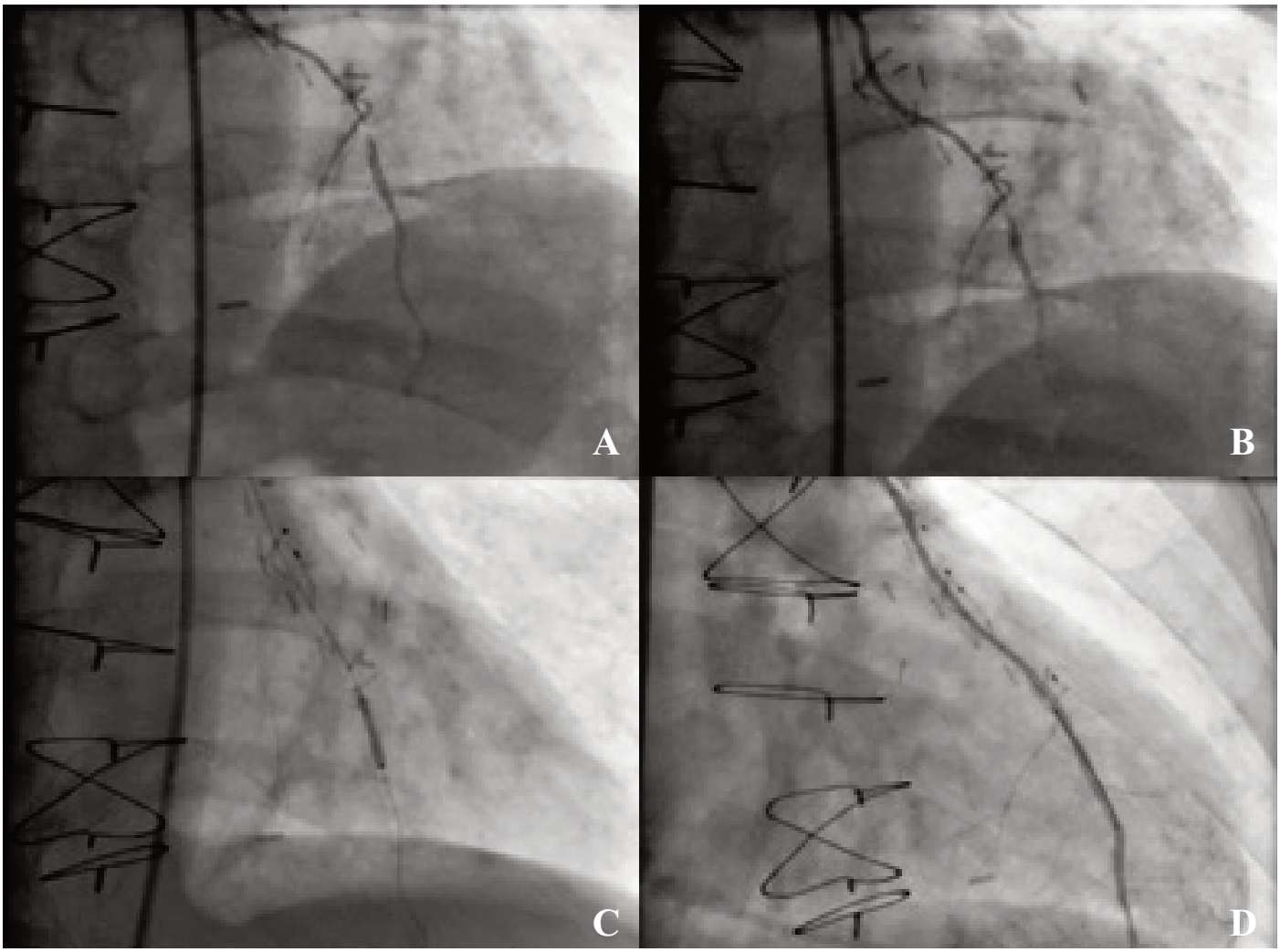

Figure 1. PCI for LITA graft stenosis on the 4th postoperative day (A and B: before intervention; C and D: during and after PCI)

peroperative myocardial infarction after CABG. The most common reasons for early graft failure are likely to be due to technical problems, and the handling of the grafts. Diagnostic criteria of myocardial infarction early after CABG is less specific and more difficult to interpret than in the non-operative setting, acute graft failure is usually suggested by new ST-segment elevation, acute heart failure, hemodynamic instability, and life-threatening ventricular arrhythmias. Although cardiac specific markers such as cardiac troponin I have promising results to discriminate graft related and non-graft-related myocardial injury 12 or 24 hours detection time seems to be too long for emergent myocardial muscle salvage. Therefore prospective randomized trials with new biomarkers for myocardial ischemia such as heart type fatty acid binding proteins or ischemia modified albumin which have recently been reported to detect myocardial ischemia within the first 30 min, may enable early reintervention to restore myocardial perfusion [25-28].

If hemodynamic status permits an emergent re-angiography is safe and valuable to determine the cause of early postoperative myocardial ischemia and helps to define the optimal treatment strategy [4, 11]. Surprisingly, it is observed in some studies that 25% to 34% of patients undergoing coronary re-angiography for suspected early graft failure after CABG have patent grafts [4, 11, 18].This important finding suggests that early graft failure should be confirmed with re-angiography (if the hemodynamic status enables) instead of carrying out a blind reoperation.

The therapeutic strategies to treat patients with acute severe ischemia after CABG are conservative medical management with the help of the intra-aortic balloon pumping, direct reoperation, balloon angioplasty and stenting.

Rescue postoperative balloon coronary angioplasty for failed CABG is being performed for over 20 years but few cases have been published which demonstrates that the procedure can be performed safely and effectively [4, 11, 21-24] (Figures 1 and 2). As another option, intracoronary thrombolytic therapy has also been used in the

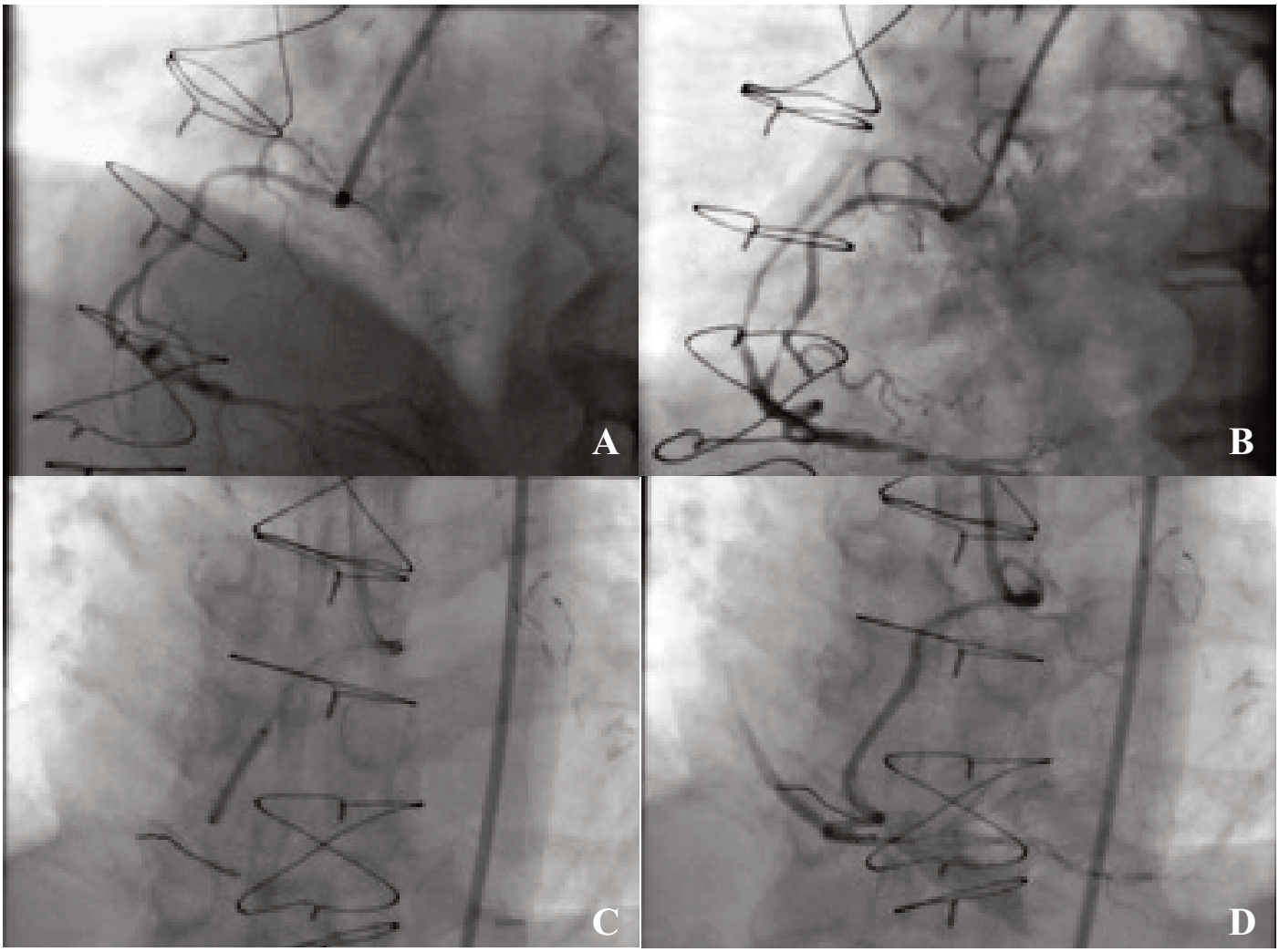

Figure 2. PCI for native right coronary artery due to saphenous vein graft failure on the 4th postoperative day (A and B: before intervention; C and D: during and after PCI)

treatment of graft closure immediately after CABG, but due to the inherent risk of hemorrhage, this has not been widely adopted in the early postoperative period [28].

Both PCI and reoperation are beneficial treatment options for early graft failure. With immediate PCI relief of ischemia is more rapid, potentially salvaging more myocardium. Repeat cardiopulmonary bypass may create additional reversible left ventricular dysfunction, and possibly elevates the risk of perioperative stroke and renal failure. On the other hand, the anticoagulation used for PCI may promote bleeding from surgical wounds, especially if glycoprotein IIb/IIIa inhibitors are used [22]. PCI also has a higher need for repeat target lesion revascularization.

Conservative medical management is the other treatment option in patients with severe ischemia after CABG. It may be considered in patients with advanced age, severe coronary artery disease, or coexisting medical problems that prevents the use of a more invasive approach. The decision of which strategy to choose should be made on an individual basis, taking the specific circumstances of each patient into account. The choice of best treatment strategy depends on individual patient characteristics.

Conclusions

To date, the best strategy for the treatment of acute graft failure after CABG is still unclear and remains controversial. Probably the majority of the cardiac surgery centers prefer to treat those patients conservatively. On the other hand the number of publications and surgeons preferring reintervention in this clinical setting are increasing. As a result in this new era emergent reintervention for the relief of postoperative ischemic complications after CABG with either catheter-based or surgical-based treatment strategies should require an integrated approach with the involvement of the cardiac intensive care physician, the interventional cardiologist, and the cardiac surgeon. This collaboration may improve the patients' outcome and lead to a new paradigm in which the cardiac cath-lab or a hybrid operating room is routinely available to help the surgeon when early postoperative ischemia is identified. Therefore, further multi-institutional randomized clinical studies are needed to clarify the appropriate treatment strategy in these patients.

Conflict of interest

The author disclosed no conflict of interest during the preparation or publication of this manuscript.

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Should endoscopy be routinely performed for bariatric surgery candidates?

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ABSTRACT

Objectives. The rationale for a routine endoscopy before bariatric surgery in asymptomatic patients remains controversial. The purpose of the present study was to compare, in a retrospective manner, the endoscopic findings of morbidly obese patients awaiting surgery with those of non-obese individuals. Methods. Between January 2014 and December 2014, preoperative endoscopic findings of 161 morbidly obese patients and 101 consecutive non-obese individuals were evaluated. ***Results.*** No significant differences were found between the two groups in terms of ulcer prevalence and the number of ulcers (p=0.120 and p=0.122, respectively). However, the frequency of bulbar ulcers was significantly higher in morbidly obese patients than in the non-obese (p=0.012). Furthermore, the ulcer activity score was significantly higher in morbidly obese patients (p=0.025). 84 patients underwent laparoscopic sleeve gastrectomy (LSG). Of those, 48 patients (57.1%) had *Helicobacter pylori* sero-positivity and 12 patients (14.3%) had peptic ulcer disease before surgery. *H. pylori* sero-positivity persisted in the resected gastric specimens of 33 patients (39.3%). ***Conclusion.*** The ulcer activation score in morbidly obese patients is higher -even when they are asymptomatic- than in non-obese individuals. Routine preoperative endoscopy should be considered in all bariatric surgery candidates to rule out pathologies such as hiatal hernia, extensive ulcers or malignant lesions which are the contraindications for a LSG.

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Keywords: Morbidly obesity; laparoscopic sleeve gastrectomy; *Helicobacter pylori*; peptic ulcer

Introduction

Obesity is an increasingly serious health problem in both developed and developing countries. Bariatric surgery has proven to be the most effective treatment for morbid obesity. Published guidelines from the European Association for Endoscopic Surgery (EAES) in 2005 and the American Society of Gastroenterology (ASGE) in 2008 recommended that upper gastrointestinal endoscopy should be performed in all symptomatic patients undergoing bariatric surgery, and considered in all candidates [1, 2]. However, the

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rationale for using routine endoscopy in asymptomatic patients before bariatric surgery remains contentious [3-10]. Several authors have now documented the lack of correlation between patient symptoms and endoscopic findings and have suggested that routine preoperative endoscopy might in fact be useful in detecting both lesions and inflammation [11, 12]. Besides, there is no long-term data available after sleeve gastrectomy, reflux esophagitis and/or hiatal hernia may contraindicate this operation, especially since the absence of preoperative symptoms cannot be relied upon.

The purpose of the present study was to compare endoscopic findings of morbidly obese patients awaiting surgery with non-obese individuals.

Methods

Between January 2014 and December 2014, upper endoscopy was performed in 101 consecutive non-obese patients (control group) and 161 morbidly obese patients (morbid obesity group) who were referred for endoscopy prior to bariatric surgery. Endoscopic findings and histopathological signs were analyzed retrospectively after approval from the local Ethical Committee of Bursa Yuksek Ihtisas Training and Research Hospital. All endoscopic procedures were performed by the same gastroenterologist and four-quadrant biopsies were taken from the gastric antrum. Additional biopsies were also taken in areas of mucosal surface irregularity. Routine screening for *Helicobacter pylori* positivity was carried out both in preoperative endoscopies and on the resected gastric specimens. The only patients placed on *H. pylori* eradication therapy were those displaying peptic ulcer disease during preoperative endoscopy: asymptomatic patients or patients with no endoscopic evidence of ulcers were not given the medication consisting of clarithromycin + amoxicillin+ proton pump inhibitor, regardless of their *H. pylori* positivity. Histopathological evaluation of the biopsy specimens was carried out by a single pathologist and according to the Sydney classification schema.

In the morbidly obese group, patients with a body mass index (BMI) ≥40mg/m^2 as well as patients with BMI ≥35kg/m^2 but with additional co-morbidities (diabetes mellitus, hypertension, chronic obstructive respiratory disease, etc.) were included in the study. A hiatal hernia was defined endoscopically as more than 2 cm separation of the upwardly displaced esophagogastric junction and the diaphragmatic impression.

Statistical Analysis

Data analysis was performed using SPSS for Windows, version 11.5 (SPSS Inc., Chicago, IL, United States). Data was shown as mean±standard deviation (SD) or median (min-max), where applicable. Mann Whitney U test was used to determine any statistical significance between groups for age, *H. pylori*, inflammation, activity and metaplasia scores. Nominal data was analyzed by Pearson's chi-square, Fisher's exact or Likelihood Ratio test, where appropriate. *p* value less than 0.05 was considered as statistically significant.

Results

Eighty-four morbidly obese patients had undergone LSG and 77 patients were on the waiting list for bariatric surgery. None of them had obvious symptomatic dyspeptic complaints, but all were scheduled for a routine endoscopy prior to the surgical intervention. The median age in non-obese patients (the control group) was 34 years (min-max: 22-52)

Table 1. Patients' demographic data and characteristics

Variables	Control Group (n=101)	Morbid Obesity Group (n=161)	*p* Value
Age (year, range)	34 (22-52)	36 (21-66)	0.063†
Gender			**<0.001‡**
Male	43 (42.6%)	24 (14.9%)	
Female	58 (57.4%)	137 (85.1%)	
LES			0.990‡
Normal tension	84 (83.2%)	134 (83.2%)	
Sphincter weakness or dysfunction	17 (16.8%)	27 (16.8%)	

† Mann Whitney U test, ‡ Pearson's Chi-square Test, LES= Lesser esophageal sphincter

and in the morbid obesity group 36 years (min-max: 21-66), the difference was not significant (p=0.063). The mean BMI in the morbid obesity group was 46.9±5.4 kg/m^2. The female/male ratio was significantly higher in the morbid obesity group when compared to the control group (p<0.001). There was no significant difference between the two groups according to the status of the lower esophageal sphincter (LES) with regard to normal range or weaker pressure (p=0.990) (Table 1).

Although no significant differences were found between the two groups in terms of ulcer prevalence or the number of ulcers (p=0.120, p=0.122), the localization of ulcers were significantly different between the two groups (p=0.008) and the frequency of bulbar ulcers was significantly higher in the morbid obesity group when compared to the control group (p=0.012). The frequency of bulbitis or alkaline reflux gastritis did not significantly differ between the two groups (p=0.547, p=0.377). On the other hand, the frequency of esophagitis was significantly lower in the morbid obesity group when compared to the control group (p=0.021) (Table 2).

The prevalence of additional pathologies and the frequency of hiatal hernia were significantly higher in the control group (p=0.004, p=0.049) (Table 3).

The distribution of *H. pylori* grading and the severity of inflammation revealed no significant difference between the two groups (p=0.171, p=0.581). However, the ulcer activity scores were found to be significantly higher in the morbid obesity group (p=0.025). The incidence of gastric atrophy was also higher in the morbid obesity group, but the difference was not statistically significant (p=0.212). No significant difference was found between the two groups according to the distribution of metaplasia or the severity and incidence of dysplasia (p=0.238, p=1.000) (Table 4).

Table 2. The distribution of endoscopic findings according to the groups.

Variables	Control Group (n=101)	Morbid Obesity Group (n=161)	*p* Value
Existence of ulcer			0.120†
No	91 (90.1%)	134 (83.2%)	
Yes	10 (9.9%)	27 (16.8%)	
Number of ulcers			0.122†
Solitary	6 (5.9%)	9 (5.6%)	
Multiple	4 (4.0%)	18 (11.2%)	
Localization of ulcer			**0.008**‡
Pre-pyloric	7 (6.9%)	5 (3.1%)	
Bulbus	3 (3.0%) [a]	19 (11.8%) [a]	
Pre-pyloric + bulbus	-	3 (1.9%)	
Existence of bulber patology			0.547‡
Bulbitis	1 (1.0%)	4 (2.5%)	
Ulcer	7 (6.9%)	8 (5.0%)	
Existence of alkaline reflux	3 (3.0%)	2 (1.2%)	0.377¶
Existence of esophagitis	4 (4.0%)	-	**0,021**¶

† Pearson's Chi-square Test, , ‡Probability Ratio Test, ¶ Fisher's exact Test,
a: The difference between the control group and the surgery group is statistically significant (p=0,012).

Table 3. The distribution of additional pathological findings according to the groups

Variables	Control Group (n=101)	Morbid Obesity Group (n=161)	*p* Value
Existence additional pathology			**0.004**†
No	90 (89.1%)	157 (97.5%)	
Yes	11 (10.9%)	4 (2.5%)	
Additional pathologies			
Antral polyp	2 (2.0%)	-	0.148‡
Barret esophagus	1 (1.0%)	-	0.385‡
Diverticula in bulbus	1 (1.0%)	-	0.385‡
Hiatal hernia	7 (6.9%)	3 (1.9%)	**0.049**‡
Diverticula in esophago-cardiac junction	-	1 (0.6%)	1.000‡

†Pearson's Chi-square Test, ‡Fisher's exact Test

Table 4. The distribution of other clinical signs according to the groups

Variables	Control Group (n=101)	Morbid Obesity Group (n=161)	*p* Value
H. pylori			0.171†
None	26 (25.7%)	58 (36.0%)	
1+	44 (43.6%)	61 (37.9%)	
2+	21 (20.8%)	23 (14.3%)	
3+	10 (9.9%)	19 (11.8%)	
Inflammation			0.581†
None	-	1 (0.6%)	
1+	57 (56.4%)	90 (55.9%)	
2+	42 (41.6%)	52 (32.3%)	
3+	2 (2.0%)	18 (11.2%)	
Ulcer Activity			**0.025**†
None	34 (33.7%)	38 (23.6%)	
1+	44 (43.6%)	76 (47.2%)	
2+	23 (22.8%)	23 (14.3%)	
3+	-	22 (13.7%)	
4+	-	2 (1.2%)	
Existence of atrophy	2 (2.0%)	9 (5.6%)	0.212‡
Metaplasia			0.238†
None	93 (92.1%)	154 (95.7%)	
1+	6 (5.9%)	4 (2.5%)	
2+	2 (2.0%)	1 (0.6%)	
3+	-	2 (1.2%)	
Existence of dysplasia	1 (1.0%)	3 (1.9%)	1.000‡

† Mann-Whitney U Test, ‡ Fisher's exact Test.

Table 5. The incidence of *Helicobacter pylori* positivity

	Preoperative biopsy n (%)	Gastric specimen n (%)	*p* Value
H. pylori positivity	48 (57.1%)	33 (39.3%)	0.001

The *H. pylori* sero-positivity was found in 75 patients (74.25%) of 101 non obese patients. Of the 84 patients who underwent LSG, *H. pylori* was detected in the preoperative endoscopic biopsies of 48 patients (57.1%). *H. pylori* positivity continued in the resected gastric specimens of 33 patients (39.3%). Peptic ulcer disease was found with preoperative endoscopy in 12 of the 84 patients receiving LSG and these patients were placed on eradication therapy. Of these 12 patients, 6 were *H. pylori* sero-negative both preoperatively and postoperatively; 3 patients were *H. pylori* sero-positive both pre- and postoperatively; and in the remaining 3 patients, *H. pylori* was eradicated and not detected in the gastric specimen (Table 5). Control endoscopy was not performed after eradication treatment.

Postoperative complications after LSG developed in 5 of the 84 patients (5.96%). In 2 patients there was postoperative bleeding from the stapler line: one had multiple gastric ulcers and the other a pre-pyloric ulcer. However, both patients were preoperatively asymptomatic and *H. pylori* sero-negative. Wound infection occurred in two patients with positive *H. pylori* infection and the last remaining patient had a liver subcapsular abscess which was *H. pylori* sero-positivite preoperatively.

Discussion

Peptic ulcer disease is strongly associated with *H. pylori* infection and, when present, eradication of *H. pylori* reduces ulcer recurrence. However, the prevalence of *H. pylori* infection in morbidly obese patients and its effect on ulcer progression or the response to eradication treatments is unresolved [13-18]. Furthermore, it is also unclear whether the detection and eradication of *H. pylori* prior to bariatric surgery can reduce the risk of postoperative peptic ulcer disease [19, 20]. These dilemmas are not surprising when we consider the variation in *H. pylori*

prevalence according to geographical region, which is influenced by socio-economic environments and eating habits. The lack of large randomized controlled studies precludes a definite conclusion.

In the present study, *H. pylori* infection and its related dyspeptic complaints were high in both morbidly obese and non-obese patients which is similar with the results of Ozden *et al.* [21] who studied the sero-epidemiology of *H. pylori* in Turkish population. For this reason, upper endoscopy is performed routinely in our clinic prior to bariatric surgery. Subsequently, all our morbidly obese patients with dyspeptic symptoms or peptic ulcer disease, confirmed by histopathological examination after upper endoscopy, are placed on a standard six-week *H. pylori* eradication treatment before surgery.

Results of the present study indicate that the existence of *H. pylori* sero-positivity does not seem to have a negative impact on early postoperative outcome after LSG. However, long term effects of *H. pylori* sero-positivity on the gastric pouch with a risk of cancer development remains unknown. Another noteworthy point is the high ulcer activity scores in morbidly obese patients. Additionally, bulbar ulcers were significantly more frequent in morbidly obese patients than in the non-obese. Remarkably, *H. pylori* positivity was less frequently found in resected gastric specimens than in the preoperative endoscopic biopsies. This may be related to the localization of *H. pylori* and suggest that the presence of *H. pylori* continues in gastric pouches well after LSG. Finally, it is of interest that all of the patients with peptic ulcer disease were asymptomatic before endoscopy. In the light of these findings, we recommend routine *H. pylori* eradication therapy before bariatric surgery not only in those with peptic ulcer disease but also in *H. pylori* sero-positive patients.

The Limitations of the Study

The present study has several limitations. Firstly, upper endoscopy was performed in our control group patients for a variety of dyspeptic complaints, whereas all morbid obesity patients preparing for surgery underwent routine endoscopy, and this may have distorted the true prevalence of *H. pylori* in healthy individuals. Secondly, postoperative long-term follow-up is not available and the sample size is too small to conclude whether the *H. pylori* eradication treatment has had an impact on the reduction of postoperative ulcer recurrence in morbidly obese patients.

Conclusions

Our results indicate that *H. pylori* sero-positivity does not seem to significantly alter early postoperative outcome. However, long term effects of *H. pylori* sero-positivity on the gastric pouch with a risk of cancer development remains unknown. The ulcer activation score in morbidly obese patients is higher -even when they are asymptomatic- than in non-obese individuals. Routine preoperative endoscopy should be considered in all bariatric surgery candidates to rule out pathologies such as hiatal hernia, extensive ulcers or malignant lesions which are contraindications for a LSG.

Conflict of interest

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Bacterial etiology in acute hospitalized chronic obstructive pulmonary disease exacerbations

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ABSTRACT

Objectives. The most common cause of acute COPD exacerbation (AECOPD) is the respiratory tract infections. We sought to determine the bacteriological etiology of hospitalized acute exacerbations of COPD requiring hospitalization in consecutive two years. ***Methods.*** We aimed to determine the bacteriological etiology underlying in patients whom admitted to Uludag University Faculty of Medicine, Department of Pulmonary Medicine and hospitalized with AECOPD in the last two years. Medical records of the study participants were screened retrospectively and sociodemographic characteristics, routine laboratory tests and sputum culture results were analyzed. ***Results.*** A total of 242 patients hospitalized for AECOPD were enrolled. Of these 86.4% (n=209) were male. The mean age of the group was 66.6±11 years old. Sputum cultures were available in the 45 % (n=109) of the study group. The most frequent bacteria isolated from the sputum cultures of the study group were *Pseudomonas aeruginosa*, *Streptococcus pneumonia*, *Haemophilus influenzae* and *Acinetobacter baumanii*. Length of stay was longer in patients with the *A. baumanii* isolate than the rest of the group (p=0.024). Length of stay in hospital was independently associated with in-hospital mortality (OR: 1.37, 95% CI: 1.05–1.78). Isolation of *A. baumanii* and/or *Staphylococcus aureus* in sputum culture were identified as independent risk factors for prolonged length of stay in-hospital (b=0.26, p=0.008; b=15.40, p=0.003). ***Conclusions.*** Our study shows that *P. aeruginosa*, *S. pneumonia*, *H. influenzae* are common sputum isolates in AECOPD patients requiring hospitalization. Isolation of *A. baumanii* and/or *S. aureus* in sputum culture is associated with prolonged length of stay in hospital, which is an independent risk factor for in-hospital mortality.

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Keywords: Acute exacerbation; chronic obstructive pulmonary disease; sputum; bacteriology

Introduction

Chronic obstructive pulmonary disease (COPD) is a major cause of chronic morbidity and mortality worldwide. It is also common in Turkey and leads to high mortality, morbidity and frequent use of health care resources [1-3]. COPD exacerbation is an acute event characterized by a worsening of the patient's

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respiratory symptoms that is beyond normal day-to-day variations, and leads to a change in medication [4]. Common symptoms are worsening dyspnea, cough and increased sputum production. Exacerbation of COPD are important events in the course of the disease related with impairment in quality of life [5], accelerate disease progression [6], and cause substantial economic burden of COPD [7], particularly if they require hospitalization. Exacerbations of COPD requiring hospitalization are prognostic factors for poor survival in COPD [8].

Acute exacerbation of COPD (AECOPD) can be precipitated by several factors. The most common causes are bacterial or viral respiratory tract infections. *Streptococcus pneumonia*, *Haemophilus influenzae* and *Moraxella catarrhalis* were the most frequently isolated microorganisms in AECOPD patients [9, 10]. Prevention, early detection, and prompt treatment of exacerbations are vital to reduce the burden of COPD. In the present study, we sought to determine the bacteriological etiology of hospitalized acute exacerbations of COPD requiring hospitalization in consecutive two years in a large patient group. Primary and secondary study outcomes were in-hospital mortality and length of stay (LOS) in hospital.

Methods

Study Population and Definitions

COPD patients with acute exacerbation hospitalized in Uludag University Faculty of Medicine, Department of Pulmonary Medicine Inpatient Clinic, between January 2011 and January 2013 were retrospectively enrolled into the study. Medical records of the study participants were screened; demographic characteristics, comorbid diseases, routine laboratory tests, arterial blood gas analyses, sputum microscopic evaluation and bacterial culture results, antibiotic treatment choice during hospital stay, length of stay in hospital, and in-hospital mortality were analyzed. Each patient was only recruited once. Presence of pneumonia or sign of any other active infection, asthma, bronchiectasis, and presence of tuberculosis, inflammatory diseases such as connective tissue disorder, arthritis, inflammatory bowel disease and malignancy were accepted as exclusion criteria.

COPD was diagnosed according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines and defined by persistent airway limitation (post-bronchodilator FEV1/FVC<0.70) in presence of ≥10 pack-years of smoking history [4]. For COPD diagnosis, previous pulmonary function tests available in the medical records were recorded. COPD exacerbation was defined as an event in the natural course of the disease characterized by a change in the patient's baseline dyspnea, cough and/or sputum that is beyond normal day-to-day variations requiring treatment with systemic steroids or antibiotics, and/or visit to emergency room or admission to hospital [4]. Acute COPD exacerbations in the previous 12 months were assessed by patients' recall of exacerbation events and according to medical records. Respiratory insufficiency was defined as an arterial oxygen tension (PaO_2) of <60 mmHg, an arterial carbon dioxide tension ($PaCO_2$) of >45 mmHg, or both [11].

Bacteriological Analyses

Sputum was collected in sterile sputum culture cups. Patients were asked to expectorate sputum in these sterile cups after washing the oral cavity and samples sent microbiology laboratory within 2 hours. Sputum was assessed macroscopically firstly: mucoid or purulent. Once the specimen reached the laboratory, first it was microscopically screened to exclude those samples with upper airway contamination. Only sputa showing fewer than 10 squamous epithelial cells and more than 25 leucocytes in at least 5 low power fields (×100) were accepted for further culture examination [9]. Sputum samples that do not fulfill these criteria were not cultured. Standard quantitative bacterial culture and identification procedures were performed as described previously [9, 12]. Blood agar was used for isolation and identification of Gram-positive organisms, MacConkey agar for Gram-negative bacteria, and enriched chocolate agar for *Haemophilus spp*. Plates were incubated at 37°C and 5% CO_2, and were checked for growth after 24 and 48 hours of incubation [12]. At least 106 colony forming units/ml indicated significant growth. In cases where multiple bacterial isolates were found in samples; the predominant species were considered as the leading pathogen.

Bacterial agents were classified as potential pathogenic microorganism (PPM) and non-PPMs. PPMs were microorganisms that cause respiratory infections such as Gram-negative rods, *Pseudomonas aeruginosa*, *Enterobacteriaceae* and *Haemophilus spp*.; Gram-positive cocci, such as *Staphylococcus*

aureus, *S. pneumonia*; Gram-negative cocci, such as *M. catarrhalis*. Non-PPMs were the microorganisms that belong to oropharyngeal or gastrointestinal flora and usually not responsible from respiratory infections (*Streptococcus viridians* group, *Neisseria spp*., *Corynebacterium spp*., *Candida spp*., and others) in immunocompetant hosts [13].

Statistical Analysis

Statistical analyses were performed using the IBM SPSS Statistics for Windows, Version 22.0 software program (Armonk, NY: IBM Corp.). Variables were investigated using visual (histograms, probability plots) and analytical methods (Kolmogorov-Simirnov / Shapiro-Wilk's test) to determine whether or not they were normally distributed. Data were expressed as mean ± SD or median (min-max) and median [interquartile range (IQR) 25 - 75] as appropriate unless otherwise specified. Categorical variables were reported as proportions. A chi-square test was used to compare proportions between two groups and a two-sample t-test for continuous outcome variables. For non-normal data Mann Whitney-U test was performed. For the multivariable analyses, possible factors identified with univariate analyses were further entered into the logistic regression analyses to determine independent predictors of in-hospital mortality. Hosmer-Lemeshow goodness of fit statistics were used to assess model fit. In a separate model, a multiple linear regression model was used to identify independent predictors of length of stay in hospital. The model fit was assessed using appropriate residual and goodness-of-fit statistics. A 5% type-I error was used to infer statistical significance.

Results

We identified a total of 242 patients hospitalized for AECOPD. Of these 242 patients, 86.4% (n=209) were male. The mean age of the group was 66.6±11 years old. Characteristic features of the study participants are presented in Table 1. Almost 61% of the study group had respiratory insufficiency at first admission.

Sputum cultures were available in the 45% (n=109) of the study group. There were no growth in cultures of 61.5% of these patients; whereas 38.5% (n=42) of the group yielded positive on sputum cultures. The most frequent bacteria isolated from the sputum cultures of the study group were *P. aeruginosa* (n=9; 21.4%), *S. pneumonia* (n=7, 16.7%), *H. influenzae* (n=6, 16.7%), *Acinetobacter baumanii* (n=6, 16.7%), *Enterobacteriaceae* (n=4, 9.5%), *S. aureus* (n=4, 9.5%), *Escherichia coli* (n=4, 9.5%), *Klebsiella pneumoniae* (n=2, 4.8%),

Table 1. Characteristics of the Patients

Characteristics	Values
Male/female (n)	209/33
Age (mean±SD)	66.6±11
Males	68.5±10.8
Females	63.8±8.6
Comorbid disease (%)	
Diabetes mellitus	27.6
Hyperlipidemia	7.5
Hypertension	41
Obesity	8.3
Coronary artery disease	25.3
Lung cancer	20
Arterial blood gas analyses	
pH	7.38 ± 0.05
pO_2	73.2 ± 33.3
pCO_2	47.8 ± 14.7
HCO_3	27.6 ± 6.3
SaO_2	90.9 ± 9.1
Respiratory insufficiency, n (%)	131 (60.9)

n=number of patients

Stenotrophomonas maltophilia (n=2, 4.8%), and *Serratia marcescens* (n=1, 2.4%), (Figure 1).

Treatment and outcomes

The median prior admission rates of the subjects were 1 (min - max: 0 - 9). 14.9% of the group had at least two prior admissions. The mean duration of hospitalization was 9 [IQR 25-75: 7-14] days. Overall in-hospital mortality rate was 9% (n=21).

In hospital mortality was significantly higher in patients with any growth in sputum culture (78.6 % vs. 41.5%, $p<0.05$). The univariate analyses to identify variables associated with in-hospital mortality during hospitalization for AECOPD are summarized in Table 2. When baseline characteristics were compared, sex, age and most of the comorbidities except lung cancer were not different between survived and the patients died. Length of stay in hospital was significantly increased in patients died ($p=0.040$). We found that in-hospital mortality was higher in patients whom *A. baumanii* was isolated from the sputum culture than the other patients (mortality rate for *A. baumanii* group 30.8% vs. mortality rate for the rest of the group 2.1%, $p<0.0001$**).** The isolation frequency of *E. coli* and *S. aureus* were significantly higher in deceased patients when compared with the survivors ($p=0.025$, and $p=0.025$, respectively).

Patients with the *A. baumanii* isolate were significantly younger than the other patients (46±9.9 vs. 67±10.3 years old, $p<0.05$). Length of stay was longer in AECOPD patients with *A. baumanii* compared to rest of the study group (19 [min - max: 4-85] days vs. 8.5 [min - max: 1-36] days; respectively; $p=0.024$). We did not observe a significant difference in LOS duration among other bacterial isolates. We observed a higher rate of respiratory insufficiency in patients with the *A. baumanii* isolate compared to COPD patients with

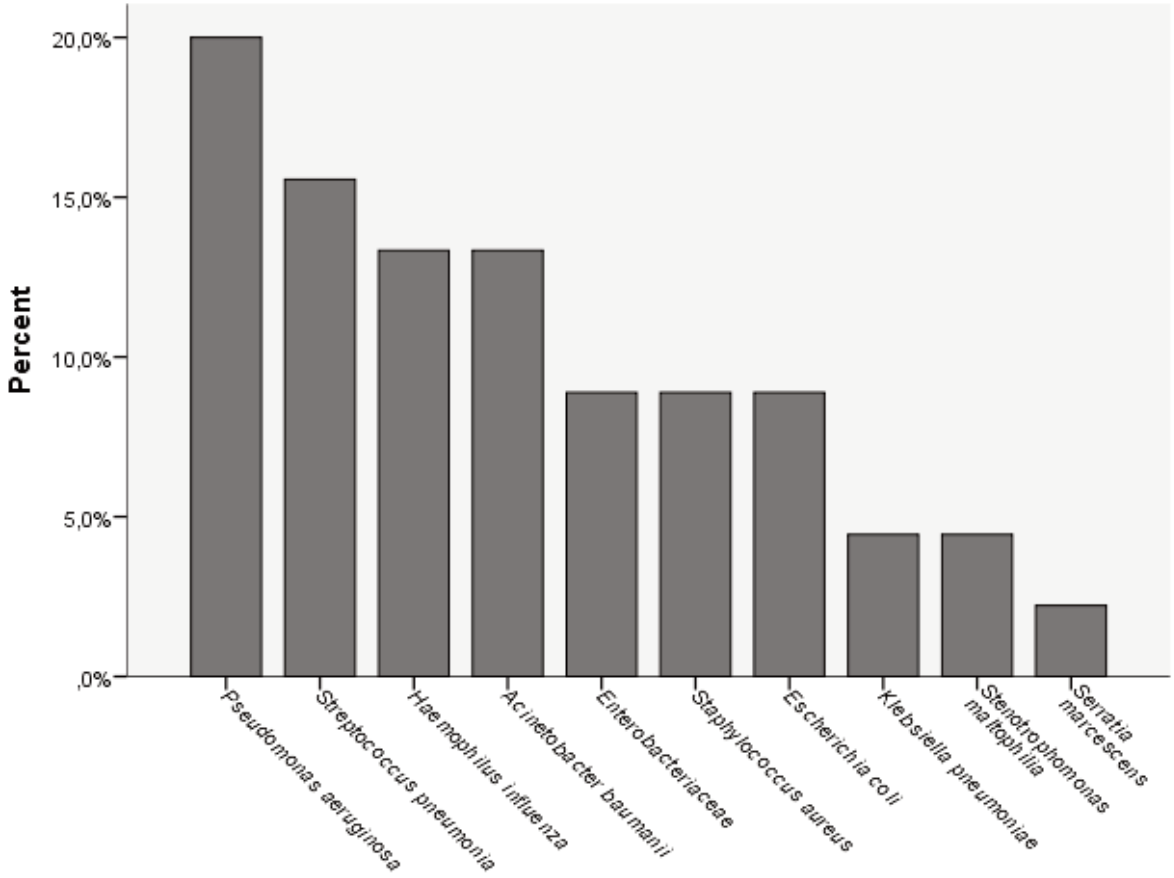

Figure 1. Distribution of potentially pathogenic microorganisms yielded on sputum culture of hospitalized COPD patients with acute exacerbation.

Table 2. The univariate analyses to identify variables associated with in-hospital mortality during hospitalization for AECOPD

	Survived (n=221)	Died (n=21)	*p*
Age; *years*	66.9 ± 11.1	63.4 ± 9.2	0.163
Sex, Males; *n*	181	20	0.210
LOS, *days*	9 [7 - 13]	14 [7 - 19]	0.040
Comorbidities; *n (%)*			
Diabetes mellitus	31 (27.4)	2 (25)	0.881
Hyperlipidemia	8 (100)	0 (0)	0.401
Hypertension	49 (90.7)	5 (9.3)	0.749
Obesity	9 (8.9)	0 (0)	0.409
Coronary artery disease	29 (27.9)	0 (0)	0.104
Lung cancer	16 (76.2)	5 (5.7)	0.010
# of previous hospitalizations	0.83 ± 1.24	0.81 ± 1.28	0.454
Repiratory insufficiency; *n (%)*	121 (61.4)	10 (55.6)	0.623
Sputum isolates; *n (%)*			
PPM			
Haemophilus. influenzae			
Streptococcus pneumonia	6 (6.4)	0 (0)	0.331
Pseudomonas aeruginosa	8 (8.5)	1 (7.1)	0.863
Acinetobacter baumanii	2 (2.1)	4 (30.8)	< 0.0001
GNEB			
Escherichia coli	2 (2.1)	2 (14.3)	0.025
Enterobacteriaceae	4 (4.3)	0 (0)	0.432
Serratia marcescens	1 (1.1)	0 (0)	0.698
Klebsiella pneumoniae	2 (2.1)	0 (0)	0.582
Stenotrophomonas maltophilia	2 (2.1)	0 (0)	0.582
Staphylococcus aureus	2 (2.1)	2 (14.3)	0.025
Non-PPM	17 (8)	4 (19)	0.092

n=number of patients, LOS=length of stay in hospital, # represents number of, PPM= potentially pathogenic organism, GNEB=Gram-negative enteric bacilli

other isolates (p=0.043). Rate of respiratory rate were not different among patients stratified according to isolation of other bacteria.

Possible factors identified with univariate analyses (length of stay in hospital, lung cancer, presence of sputum *A. baumanii*, *E. coli* or *S. aureus* isolates, non-PPM) were further entered into the logistic regression analyses to determine independent predictors of in-hospital mortality. Only, increasing length of stay in hospital was independently associated with in-hospital mortality (Table 3).

In a separate model, a multiple linear regression model was used to identify independent predictors of length of stay in hospital. Isolation of *A. baumanii*, *S. aureus*, and PaO_2 levels were identified as significant risk factors for prolonged length of stay in-hospital (Table 4).

Discussion

The underlying etiology of acute COPD exacerbations is often infectious and mostly related with a bacterial and/or viral infection. *H. influenzae*, followed by *S. pneumonia* and *M. catarrhalis* were the

Table 3. Factors independently associated with in-hospital mortality of AECOPD

	B	SE	Wald	*p*	OR	95%CI OR
Length of stay in hospital, days	0.31	0.13	5.34	0.020	1.37	1.05 – 1.78
Escherichia coli in sputum	3.98	2.77	2.07	0.150	53.75	0.24–12178.00
Staphylococcus aureus in sputum	3.36	1.80	3.4	0.063	28.74	0.84–985.59

SE=standard error; OR=odds ratio; CI=confidence interval

Table 4. Factors affecting length of stay in-hospital in AECOPD

	Univariate Regression				*Multivariate Regression*			
Variable	**B**	**SE**	**β**	***P***	**B**	**SE**	**β**	***p***
Age, years	16.49	3.25	-0.11	0.09	-	-	-	-
Sex	12.52	1.46	-0.07	0.29	-	-	-	-
Lung Cancer	0.50	2.20	0.022	0.82	-	-	-	-
PCO_2	0.07	0.04	0.13	0.06	-	-	-	-
Pseudomonas aeruginosa	3.19	3.34	0.09	0.34	-	-	-	-
PO_2	0.03	0.02	0.12	0.07	0.04	0.02	0.17	0.06
Acinetobacter baumanii	16.94	3.67	0.41	<0.0001	10.92	4.05	0.26	0.008
Staphylococcus aureus	18.69	4.56	0.37	<0.0001	15.40	4.97	0.31	0.003

β=unstandardized regression coefficient; SE=standard error of the coefficient; β=standardized coefficient

most frequent bacterial isolates in sputum samples of COPD patients with exacerbation [10, 14]. Besides, non-fermentative Gram-negative bacilli (*P. aeruginosa*, *S. maltophilia, A. baumanii*) were reported as the leading causative pathogens for severe COPD exacerbations that require mechanical ventilation [15].

This retrospective study of bacterial isolates associated with AECOPD in a tertiary hospital in Bursa, Turkey found that potential bacterial pathogens were isolated from sputum in approximately 40% of the patients. This isolation rate is in accordance with previous studies reporting an isolation rate of 32 % to 51 % performed in similar settings [16-19]. Our results demonstrated a predominance of *P. aeruginosa*, *S. pneumonia*, *H. influenzae*, and *A. baumanii* as the most common sputum isolates in AECOPD patients requiring hospitalization. Microbial patterns observed in our study correspond to mostly to *P. aeruginosa* in 21.4%, Gram-negative enteric bacilli (GNEB) in 26.2%, *A. baumanii* in 16.7%, and *S. aureus* in 9.5%. Community acquired pathogens (*S. pneumonia*, *H. influenzae*) were responsible in 31% of the total isolates. Our findings are in accordance with Miravitlles *et al.* [10] reports including *H. influenza*, *P. aeruginosa*, and *S. pneumonia* as the most frequent isolates in sputum samples of COPD patients with exacerbation [11]. Interestingly, we observed *P. aeruginosa* as the leading pathogen isolated from sputum samples of COPD patients with exacerbation. Moreover, rates for isolation of *A. baumanii* was high and noteworthy (as high as *H. influenzae* isolation rates, 16.7% for both isolates) in our study. To the best of our knowledge, our study is one of the first reports showing A. *baumanii* as a remarkably frequent isolate in sputum samples of hospitalized COPD patients with exacerbation. Recently, Dai *et al.* [20] reported that *Pseudomonas*, followed by *A. baumanii*, *Klebsiella*, *E. coli* and *S. pneumonia* in bacteriologic analyses of sputum in patients with hospitalized AECOPD patients [20]. Moreover, Li *et al.* [19] reported *Pseudomonas* as the most common pathogen in patients with COPD exacerbation. Besides Soler *et al.* [21] reported a high rate of Gram-negative bacteria and *Pseudomonas/Stenotrophmonas spp*. isolates in respiratory samples of COPD patients with severe exacerbations. Previous studies have demonstrated a significant variation in the relative incidence of specific pathogens in AECOPD, which may relate to patient inclusion criteria, settings and environmental or epidemiological factors [10, 19-22]. Nearly 15% of our study group had at least two prior admissions in the previous year before enrollment into this study. Moreover, 61% of the overall study participants had respiratory insufficiency at first admission. We suggest that high prior admission and respiratory insufficiency rates may reflect a study group mainly including severe COPD patients, which can be an explanation for the relatively high *P. aeruginosa*, GNEB, *A. baumanii* and *S. aureus* isolation rates observed in our study. We observed a significantly higher respiratory insufficiency rate for patients with *A. baumanii* isolates. Infections due to *P. aeruginosa*, GNEB, *A. baumanii* and *S. aureus* are of special concern in terms of treatment as these pathogens would require specific and prolonged antimicrobial treatment.

The other aim of our study was to evaluate the potential relationship between causative bacterial agents for AECOPD and LOS in hospital. Despite, isolation of *A. baumanii*, *E. coli* or *S. aureus* in sputum, accompanying lung cancer, and length of stay in hospital were identified as possible risk factors for in-hospital mortality on univariate analyes; logistic regression analyses revealed that only increasing

length of stay in hospital was independently associated with in-hospital mortality. Our results demonstrated that exacerbations associated with *A. baumanii* resulted in a significantly longer LOS in hospital, higher rates for respiratory insufficiency and in-hospital mortality. Nakau *et al*. [22] also identified *A. baumanii* to be associated with prolonged hospitalization in AECOPD. It was also identified as an independent risk factor for prolonged in-hospital stay with *S. aureus* and arterial oxygen tension. Therefore, we suggest that bacterial infectious phenotypes seem to associate with LOS and in-hospital mortality in AECOPD. But we were not able to explore all of the possible risk factors that may cause prolonged stay in hospital and mortality in our study because of its retrospective design. Further research is warranted to explore the impact of all possible risk factors in LOS and in-hospital mortality in AECOPD with special consideration to bacterial infectious etiology.

The Limitations of the Study

This study has several limitations. Firstly, our study population included only hospitalized AECOPD events and for that reason, we are unable to evaluate bacteriological profile of milder exacerbations that do not require hospitalization. Secondly, because of the retrospective design of the present study; we were unable to fully evaluate potential factors such as severity of the airflow obstruction, chronic corticosteroid use, recent antibiotic therapy, factors related with respiratory insufficiency and referral to intensive care unit, etc., which may effect in-hospital mortality. Thirdly, we did not isolate sputum specimens for viral etiology. On the other hand, present study shows that isolation of *A. baumanii* was associated with younger age and adverse clinical outcome in terms of length of stay, higher rates for respiratory insufficiency and in-hospital mortality. Although, we did not explore *A. baumanii* positive sputum culture as an independent risk factor for increased in-hospital mortality; we have shown that *A. baumanii* positive sputum culture is an independent risk factor for prolonged LOS in hospital. Further larger scale prospective studies are warranted to explore the impact of all possible risk factors in LOS and in-hospital mortality in AECOPD with special consideration to bacterial infectious etiology.

Conclusions

In conclusion, present study demonstrates that *P. aeruginosa*, and *A. baumanii* are frequent bacterial isolates in addition to community acquired pathogens (*S. pneumonia*, *H. influenzae*) in AECOPD patients requiring hospitalization. In addition, this study indicated that *A. baumanii* or *S. aureus* positive sputum cultures are independent risk factors for prolonged LOS in hospital. Prolonged length of stay in hopital is an independent risk factor for in-hospital mortality in hospitalized acute exacerbations of COPD.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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Efficacy of preoperative trimetazidine for preventing myocardial injury in patients undergoing off-pump coronary artery bypass grafting

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ABSTRACT

Objective. Off-pump coronary artery bypass grafting (CABG) with median sternotomy have been shown to be beneficial and associated with reduced myocardial injury. However, there is still a risk for ischemic myocardial injury that results from the normothermic and metabolically active myocardium during the occlusion of the target coronary artery. We aimed to evaluate the efficacy of trimetazidine in prevention of myocardial tissue injury in patients undergoing off-pump CABG by measuring serum levels of cardiac troponin I (cTnI). ***Methods.*** Thirty patients undergoing first-time elective off-pump CABG were randomly assigned to two groups: 15 patients received trimetazidine 60 mg orally per day (trimetazidine group) for three weeks and 15 patients received placebo (control group). As a parameter of myocardial injury, we measured cTnI levels. Blood samples were taken sequentially from the patients before surgery (t1), 30 minutes after the last distal anastomosis (t2), at postoperative 12th hour (t3) and at postoperative 24th hour (t4). cTnI measurements were made by direct chemiluminometric technology. ***Results.*** Baseline and operative characteristics of patients are similar. All preoperative serum cTnI concentrations were within the normal range and rose with the beginning of the operation which reached to its peak value at t3 in the control group and t4 in trimetazidine group. When the increase in the serum cTnI concentrations of trimetazidine group and control group were compared there was a slight numerical increase in cTnI levels in all measurements after reperfusion but reached to statistical significance only at t3 (mean: 0.40 ng/ml; mean rank: 12.20; range: 0.05-1.66 vs. mean: 0.20 ng/ml; mean rank: 18.80; range: 0.11-0.30; p=0.041). ***Conclusion.*** Preoperative treatment with trimetazidine might reduce postoperative myocardial injury in patients undergoing first time isolated off-pump CABG, but larger randomized placebo controlled trials are still for recommendation of routine pretreatment with trimetazidine.

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Keywords: Off-pump CABG; trimetazidine; troponin I

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Introduction

Metabolic treatment with trimetazidine has been suggested to be effective in patients undergoing cardiac surgery by reducing the risk of ischemia reperfusion injury and risk of recurrent angina and improving the patients' postoperative condition. There are several studies concerning about myocardial protective effects of trimetazidine either used preoperatively or as an addiction to the cardioplegic solution in patients undergoing cardiac surgery with cardiopulmonary bypass [1].

Coronary artery bypass grafting (CABG) by the help of cardiopulmonary bypass and global cardiac arrest is effective, safe and has an acceptable mortality rate but still there is risk of morbidity and ischemic myocardial injury. Although these adverse effects of cardiopulmonary bypass are mostly reversible avoiding the use of cardiopulmonary bypass either by minimally invasive CABG or off pump CABG with median sternotomy has been shown to be beneficial and to be associated with reduced myocardial injury [2-5]. Off-pump CABG is performed on beating heart without the use of cardiopulmonary bypass and global cardiac arrest. However there is still a risk of ischemic myocardial injury that results from normothermic and metabolically active myocardium during the occlusion of the target coronary artery. In the present study we aimed to evaluate the efficacy of preoperative trimetazidine in the prevention of myocardial tissue injury in patients undergoing offpump CABG by measuring serum levels of cardiac troponin I (cTnI).

Methods

Patients

After approval of the local ethics committee written informed consent was obtained from every patient. Thirty patients undergoing first time elective off-pump CABG were randomly assigned into two groups: 15 patients received 3 times 20 mg/day trimetazidine preoperatively (trimetazidine group) and 15 patients received placebo (control group). Because of the its optimal dose and optimal time period of pretreatment, during the 3 weeks preoperatively, patients received trimetazidine orally 3 times 20 mg/day [1, 5, 6]. The exclusion criteria were the presence of unstable angina, acute myocardial infarction of less than one month duration, chronic renal insufficiency, ejection fraction of less than 40%, and concomitant valvular disease or skeletal muscle disease. In addition, patients with electrocardiographically confirmed myocardial infarction in the immediate postoperative period and showing significant increases in cardiac enzymes were also excluded. This design was chosen in order to explore the efficacy of trimetazidine only on the myocardial injury occurring due to the procedure not from the perioperative myocardial infarction which may have a serious impact on the results in a small patient group.

Surgical Technique

After a median sternotomy and harvesting the bypass grafts, heparin (150 U/kg) was administered. The Octopus Tissue Stabilizer (Octopus 28400, Medtronic, Cardiac Surgical Products, MI, USA) was used for the stabilization of the target coronary artery. First, the proximal anastomosis of the vein grafts was constructed by the help of a partially occluding aortic-side clamp. In all the cases, the left anterior descending artery was the first coronary artery to be revascularized. The target coronary artery was stabilized and occluded proximally with the help of a bulldog clamp and then the distal anastomosis was performed. No coronary shunts were used during the distal anastomosis. Heparin was antagonized with protamin sulphate until the activated clotting time decreased below 200 seconds.

Blood Sampling

As a parameter of myocardial injury, we measured cTnI levels. Blood samples were taken sequentially from the patients before surgery (t1), 30 minutes after the last distal anastomosis (t2), at postoperative 12th hour (t3) and at postoperative 24th hour (t4). cTnI measurements were made by direct chemiluminometric technology (Automated Chemiluminescence System: ACS-180, Chicron Diagnostics, East Walpole, MA, USA). The ACS system detects free cTnI in addition to the complex forms.

Statistical Analysis

Statistical analyses were performed using the SPSS statistical software (SPSS Inc, Chicago, IL, USA). Continuous variables were expressed as mean ± standard deviation. Analyses were made with Mann-Whitney U, chi-square, and Fischer's exact tests. Because of the small no patients involved in the study and the cTnI levels are not normally distributed Mann-

Table 1. Baseline and operative characteristics of patients

	Trimetazidine Group (n=15)	Control Group (n=15)	*p*
Age (mean)	59.6 ± 9.5	56.9 ± 9	.325
Gender (male/female)	10/5	11/4	.500
Prior myocardial infarction	7 (46.7)	7 (46.7)	1
Ejection fraction	52.1±8.5	50.8 ± 8.2	.595
Presence of hypertension	6 (40)	6 (40%)	1
Presence of diabetes Mellitus	5 (33.3)	3 (20)	.341
Chronic obstructive pulmonary disease	3 (20)	4 (26.7)	.500
Use of left internal mammary artery	15 (100)	14 (93.3)	.500
Number of vessels grafted (range)	2.4 ±0.7(1-3)	2.2 ± 0.7 (1-3)	.512
Ischemic time (minutes)	25.7± 9.1	23.9 ± 9	.653

Data are presented mean±standard deviation or number (%).

Whitney U-test was used for comparison of changes in levels of cTnI between the two groups, mean rank and range values are presented for description. A *p* value of less than 0.05 was considered to indicate statistical significance.

Results

Baseline and operative characteristics of patients are shown in Table 1. There were no mortalities in both groups. Mean ischemic time was 25.7±9.1 minutes in trimetazidine group and 23.9±9 minutes in the control group. There were no peroperative myocardial infarction in both groups. All preoperative serum cTnI levels were within the normal range and rose with the beginning of the operation which reached to its peak value at t3 in the control group and t4 in the trimetazidine group (Table 2). When increase in the serum cTnI levels of trimetazidine group and control group were compared, there was a slight numerical increase in cTnI levels in all measurements after reperfusion but reached to statistical significance only at t3 when control group was compared with trimetazidine group (mean 0.40 ng/ml; mean rank 12.20; range .05-1.66 vs. mean 0.20 ng/ml; mean rank 18.80; range .11-.30 ; *p*=0.041). The cTnI levels was higher in the control group at t4 but it did not reach to a statistical significance (mean: 0.39 ng/ml; mean rank: 12.40; range: 0.02-3.25 vs mean: 0.31 ng/ml; mean rank: 18.60; range: 0.30-0.34; *p*=0.056) Table 2.

Discussion

Trimetazidine has been shown to reduce myocardial injury during conventional CABG [1, 6- 8]. Trimetazidine selectively inhibits the last enzyme (3-ketoacyl coenzyme A thiolase) participating in the betaoxidation of free fatty acids. which leads to the

Table 2. Measurements of cTnI in both groups

	Control Group Mean (ng/ml); mean rank; range	Trimetazidine Group Mean (ng/ml); mean rank; range	$p^{¥}$
t1	0.07; 15.10; 0.01-0.23	0.05; 15.90; 0.01-0.07	0.806
t2	0.34; 15.20; 0.02-1.57	0.20; 15.80; 0.08-0.30	0.870
t3	0.40; 12.20; 0.05-166	0.20; 18.80; 0.11-0.30	**0.041**
t4	0.39; 12.40; 0.02-3.25	0.31; 18.60; 0.30-0.34	0.056

¥: Mann-Whitney U test; cTnI levels measured (t1:before surgery, t2:30 minutes after the last distal anastomosis, t3:postoperative 12th hour, t4:postoperative 24th hour)

inhibition of free fatty acid oxidation and an increase in glucose oxidation. Trimetazidine reduces the formation of free oxygen radicals, inhibits neutrophil infiltration and also limits the accumulation of sodium and calcium in the cytoplasm of cardiomyocytes [7]. There are several reports suggesting that the restoration of ischemia impaired mitochondrial function is affected by trimetazidine and the sites of trimetazidine binding to the mitochondrial membrane have been identified, that confirms the anti-ischemic property of the drug. The inhibition of apoptosis in cardiomyocytes is another possible mechanism of trimetazidine [6, 7]. Argaud *et al.* [9] confirmed these findings in their study in which they showed that administering trimetazidine 10 min before ischemia significantly protects the myocardium from ischemia reperfusion injury, including inhibition of apoptosis in the cardiomyocytes. Ruixing *et al.*[10] obtained similar results in a rabbit model experimental study. cTnI is a structural peptide in cardiac myocytes and is a well documented marker of myocardial injury even in patients with uneventful recovery [3, 11, 12]. On-pump CABG causes higher release of serum markers of myocardial injury that might be due to inadequate perfusion of subendocardium and remaining ischemic areas that could not be grafted, unexpected aortic regurgitation and due to reperfusion (whose consequences are not well known) through the bypass grafts after unclamping or direct trauma to myocardium [12, 13]. Although off-pump CABG has been shown to be associated with lesser myocardial injury in terms of biochemical blood markers there is still a potential risk of ischemic myocardial tissue damage due to normothermic, metabolically active myocardium during the occlusion of the target coronary artery [2, 3, 14].

The present study shows that the amount of myocardial injury might be lesser in patients undergoing off-pump CABG and received 60 mg trimetazidine preoperatively than those did not receive. This is expressed by lower release of cTnI. This finding leads to a suggestion that myocardial injury that occurs due to the regional normothermic warm ischemia and ischemia reperfusion injury because of the target coronary artery occlusion during off-pump CABG might be reduced by prophylactic trimetazidine medication.

Our findings about reducing the myocardial tissue injury with the usage of trimetazidine was supported by several studies which were consisted of patients undergoing on-pump conventional CABG [1, 8]. Somewhat the cTnI levels in our study were higher than some previous reports, which may be related to different assay technology and kits used [2]. ACS method applied in our study detects free cTnI in addition to complex forms. Similar cTnI levels were reported by Kilger *et al.* [14] who used a fluorogenic sandwich enzyme immunoassay method and by Wan *et al.* [15] who used the same method in our study. Several studies showed that the increase in cardiac specific serum markers of myocardial injury during coronary procedures especially cTnI may be used as an indicator of the efficiency of cardio protective procedures [12, 16]. Without cellular necrosis reversible myocardial ischemia can cause functional disintegration of the myocardial cell membranes and consecutive release of cytocolic molecules [14]. The present study showed that this release of cytocolic molecules leaking from reversibly injured myocytes is significantly lower in patients undergoing off-pump CABG and receive trimetazidine than those who did not.

The main drawbacks of our study are limited no of patients enrolled in our study and disadvantage of showing early graft patency by angiography. Our findings might be influenced by the small number of patients included in the present study. Slightly numerical increase in the cTnI concentrations might reach to a statistical significance in all reperfusion measurements in a larger group. Besides we showed a statistically significant increase in cTnI concentrations of the control group when compared with trimetazidine group at 12th hour after the reperfusion.

Conclusions

On the basis of available studies and our study we can say that metabolic treatment with trimetazidine might be effective in patients subjected to CABG by reducing the risk of ischemia reperfusion injury in terms of biochemical blood marker cTnI. However, there are only a few studies so far, and a very small number of patients are included in most of the studies. Therefore this therapy cannot be recommended until large, randomized, preferably multicentre trials are performed. On the other hand, trimetazidine can obviously be considered as an additional pretreatment in patients subjected to CABG.

Conflict of interest

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Original Article

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Trans-axillary approach in surgery for thoracic outlet syndrome

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ABSTRACT

Background. Thoracic outlet syndrome may be due to various reasons and be classified as neurogenic, arterial, and venous thoracic outlet syndrome. The surgical treatment of neurogenic thoracic outlet syndrome can be performed using either a trans-axillary or a supraclavicular approach. The aim of this study is to report on such patients operated in a single institution by a single thoracic surgeon using trans-axillary approach. ***Methods.*** The patient files were screened for patients operated due to neurogenic thoracic outlet syndrome related symptoms between September 1, 2002 and April 1, 2015 in the Department of Thoracic Surgery of Bursa Yuksek Ihtisas Training and Research Hospital. ***Results.*** There were 22 female and five male patients with an average age of 31.9±11.7 years. The most common symptom was pain in the affected limb and shoulder (n=29). Of the diagnostic maneuvers abduction external rotation (Roos) test was the most frequently found positive test (n=27). Nerve conduction velocity studies revealed an average ulnar nerve conduction velocity of 62.7±6.6 m/s. Limited pneumothorax uneventfully resolved in 2 days was seen following 12 operations. ***Conclusion.*** We conclude that trans-axillary approach may provide good exposure with favorable opportunity to excise the 1st and the cervical rib, and neurolysis with a low rate of complication.

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Keywords: Thoracic outlet syndrome, surgery, trans-axillary approach

Introduction

Thoracic outlet syndrome (TOS) may be due to various reasons including bone anomalies, aberrant muscle and soft tissue structures, trauma and even malignancies involving the area. According to patient complaints and symptoms, TOS can be classified as neurogenic (NTOS), arterial (ATOS), and venous TOS (VTOS) [1-6]. ATOS and VTOS may require correction of vascular anomalies and are beyond the scope of this study. NTOS presents a challenge in treatment as the real reason is not always clear. Nevertheless, the surgical treatment of NTOS comprises resection of the first rib, anomalous soft

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tissue structures, and the cervical rib, if present, using either a trans-axillary or a supraclavicular approach [1, 2, 4-12].

The aim of this study is to report on the NTOS patients operated in a single institution by a single thoracic surgeon (SY) using trans-axillary approach, and compare the findings with literature.

Methods

Data Recruitment

After Institutional Review Board approval, the patient files were screened for patients operated due to NTOS related symptoms between September 1, 2002 and April 1, 2015 in the Department of Thoracic Surgery of Bursa Yuksek Ihtisas Training and Research Hospital. The patient demographics such as age, gender, affected side, symptoms, results of TOS diagnostic maneuvers, presence of cervical rib, results of nerve conduction velocity (NCV) studies, operation side, operation type, early complications, and length of postoperative hospital stay were noted from the files.

Treatment Algorithm for NTOS

All patients applied to our department with complaints indicating TOS are examined for TOS maneuvers, sent for PA chest x-ray, AP and lateral cervical x-rays, and NCV studies. Patients diagnosed as probable NTOS are first referred to the Neurosurgery Department to exclude trap neuropathies and cervical discopathies. The patients are then referred to the Department of Physical Therapy and Rehabilitation for a three-month course of medical treatment. We reserve surgical treatment for NTOS patients did not benefit from the medical treatment or got worse and those willing to undergo operation as the only means of treatment.

Operative Technique

Under general anesthesia, all patients were placed with the affected side up and the arm fixed to a designated arm holder. We used trans-axillary incision to reach the first rib. The front end of the 1st rib was first incised using a Sauerbruch-Frey first rib shear. Then the muscles, their tendons, and any aberrant soft tissue were dissected and the rib is excised as a whole, disarticulated at the rear end. Then the cervical rib, if present is excised, as well. Following hemostasis, a 19 F silicone drain is placed in the operation site and is attached to a drainage bag. The layers are than sutured using absorbable materials. On the first postoperative day, a chest x-ray and AP cervical x-ray is performed.

Statistical Analysis

For statistical analysis we used MedCalc Statistical Software version 15.2.2 (MedCalc Software bvba, Ostend, Belgium; registered to S.Y.)

Results

Thirty-six operations were performed on 31 patients for NTOS within the aforementioned period. Four case files were missing. The remaining 32 operations were performed on a total of 27 patients. There were 22 female and five male patients (F:M ratio was 5.4:1) with an average age of 31.9±11.7 years (range 17-63 years). Demographic data and clinical characteristics of the patients are shown in Table 1.

Table 1. Patients' demographic data and clinical characteristics

Variables	Patients n (%)
Gender	
Female	27 (84.4)
Male	5 (15.6)
Affected Side	
Right	19 (59.4)
Left	13 (40.6)
Symptoms at admission	
Pain	29 (90.6)
Numbness	25 (78.1)
Frustration	14 (43.8)
TOS Maneuvers	
Abduction external rotation (Roos)	27 (84.4)
Hyperabduction (Wright)	20 (62.5)
Adson's	16 (50)
Costoclavicular (Halstead)	13 (40.6)
Operation type	
First rib resection	18 (56.3)
First and cervical rib resection	14 (43.8)

The most common symptom was pain in the affected limb and shoulder (n=29), followed by paresthesia (n=25), and frustration of the affected extremity (n=14). Of the diagnostic maneuvers, abduction external rotation (Roos) test was the most frequently found positive test (n=27 patients, 84.4%). Hyperabduction (Wright) test was positive in 20 patients (62.5%), Adson test was positive in 16 (50%), and costoclavicular (Halstead) test was positive in 13

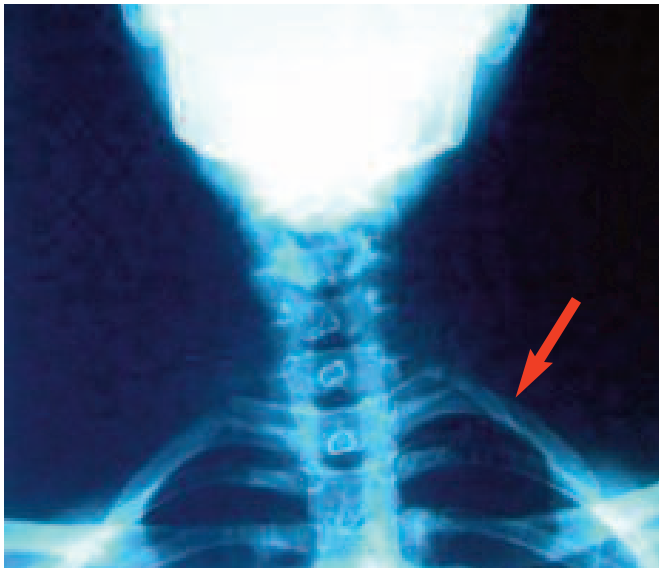

Figure 1A. Cervical anteroposterior (AP) X-ray shows cervical rib (arrow) on the left side in a female patient.

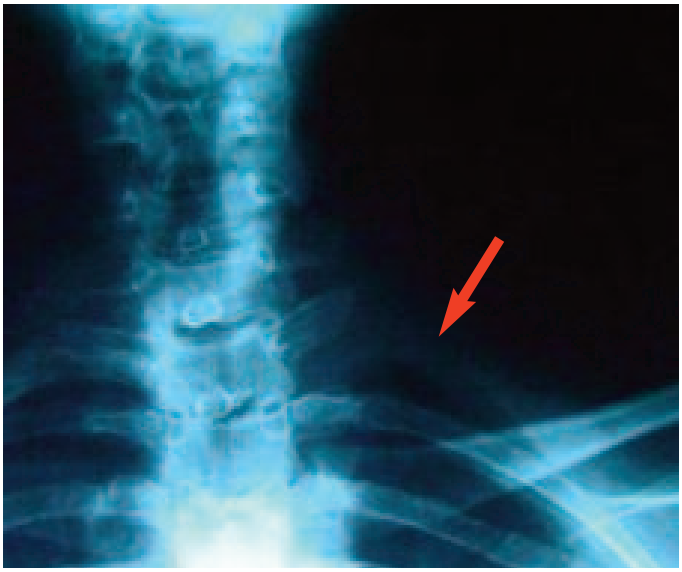

Figure 1B. Cervical AP x-ray view (arrow) of the same patient following operation.

patients (40.6%). In cervical x-rays, 14 patients had cervical ribs (Figures 1A and B).

NCV studies revealed an average ulnar nerve conduction velocity of 62.7±6.6 m/s (range 50-73 m/s). In eight patients NCV was 70 m/s and higher. The operation side was right in 14, and left in 8, and bilateral in five patients. All bilateral cases were female. In 18 operations the first rib and accompanying soft tissue structures were resected, whereas in 14 operations the accessory cervical rib was resected as well (Figure 2).

Figure 2. An image of surgically removed first rib and cervical rib in the same patient.

Limited pneumothorax uneventfully resolved in 2 days was seen following 12 operations, and venous injury was encountered in 2 operations, repaired immediately using prolene sutures. Postoperative average length of hospital stay was 3.7±0.9 days (range 2-6 days).

Discussion

Since first described in 1956 by Peet, TOS still presents a treatment challenge for the physicians. TOS may be due to many reasons affecting the area including bony anomalies, presence of anomalous soft tissue structures, fractures, inflammation, and local invasion of malignancies [1, 4-6, 10-12]. In our series 14 patients had cervical rib, and eight patients had overgrown C7 transverse process. None of our patients had malignancy.

TOS affects mostly young, working people. The great majority of cases are within the 2nd and the 4th decades [2-4, 7-9, 12]. Although some reports indicate a slight preference, female patients are more common [3, 4, 7-9, 12]. In our series the average age was 31.9±11.7 years, and there was a female predominance as 5.4:1.

NTOS patients are usually referred to the physician due to pain, frustration during exertion, numbness, and paleness of the affected upper limb [2-4, 6-9, 11, 12]. The most common symptoms were pain in the affected limb and shoulder (n=29), paresthesia (n=25), and frustration of the affected extremity (n=14) in our series.

There are several diagnostic maneuvers including Adson's, Wright's, Roos', and Halstead's [1, 4, 8, 12]. The main purpose of all these maneuvers is to squeeze the vessels and nerve bundle between the bony and

soft tissue to provoke the symptoms. Unfortunately none of these maneuvers is of pathognomonic value. Of all these tests, we found the Roos' test as the most valuable as we had the most positive results in patients using this test (see Table 1).

NCV studies reflect the neural status to some extent, but most authors advocate not to rely on such studies as in many patients the results are normal [1-3, 7, 12]. Normal ulnar nerve NCV is 70-72 m/s. Some authors prefer to operate right away on patients with NCV results lower than 60 m/s, and refer the patients with NCV results over 60 m/s for physiotherapy [2, 8, 9, 11]. We referred all patients for a three-month period of physiotherapy prior to operation regardless the NCV results.

There are several reports debating whether operate or not the TOS patients [4]. Yet, the treatment of choice is recommended as physiotherapy followed by surgery [1, 2, 5, 6, 8, 12]. Surgical removal of the anomalous structures is mostly performed using either trans-axillary or supraclavicular approach [1, 2, 5-12].

Although some surgeons report excellent results using supraclavicular approach, some of their patients have ATOS and VTOS requiring vascular surgery [1, 4]. Others advocate trans-axillary approach especially in female patients [3, 5-10]. Trans-axillary approach provides adequate surgical exposure for resection of the first rib, the cervical rib, if present, the soft tissue structures and membranes, and neurolysis in experienced hands. Complications are rare and limited to pneumothorax, vascular injury, nerve injury, and wound infection [1, 3-12]. In our series all patients were operated using trans-axillary approach. We experienced pneumothorax in 12, and vascular injury in 2 patients. Our routine application of Blake silicone drain following resection resolved the pneumothorax without any consequences. Vascular injuries were repaired during the operation using prolene sutures.

The limitations of the study

The limitations of our study include the small number of patients and the lack of follow up, especially postoperative NCV studies and outcome questionnaires. Further studies with larger number of patients with close follow-up may provide more valuable information regarding efficacy of this surgical approach.

Conclusions

We believe that supraclavicular approach may provide a good exposure of the vascular structures, leading to good to excellent outcomes. However, we believe that trans-axillary approach provides good enough exposure with favorable opportunity to excise the 1st and the cervical rib, and neurolysis with a low rate of complication.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

Financing

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The effect of treatment protocol on calcaneus bone mineral densitometry after intra-articular calcaneal fractures

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ABSTRACT

Objectives. To identify the effect of treatment protocol on calcaneus bone mineral density of calceneal fractures treated with different methods. ***Methods.*** Sixty-three patients with intra-articular calcaneal fractures were observed prospectively. Patients were classified according to their treatment protocols such as; conservative treatment with short leg plaster cast (Group C), closed reduction and fixation with cannulated screws (Group S) and open reduction internal fixation with plate and screws (Group P). All patients' bilateral radiographies, CT scans, the American Orthopaedic Foot and Ankle Society (AOFAS) scores and calcaneus bone mineral density measurements by G&E Archilles Quantitative Ultrasound method were obtained at 15th month of follow up period. ***Results.*** Fourteen (22%) patients were female and 49 (88%) were male. The mean age was 43.7±12.1 years. The mean follow-up was 33.7±14.7 months. Bone mineral density measurements were calculated as; t scores; -1.48±1.24 for group C, -1.48±1.31 for group S, -0.27±1.68 for group P and z scores; -0.18±1.41 for group C, -0.17±1.9 for group S, 0.96 ± 1.54 for group P. Group P had the higher t and z scores of injured sides than other groups (p=0.008 and p=0.026, respectively). Average AOFAS scores were 78.13±13.04 in group S, 82.58±10.81 in group P and 79.82±11.75 in group C. No significant differences were detected between groups regarding AOFAS scores. ***Conclusion.*** Measurement of calcaneus bone mineral density which we used in our study is a method for evaluation of calcaneal fracture treatments and higher density values were found in open reduction and internal fixation group. This may be owing to better control of defect with the allograft and early mobilization by the evident improvement in angular correction..

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Keywords: Calcaneal fracture; quantitative ultrasound method; bone mineral density; plaster; American Orthopaedic Foot and Ankle Society (AOFAS) scores; treatment protocol

Introduction

Calcaneus fracture is the most common tarsal bone injury and 1-2% of all fractures in the human body [1]. The optimum treatment of patients with intra-articular calcaneal fractures is still controversial. As a consequence of computed tomography (CT)'s invention, improvement of operation techniques and

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implant designs, more successful outcomes are achieved by surgical treatment [2]. Despite this, calcaneal fractures are related with many complications and reduce life quality regardless which treatment method is used. Goal of the treatment of intra-articular calcaneal fractures is to gain a functional and painless foot. Therefore early articular motion, exact angular correction and union of the bone must be achieved in the earliest time. Otherwise complex regional pain syndrome (CRPS), which may result with chronic pain and osteopenia, is encountered frequently.

One of the important problems concerning this calcaneal fractures is the loss in mineral density leading calcaneal osteopenia. Calcaneal osteopenia may increase morbidity, cause union problems and increase risk of re-fracture.

The primary purpose of this study was to determinate which treatment method had the significant effect on calcaneal bone mineral density and it's correlation with clinical outcomes.

Methods

A prospective study was conducted in patients with intra-articular calcaneal fractures, treated with different methods such as open reduction and internal fixation, closed reduction and fixation with cannulated screws described by Essex-Lopresti and conservative treatment between 2008 and 2015. Sixty-three patients who came up to postoperative controls regularly and who had consent to attend the study have been observed. This study was performed under approval and supervision of Diskapi Training and Research Hospital Local Ethical committee.

The patients were classified according to treatment protocols as; conservative treatment with short leg plaster cast (group C), closed fixation with cannulated correcting screws (group S), open reduction and fixation with a plate (group P). In group P, to achieve articular restoration and angular correction, allograft was used during the operation.

Sander's classification was made on coronal CT images, Bohler and Gissane angles were measured on the radiographies taken before and after treatment. Sanders type II, III and IV fractures were included in this study. Sanders type I fractures were excluded since this fracture is treated only conservatively. Patients with bilateral calcaneal fracture were excluded just to compare the injured feet with the healthy ones. Patients with operation site problems and infections were also excluded.

In group C, after 6 weeks of immobilization, range-of-motion exercises were instructed followed by partial weight bearing (PWB) at 3rd month and weight bearing as tolerated (WBAT) at 4th month. In group S, range-of-motion exercises were instructed after 3 weeks' immobilization with a short leg splint and PWB at 2nd month and WBAT at 3rd month. In group P, range-of-motion exercises were instructed immediately after operation, PWB allowed at 2nd month and WBAT at 3rd month.

Bilateral antero-posterior and lateral radiographies of feet, the American Orthopaedic Foot and Ankle Society (AOFAS) scores and bilateral calcaneal mineral density measurements were taken on the 15th month of treatment. All implants were removed in group S and P on the 12th month of the treatment for proper measurement of bone mineral density. GE Achilles Bone Ultrasonometers® (General Electric Company) device was used for bone mineral density measurements. T and Z scores were assessed for each patient injured and non-injured calcaneal bones. Scorings, angle and density measurements were performed by the same physician.

Statistical Analyses

Significance of difference between groups was analyzed by student's t test when two groups existed and One way variance analyze (one way ANOVA) when more than two groups existed. Group's pre-operative vs. postoperative values and injured vs. none injured side measurement averages were analyzed by dependent t test to reveal any statistically significant difference. Whether there is a significant relationship between continuous or non-continuous variables was examined using Spearman's correlation test. For $p<0.05$ the results were accepted to be significant but in all probable multiple comparisons Bonferroni correction was carried out to control type 1 bias.

Results

Fourteen (22%) of 63 patients included in the study were female while 49 (88%) were males. Mean age was 43.75±12.1 years. Mean follow-up period was 33.68±14.67 months. Thirty-four (53.9%) of patients were injured from right foot while 29 (46.1%) of them

Table 1. Demographics and lesion localization of the groups

Variables	Group S (n=15)	Group P (n=26)	Group C (n=22)	*p*
Age	39.8±14.2	46.1±11.2	43.5±11.5	0.276
Sex				
Male	10 (66.7)	22 (84.6)	17 (77.3)	0.419
Female	5 (33.3)	4 (15.4)	5 (22.7)	
Side				
Right	8 (53.3)	13 (50.0)	13 (59.1)	0.171
Left	7 (46.7)	13 (50.0)	9 (40.9)	

Data are given as mean±SD or n (%), n=number of the patients

were injured from left. No gender and age differences were existent between three groups (Table 1).

Twenty-two of the patients (group C) were treated conservatively, 15 of them were treated closed reduction and fixation with cannulated screws (group S) and 26 of them were treated by open reduction and internal fixation (group P).

Distribution of fracture type according to Sanders classification between treatment groups were summarized in table 2.

Mean Bohlers' angle at admission were 20.9±12.3 in group C, 10.4±13.5 in group S and 12.2±11.4 in group P. Mean Bohlers' angles at first follow-up were 16.6±15.7 in group C, 21.7±6.3 in group S and 30.6±3.1 in group P. For group C and S, no difference was observed between mean angle values (p=0.019 and p=0.397, respectively), nevertheless group P follow-up mean Bohlers angle values were higher than the admission measurements (p<0.001). Mean postoperative angle differences were 4.3±18.9 for group S, -4.3±8.0 for group C and 8.9±10.8 for group P. Group P had the highest increase with regard to Bohler angles (p=0.002) (Table 3).

Mean preoperative Gissane angles were 111.9±9.4 in group C, 119.1±12.0 in group S and 118.7±14.4 in group P. Mean postoperative angles were 112.7±12.8

Table 2. Distribution of Sander's type between treatment groups

Sanders Type	Group C n (%)	Group S n (%)	Group P n (%)	*p**
II	**15 (68.2)**	**2 (13.3)**	5 (19.3)	***<0.001***
III	**7 (31.8)**	**12 (80.0)**	20 (76.9)	***<0.001***
IV		1 (6.7)	1 (3.8)	

*Sander's IV values were neglected while chi-square test was performed. Intergroup differences are marked boldly.

Table 3. Pre- and postoperative Bohler/Gissane angle measurements of groups

	Preoperative	Postoperative	*p*[a]	Difference
Bohler				
Group S	11.3±14.1	15.6±13.3	0.397	4.3±18.9
Group P	12.2±11.4	21.1±11.5	<0.001	8.9±10.8[c]
Group C	20.9±12.3	16.6±15.7	0.019	-4.3±8.0[c]
p				**0.002**[b]
Gissane				
Group S	119.1±12.0	114.0±7.6	0.162	-5.1±13.3
Group P	118.7±14.4	114.2±11.3	0.089	-4.5±13.0
Group C	111.9±9.4	112.7±12.8	0.774	0.8±13.2
p				0.287[b]

Data are given as mean±SD. [a] p<0.0083 values were approved as significant for in-group pre- and postoperative angle comparisons according to Bonferroni Correction, [b] p<0.025 values were approved as significant for inter-group mean angle difference comparisons according to Bonferroni Correction, [c] Differences between Grup P and Grup C were statistically meaningful (p=0.002)

Table 4. t and z scores of injured and noninjured extremities

Variables	Injured extremity	Uninjured extremity	p^a
T Score			
Group C	-1.48±1.24	-1.10±1.07	0.273
Group S	-1.48±1.31	-1.13±0.94	0.191
Group P	-0.27±1.68	-1.25±1.33	**0.004**
p	**0.008**	0.897	
Z Score			
Group C	-0.18±1.41	0.18±1.19	0.304
Group S	-0.17±1.9	0.79±1.32	0.020
Group P	0.96±1.54	0.3±1.34	**0.017**
p	0.026	0.348	

Data are given as mean±SD. [a]In each group comparisons of injured and noninjured side, results were accepted statistically significant for $p<0.017$ according to Bonferroni correction

in group C, 114.7±7.6 in group S and 114.1±10.8 in group P. No difference was observed between preoperative and postoperative mean angle values for any group. Mean postoperative angel differences were 0.8±13.2 for group C, -5.1±13.3 for group S and -4.5±13.0 for group P (p= 0.287).

Group C t scores were -1.48±1.24 for injured side, -1.10±1.07 for non-injured side and z scores were -0.18±1.41 for injured side, 0.18±1.19 for non-injured side. Group S t scores were -1.48±1.31 for injured side, -1.13±0.94 for non-injured side and z scores were-0.17±1.9 for injured side, 0.79±1.32 or non-injured side. Group P t scores were -0.27±1.68 for injured side and -1.25±1.33 for non-injured side and z scores were 0.96±1.54 for injured side, 0.3±1.34 for non-injured side (Table 4). For group P, injured extremities had higher t and z scores than non-injured sides (p=0.004 and p=0.017, respectively) and group P had higher injured extremity t scores compared with other groups (p= 0.008).

Mean AOFAS scores were 79.82±11.75 in group C, 78.13±13.04 in group S and 82.58±10.81 in group P (p=0.475).

Discussion

Quantitative Ultrasound Index (QUI), which we used in our study, is a method for evaluation of osteoporotic fracture risk in both genders. Since calcaneus is a superficial bone with thin soft tissue coverage, it is a good candidate for densitometric sonographic evaluation. Advantages of using ultrasound are its low cost, wide using area and having no radiation exposure. It is used mostly in calcaneus because of its similarity to vertebral bone. In a wide study on 14,824 patients it was reported that calcaneal QUS is a good method to evaluate the risk for hip fractures and in another study performed on 6,189 patients' calcaneal QUS was shown to be as hip and femur dual-energy X-ray absorptiometry (DEXA) measurements. Despite favorable results, QUS is not accepted as a standard diagnostic tool for determination of fracture risk worldwide. More improvements are necessary with further studies for its wide usage [5-8].

In literature, many studies are available regarding biomechanical and plantar pressure evaluation, clinical and radiographic outcome regarding calcaneal fracture treatment [2, 3, 9, 10]. However, calcaneal bone mineral densitometric status following calcaneal fractures was not investigated previously. Bone mineral density measurement is a method that gives physician an opinion about bone microstructure. Hence it would be useful to use QUS in future studies in order to make a comprehensive evaluation of the methods. In our study, calcaneal QUI measurement is performed after implant removal given the fact that implants could lead calculation mistakes due to its metal content. As a consequence, density measurement should be carried out on patients without implants.

Avoidance of weight bearing and possible complications may alter bone mineral density of calcaneus negatively. Most important finding of this study is that higher calcaneal densities can be achieved with open reduction and internal fixation after treatment of intra-articular calcaneal fractures. In our study, t and z scores of patients in group P were found to be higher than other groups. This situation may depend on the fact that better reduction is achieved in open surgical treatment and that the defect is

supported by the bone graft. In addition, open reduction and plate fixation enables early weight bearing and this may contribute the mineral density of calcaneus.

Better anguler correction and higher Bohlers measurements were achieved with open reduction in this study. Open reduction of the bone fragments and maintaining the position with plate, screws and bone graft provides better geometrical correction of calcaneus compared to conservative or closed surgical treatment. Similar results were reported before about Bohlers angle [16]. Although open reduction provides better anguler correction of Bohler angle, no difference was observed between groups about Gissane angles before and after treatment.

Another important problem about evaluating patients with calcaneus fracture is not having a score to determine the outcomes [11-14]. Contemporarily Maryland and AOFAS foot evaluating scales are applied usually [8]. Maryland foot scoring system deals with patients' pain, walking functions, cosmetic view and functional activities. As for AOFAS, it contains about pain, function and anatomic sequence. Although both scales comprise similar properties, there is still not a consensus on which scale yields more accurate results [14]. In our study, AOFAS foot evaluation score is preferred which is applied widely [9]. Contrary to findings of Griffin *et al.* [15] we observed that patients who treated with open reduction and plate fixation had slightly higher AOFAS scores compared to conservative treatment. Although this difference was not significant we believe that early functional recovery with open reduction and plate fixation may provide better functional scores.

Conclusions

We conclude that, significant angular reduction and higher bone mineral density can be achieved with open reduction and internal fixation for treatment of intraarticular calcaneal fractures.

Conflict of interest

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The evaluation of children referred for health measure ruling according to the Child Protection Law

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ABSTRACT

Objectives. To assess the children referred to our clinic with a health measure ruling which was given in accordance with Turkey's no. 5395 Child Protection Law, in terms of socio-demographic characteristics, psychiatric diagnosis, and follow-up. ***Methods.*** Thirty children referred to our clinic with a health measure ruling given according to Turkey's no. 5395 Child Protection Law were assessed. ***Results.*** The mean age was 13.20±3.86 (min-max: 2-17). Referral reasons of the children with a health measure ruling included driven to crime in 7 (23.3%), family therapy in 8 (26.7%), sexual abuse in 8 (26.7%), substance abuse in 3 (10%), physical abuse in 1 (3.3%), and medical care and rehabilitation in 3 (10%) children. Of the children referred for a health measure, 19 (63.3%) did not continue following the initial assessment. ***Conclusions.*** To enhance the effectiveness of the protective and preventive mental health services, children and adolescents who have a health measure ruling should be treated, followed-up, and rehabilitated at every stage of the process. It is necessary to increase in-house and inter-agency communication in order to implement the system effectively for the benefit of these children.

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Keywords: Children; health measure ruling; Child Protection Law; follow-up.

Introduction

The concept of the child in need of protection is described as a child whose personal security in terms of physical, mental, moral, social, and emotional development is in danger, or a child who is neglected or abused, or who is victim of crime [1].

The United Nations Convention on Children's Rights (CCR) is the most important international legal basis of the child protection system. There are also articles about child protection in the Constitution of the Republic of Turkey, the Turkish Civil Code (TSC), the no. 2828 Law on Social Services and the Child Protection Institution (LSSCPI), and the no. 5395 Child Protection Law [2-5].

The child protection systems were developed

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based on the basic principle of "High Benefit of the Child" included in the CCR, and the Child Protection Law (CPL) was prepared for the protection of children who are in need of protection or who are delinquents, and for safe guarding their rights and well-being [3, 6]. In addition, the aforementioned no. 5395 law also aims to protect and safe guard of children's rights and well-being, and contains protective and supportive measures [5-8].

The protective and supportive measures include counseling, education, care, health, and housing rights towards providing protection to children first of all in their family environment. The counseling and education measures are carried out by institutions of the Ministry of Education, health measures by the Ministry of Health, and care and housing measures by the Social Services and Child Protection Institution [5-8].

Counseling measures aim to guide the caregiver about raising the child and assisting the children in problem solving regarding their education and development. Education measures aim ensuring a child to continue educational institutions and join to a vocational training course or art course in order to acquire a job or profession. Care measures aim ensuring a child to benefit from the service or to be placed in public or private child care centers or foster families if anyone responsible for the care of the child for any reason is unable to fulfill their duty. Health measures aim to ensure the protection of the child's physical and mental health and the treatment required for temporary or permanent medical care and rehabilitation of substance abusers. Housing measures intend to provide shelter to people with children without shelter or women who are in danger [1].

The problem of children who are in need of protection remains worldwide. Whatever the reason, the problems created by the children who need protection are the concern of entire society, and not just these children. Therefore, objective of this study is to assess the children referred to our clinic with a health measure ruling which was given in accordance with Turkey's no. 5395 Child Protection Law in terms of socio-demographic characteristic, psychiatric diagnosis, and follow-up. It is expected to provide contribution to increase the efficiency of the services provided for the benefit of children.

Methods

Out of 57 children referred to the child and adolescence psychiatry clinic between January 2012 and March 2015 for a health ruling within the scope of no. 5395 Child Protection Law, 27 were excluded from the study, because they never came to their appointment, and finaly 30 children were included. Files of these children were retrospectively screened to be researched for which their patient folders were examined retrospectively. Assessment of the files was performed with a standard process sequence.

All of the cases included in the study were examined by a child and adolescence psychiatrist and at the same time, a family interview was also performed if they were accompanied by their family during the clinical examination. The socio-demographical information, psychiatric diagnosis, and whether they have continued their clinical follow-up were recorded from the patient files on a form prepared by the examiners. Psychiatric diagnosis was made with a clinical interview based on DSM-IV on the children of interest.

Statistical Analysis

Statisticaly analysis was performed using SPSS 19.0 software. The descriptive statistics of continuous variables are expressed as median, minimum, maximum, mean, and standard deviation. The normality of variables was tested with Shapiro Wilk Test. The differences between 3 groups were compared using Kruskal Wallis and Pearson Chi-Square Tests in terms of age and gender, respectively. A p value <0.05 was considered statistically significant.

Results

Thirty of 57 children referred to our clinic for a health ruling were included with 15 being female and 15 male. The mean age was found as 13.20±3.86. It was determined that 4 of the children (13.3%) have attented went to primary school, 5 children (16.7%) secondary school and 4 children (13.3%) high school, while 17 children (56.7%) have not gone to school. Of the children included in the study, 22 (73.3%) were living with their family, 2 children (6.7%) with only one parent, 1 child (3.3%) with a grandmother / grandfather, and 5 children (16.7%) were determined

to live in social facilities.

When the reasons for referral of the children due to health measures were examined, 7 children (23.3%) were sent due to being driven to crime, 8 children (26.7%) for familial therapy, 8 patients (26.7%) due to sexual abuse, 3 children (10%) due to substance abuse, 1 child (3.3%) because of physical abuse, and 3 children (10%) for medical care and rehabilitation.

When the results were analyzed in terms of diagnosis; 3 of the children (10%) were diagnosed with depression, 5 children (16.7%) Posttraumatic Stress Disorder, 4 children (13.3%) Conduct Disorder, 3 children (10%) Attention Deficit / Hyperactivity Disorder, 5 children (16.7%) Mental Retardation, 4 children (13.3%) Substance Abuse, and 1 child (3.3%) was diagnosed with Adjustment Disorder. The remaining 5 children (16.7%) had no psychiatric diagnosis.

Inpatient treatment was recommended for 2 of the children evaluated (6.7%), 11 children (36.7%) were initiated medical treatment, 8 children (26.7%) received psychotherapy, and 4 children (13.3%) were referred to special education. Five children (16.7%) did not receive any treatment.

Of the children referred with a health measure ruling, 19 (63.3%) were determined not to have continued their follow-up after the first call. Five of the children who attended the follow-up (16.7%) did not reveal any psychopathology, and the health measure ruling of 6 children (20%) was stopped ended due to the benefit gained from the treatment given.

When the reason of the referral of children was compared with their ages, no statistically significant difference was detected between the groups (p=0.094) (Table 1).

There were significant differences between boys and girls in terms of the reason for referral (p=0.031) (Table 2). The percentage of children driven to crime was 42.9% for males and 7.7% for females. The percentage of sexual / physical abuse was determined as 14.3% for males, while this rate was 53.8% for females.

Table 1. Comparing of reasons of the referral with ages of the children[#]

	n	Mean age ± SD	Median	Min.	Max.
Drift into crime	7	14.86 ± 2.91	16.00	9.00	17.00
Counseling / Treatment and care measures	11	11.36 ± 4.30	13.00	2.00	15.00
Sexual / Physical abuse	9	13.22 ± 3.80	14.00	4.00	17.00

[#]Kruskal Wallis (p=0.094), Max=maximum, Min=minimum, n=number of the patients

Table 2. Relationship between reasons of the referral and gender of the children[*]

	Drift into crime	Counseling / Treatment and care measures	Sexual / Physical abuse	Total
Male	6 (42.9%)	6 (42.9%)	2 (14.3%)	14
Female	1 (7.7%)	5 (38.5%)	7 (53.8%)	13

[*]Pearson Chi-square (p=0.031)

Discussion

According to the United Nations Convention on Children's Rights (CCR), the responsibility to provide the necessary conditions for the development of a child as a healthy person firstly incumbent falls on the parents of child or other people who take care of child in the framework of possibilities they have. The state parties to this convention are supposed to take necessary measures to ensure the implementation of the right of protection of the child according to their national conditions and within the bounds of possibility, and to apply material assistance and support programs in particularly for issues such as nutrition, clothing, and housing [2, 3, 9].

The no. 5395 Child Protection Law, which came into force in 2005 in our country, is one of the legal

bases that is taken as a basis in the child welfare field and is executed by services [2]. In order to make the implementation of the law more clear, 'Regulations about the Implementation of Protective and Supportive Measures Decisions' according to the Child Protection Law was published in 2006 [7]. After these regulations,; all public institutions and organizations, nongovernmental organizations, or anybody who is aware of the need to help children (also the parents of children) have the obligation to inform the District/Provincial Directorate of Family and Social Policies of the situation of children [7].

Juvenile courts are tasked with making rulings of measures [6, 10]. As a result of actions taken, courts can make a ruling of one or more measures, and implementing institutions or organizations are informed about these measure rulings [6, 11].

Social services specialists assess children in need of protection, who have been notified to the District/Provincial Directorate, in the terms of social environments and physical conditions of the home in which they lived, and a social study report is prepared. The social services specialists, who are socially, economically, and psychologically assessed, have an important role in the communication between the organizations about the determination of essential interventions [5-7].

Fifteen children referred to our clinic for a health measure ruling in accordance with these laws were female and the other 15 were male. Studies carried out in our country have focused mostly on juveniles driven to crime, so there are different results about the gender ratios [10, 12, 13]. In this study, the mean age was found as 13.20±3.86, reflected in the results of the Edirne sample [12]. Seventeen (56.7%) participants were not continuing their education. When the relationship between the reason for referral and gender was compared, we found that male participants were more referred for the reason of being driven to crime, and the girls for sexual and physical abuse. In studies conducted with adolescents involved in crime, most of the children are boys, and in this case, it is indicated that delinquency is more common in boys with aggressive behavior [14]. Similarly, it was reported in another study performed in our country, that 17 children driven to crime were male and 2 were female [15]. In studies, it has been stated that more of the children for which a health measure ruling has been given due to sexual abuse are female and the findings of our study are consistent with the literature [16-19].

Nineteen children (63.3%) children referred for health measure rulings did not continued after the first psychiatric interview, which also reflects the population-based data of discontinuation. The follow-up of the children referred for health measures is mostly irregular in our country, due to inadequate number of professionals and the lack of the Child Protection Centers, which can provide multidisciplinary interventions.

Conclusion

In terms of offering the protective and preventive mental health services, the children and adolescents with a health measure rulings should be treated, followed-up, and rehabilitated at every stage of the process. For this reason, we suggest that the Child Protection Units, which can provide the assessment of child in health, education, social, and economic aspects should be extended and the in-house and inter agency communications should be increased for the effective implementation of the system for a high benefit of children.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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Establishing reference values and evaluation of an in-house ferric reducing antioxidant power (FRAP) colorimetric assay in microplates

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ABSTRACT

Objectives. The total antioxidant capacity (TAC) of a sample can be measured with a ferric reducing antioxidant power (FRAP) assay. There are commercially available kits for FRAP assays, however they are more expensive than in-house kits. We aimed to evaluate a FRAP direct measurement method under our laboratory conditions using a microplate reader and establish reference values to use in future research projects. ***Methods.*** An in-house microplate adaptation of the FRAP method was evaluated. Reference values of FRAP were established for one hundred and twenty subjects aged between 25-55 years. FRAP levels were estimated in 30 serum samples with high glucose concentration, 44 hyperbiluribinemic neonatals and 16 patients receiving renal replacement therapy (RRT). ***Results.*** The mean FRAP level was 890±235 µmol/L. The median TAC level was 904 µmol/L. This method was found to be linear up to at least 2000 µmol/L. The intra- and inter-assay coefficients of variation were 2.7-6.7% and 5.3-10.1%, respectively. The mean FRAP level was lower than normal in diabetes and RRT patients and higher in hyperbiluribinemic neonatals (687±209 µmol/L, 609±250 µmol/L and 945±187 µmol/L, respectively). ***Conclusions.*** Our reference values give comparable results with the literature. This method is simple, reliable, and inexpensive. It could be used for studies of oxidative stress-related diseases.

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Keywords: Total antioxidant capacity; ferric reducing antioxidant power; evaluation; reference range; microplate

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Introduction

Reactive oxygen species (ROS) are produced in the human body as a consequence of normal aerobic metabolism and a balance between production and inactivation is required. Excess production of ROS can lead to a situation of oxidative stress, which is responsible for many pathological processes and has an impact on the body's aging process. Oxidative damage has been implicated in the cause of many diseases, including cardiovascular disease, diabetes, neuronal degeneration, depression, cancer and probably aging [1-3].

To protect cells against oxidative stress, certain low molecular weight antioxidant molecules, either water-soluble (e.g., ascorbic acid) or lipid-soluble (e.g., vitamin E), are present in extracellular fluids [2, 3]. The concentrations of antioxidants can be measured separately but this is not practical since their antioxidant effects are additive. The sum of endogenous and food-derived antioxidants represents the total antioxidant capacity of the extracellular fluid. The total antioxidant capacity of a sample can be measured, termed the total antioxidant capacity (TAC), which is the sum of endogenous and food-derived antioxidants [4].

Several methods have been developed to measure TAC, and the most common of these methods are the oxygen radical absorbance capacity (ORAC), ferric reducing antioxidant power (FRAP) and the total radical trapping antioxidant potential (TRAP) [5-7]. A FRAP spectrophotometric assay can be performed using the method developed by Benzie and Strain [8]. FRAP is a simple and relatively inexpensive test that measures the ability of antioxidants to reduce ferric iron. At low pH, excess FeIII in the reaction mixture is reduced to the ferrous form and color formation is directly related to the reducing ability of the sample. The results are highly reproducible over a wide concentration range [8].

A microplate adaptation of the FRAP method has been described previously [9]. There are commercially available kits for the FRAP assay, however they are more expensive than in-house kits [10, 11]. We aimed to evaluate a FRAP direct measurement method under our laboratory conditions using a microplate reader and establish reference values to use in future research projects [10, 11].

Methods

All measurements were carried out according to the tenets of the Declaration of Helsinki (2013 Brazil version) of the World Medical Association. This study was approved by the Bursa Yuksek Ihtisas Training and Research Hospital ethics committee, and all participants signed written informed consent forms before the study began.

Microplate Analysis Using Ferric Tripyridyl Triazine

The FRAP assay of Benzie and Strain is based on the principle that at low pH, the ferric tripyridyl triazine (FeIII TPTZ) complex gets reduced to the ferrous form, developing an intense blue color with a maximum absorption at 593 nm.

The FRAP reagent was prepared by mixing 300 mmol/L acetate buffer (pH-3.6), 10 mmol/L TPTZ [2,4,6-tri(2-pyridyl)-s-triazine] solution, and 20 mmol/L $FeCl_3$ solution in a 10:1:1 ratio. All chemicals were purchased from Sigma-Aldrich Ltd. (St Louis, MO). 20 µL of sample (serum or plasma) was mixed with 300 µL of FRAP reagent; after 10 minutes of incubation at 37o C, the ferric tripyridyl triazine (FeIII -TPTZ) complex is reduced to the ferrous tripyridyl triazine (FeII-TPTZ) form in the presence of antioxidants. Absorbance was measured with a Readwell Touch Elisa plate analyzer (Robonik PVT Ltd. Mumbai, India). Known solutions of FeII (FeSO4X7H2O) in the range of 250-2000 µmol/L were used for calibration.

Method Verification Studies

Method verification studies were performed to determine if the assay fulfilled the specified requirements [12].

a) Limit of Detection

The detection limit of the method was determined by evaluating the zero calibrators 20 times. The detection limit was defined as the mean value of the zero calibrators + 3SD.

LOD=Xblank +3 (SD blank) [12, 13].

b) Limit of Blank

Limit of Blank (LoB) was the highest apparent analyte concentration expected to be found when

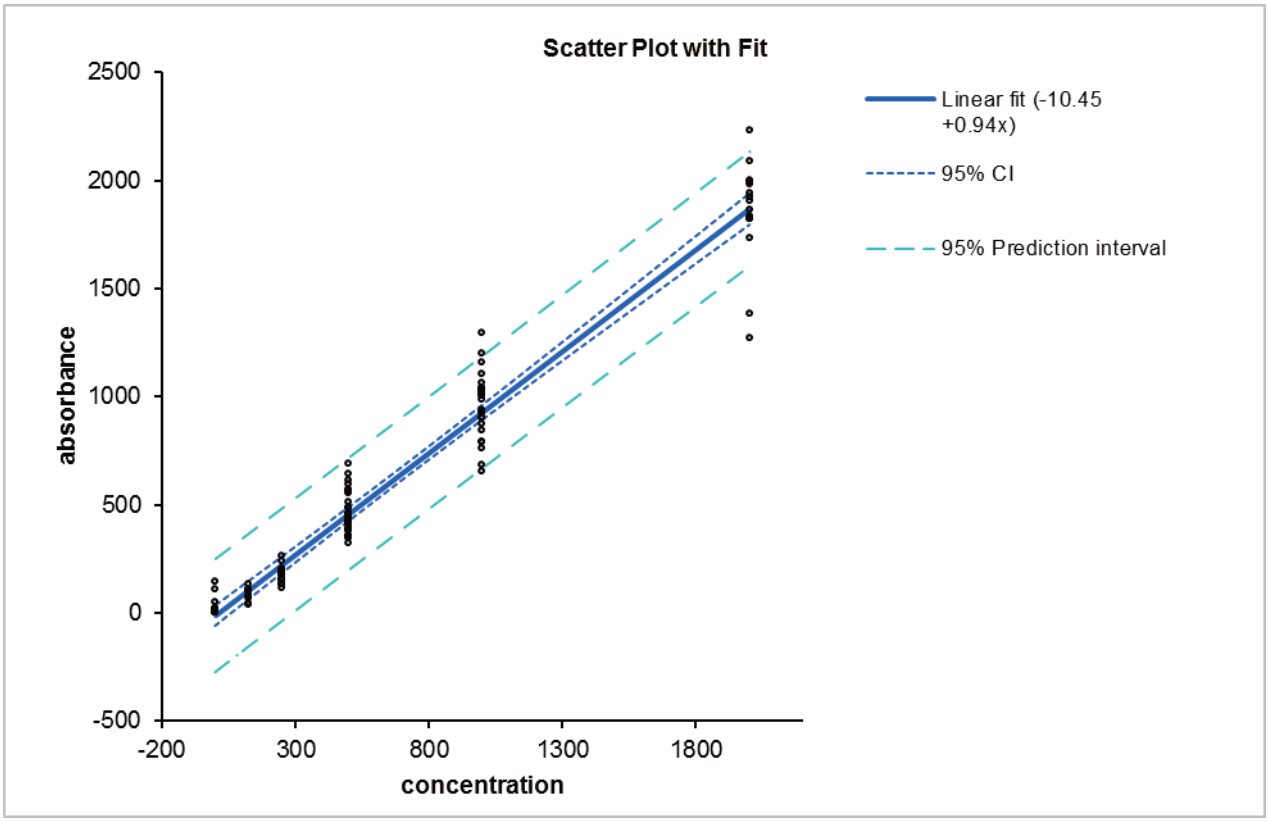

Figure 1. Linear plot of serial dilutions of ferric sulphate solution.

replicates of a sample containing no analyte were tested. LoB was estimated by measuring replicates of a blank sample and calculating the mean result and the standard deviation (SD).
LoB=mean blank +1.645(SD blank) [12, 13].

c) Linearity

Serial dilutions of the 250-2000 µmol/L ferric sulphate solutions were used for linearity analysis (Figure 1).

d) Precision

To evaluate the precision of the study, reproducibility was tested for both samples and standards. All four standards were run in 4 replicates for 20 days to determine the total coefficient of variation (between run) (Table 1). Also, four randomly chosen samples over three days were run in duplicate (Table 2).

e) Recovery of Serum Samples

Recovery was determined with a diluted serum sample having a known high FRAP activity and another with a lower FRAP activity and mixing them in the ratios given in Table 3. Mean recovery was determined in percent (%).

f) Reference Interval

To determine the reference interval for serum TAC, serum specimens from 120 healthy individuals (41 women, 79 men, 25–55 years old) were assayed [14]. They were on an average diet and were nonsmokers, but we have no information on their nutritional habits. Kolmogorov-Smirnov test was used

Table 1. Precision values for the FRAP assay. Sample; standard mean of 20 days 4 times a day

Standard value	Mean (µmol/L)	SD	CV (%)
2000 µmol/L	1923	148	7.6
1000 µmol/L	987	91	9.2
500 µmol/L	489	59	12.0
250 µmol/L	205	38	18.5

CV=coefficient of variation, FRAP=ferric reducing antioxidant power, SD=deviation of standard

Table 2. Intra-day and inter-day precision values for the FRAP assay using patient sample. Sample; human serum mean of 3 assays

TAC	Within-day			Between-day		
	Mean (µmol/L)	SD	CV (%)	Mean (µmol/L)	SD	CV (%)
Sample 1	665	18	2.7	648	44	6.7
Sample 2	1081	41	3.7	1088	86	7.9
Sample 3	473	32	6,7	495	50	10.1
Sample 4	642	23	3.5	615	33	5.3

CV=coefficient of variation, FRAP=ferric reducing antioxidant power, SD=deviation of standard, TAC=total antioxidant capacity

Table 3. Recovery was determined by a diluted serum sample with a known high FRAP activity and another with a lower FRAP activity

Low Sample	High Sample	Observed Concentration	Expected Concentration	Recovery (%)
80%	20%	431 µmol/L	439 µmol/L	99.0
60%	40%	522 µmol/L	562 µmol/L	92.8
40%	60%	646 µmol/L	688 µmol/L	94.1
20%	80%	806 µmol/L	816 µmol/L	98.7
			Mean recovery	96.3

FRAP=ferric reducing antioxidant power

to evaluate variance and normality of the data.

Patients

A total of 30 plasma samples were collected from the patients where blood glucose levels were found to be high. Diabetic patients are well known to have decreased TAC levels [15]. The level of TAC was estimated in all these 30 samples. Low TAC was also provided from chronic kidney failure patients after a renal replacement treatment session [16].

Samples of infants with neonatal icterus were selected as an indicator of high TAC levels [8]. Because it is hard to obtain neonatal serum, leftover serum samples were used for this group [17]. We did not obtain permission from the parents of neonatal patients. Because we do not have access to patients' private information, this research, by definition, would not be human subject research and would not require informed consent from neonates or parents [18].

Results

In the regression analyses with ferric sulphate solutions, the r^2 value was 0.95, the slope was 0.94 ($p<$ 0.001), and the intercept was -10.45. Analytical sensitivity, which is the slope of the calibration line, was 0.94 (Figure 1).

The FRAP assay had a limit of detection of 26.1 µmol/L of antioxidant power and the limit of the blank was 17.2 µmol/L.

The intra-day assay coefficient of variation was 6.7-2.7% and the inter-day reproducibility was between 5.3-10.1% for the samples (Table 2). The intra-day assay coefficient of variation for standards was 7.6-18.5%. Recovery is given as 96.3% (see Table 3).

Human serum samples had FRAP concentrations that ranged from 419 to 1392 µmol/L, with a mean level of 890 µmol/L, a median of 904 µmol/L and showed a normal distribution (Kolmogorov-Smirnov test result, p=0.085) in healthy subjects.

Patient with diabetes (fasting value more than 120 mg/dL, median 167 (inter quartile range: 200) mg/dL) and chronic kidney failure patients after a renal replacement treatment session had FRAP values of 687±193 and 609±250 µmol/L, respectively. In neonatal hyperbilirubinemic patients FRAP values were high; 945±187 µmol/L.

Discussion

In this study, TAC levels in serum were between

419 and 1392 µmol/L using the FRAP method in healthy subjects 25 to 55 years old. Whether FRAP levels varies with gender and with increase in age was not evaluated in this study. Our result is similar to the findings of Karajibani *et al.* [19], who reported a mean value of 789 µmol/L with a SD of 158.5 µmol/L, and Mistry *et al.* [10] who found a median of 741.2 µmol/L (range: 651.6-848.1) with a commercial kit (DetectX FRAP colorimetric detection assay K043-H1, Arbor Assays) in 472 healthy adult women. Benzie and Strain [8] found a plasma FRAP value of 1000±206 µmol/L in 141 apparently healthy Chinese adults and Kumar *et al.* [20] reported a value of 1005±203.23 µmol/L [20].

The level of oxidative indices may differ depending on the ethnicity, as observed in previous investigations [21]. The difference between studies might be associated with different diets. It is known that Mediterranean diet intervention increases plasma the total antioxidant capacity level in subjects [22, 23]. However, we did not question our study population about their eating habits.

In this study, absorbance was measured in an Elisa plate analyzer at 560 nm whereas Benzie and Strain [8] measured the absorbance at 593 nm in a spectrophotometer. As most of the Elisa plate analyzers do not have filters to measure the absorbance at 593 nm, the nearest wavelength of 560 nm was chosen in this study. Thus, the method became applicable and for the commercial Elisa kits 560 nm absorbance was determined as well [10, 11].

The linearity beyond 2000 µmol/L was not determined since none of the data from the healthy volunteers and patients was above 2000 µmol/L, and none of the results were below 288 µmol/L.

Mistry *et al.* [10] reported that with a commercial kit, the workable assay range was 31.25-1000 µmol/L and the inter- and intra-assay coefficients of variation were 9.3 and 4.3%, respectively. Our inter- and intra-assay coefficients of variation were higher [10].

In our study, serum FRAP values were found to be low in patients with diabetes and chronic kidney disease patients after renal replacement therapy with hemodialysis. Previous studies have revealed a significant imbalance of pro-oxidants and antioxidants in patients with CKD and diabetes [15, 16, 19, 24, 25]. It is also well known that bilirubin shows an antioxidant capacity, as in neonatal patients with increased bilirubin levels [26-28].

Conclusions

Our reference values gave results comparable to the literature. This method is simple, reliable, and inexpensive. It could be used for studies of oxidative stress-related diseases.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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Mean platelet volume is increased in patients with chronic hepatitis B

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ABSTRACT

Objectives. Hepatitis secondary to infection with the hepatitis B virus (HBV) is one of the most common causes of viral hepatitis worldwide. Multiple extrahepatic manifestations of HBV infection have been recognized. However, the effect of HBV infection on the mean platelet volume (MPV) is unknown. The aim of this study was to assess the MPV, an indicator of platelet activation, in patients with chronic hepatitis B. ***Methods.*** The study group consisted of 50 patients with chronic hepatitis B. An age, gender, and body mass index-matched control group consisted of 50 healthy volunteers. All patients and control participants underwent echocardiographic examination. We measured the serum MPV values in patients and control participants. ***Results.*** Mean platelet volume was significantly higher among patients with HBV when compared with the control group (9.2±2.2 vs 7.1±1.6 fl, respectively; $p<0.001$). ***Conclusions.*** We have shown that MPV was significantly elevated in patients with chronic hepatitis B compared to control participants. According to our knowledge, there has been no previous study of MPV in chronic HBV patients. Therefore, we have investigated the possible association between HBV infection and MPV.

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Keywords: Platelets; arrhythmia; hepatitis B virus; mean platelet volume; thromboembolism

Introduction

The hepatitis B virus (HBV) infection is a major public health problem worldwide. It is known that chronic HBV infection triggers autoimmune disorders. A strong relationship has been found with essential mixed cryoglobulinemia, glomerulonephritis, and porphyria tarda. Additionally, HBV infection has been associated with extrahepatic involvements such as Sjogren's syndrome, lichen planus, and Hashimato's thyroiditis [1, 2].

Recent studies revealed that the virus has extensive reservoirs of extrahepatic replication. Hepatitis C virus (HCV) and HBV proteins and nucleic acids have been found in a number of non-hepatic tissues including lymph nodes, spleen, bone marrow, kidney, colon, stomach, periadrenal ganglia, skin, thyroid, pancreas, testis, ovaries, brain, heart and lung tissue [3-6]. It is also considered that there is a relation between HBV and HCV and coronary artery

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disease. Conflicting findings on the possible association between HBsAg positivity, indicating inactive HBsAg carrier status, and atherosclerosis have been reported [7, 8]. However, there is no consensus on this issue.

Recent studies suggest that mean platelet volume (MPV) is a potentially useful prognostic biomarker in patients with cardiovascular disease such as acute coronary syndrome, valvular heart disease, pulmonary thromboembolism and hypertension [9-12].

Our present study was conducted to research the effect on MPV among the persons with HBV infection.

Methods

Selection of the patients

50 patients with mean age of 43±13 years, who has been followed in the outpatient clinic of infection diseases department because of the chronic hepatitis B, with normal liver enzymes and who has not received antiviral treatment, are included in the study. The control group was consisted of 50 successive persons, with mean age of 39±13 years who appealed to the cardiology and Infectious disease outpatient clinics because of various reasons and did not have any structural cardiac pathologies identified.

The physical examination, the medical history of patients, complete blood count and the blood biochemistry were evaluated in all groups. The subjects were defined as hypertensive if their blood pressure was ≥140/90 mmHg or if they were receiving any antihypertensive medication. Diabetes mellitus was defined as the presence of a history of antidiabetic medication usage or fasting glucose level above 126 mg/dl. Smoking status was classified as smokers or those who never smoked.

Patients with coronary artery disease, heart failure, valve disease, cardiomyopathy, hypertension, diabetes mellitus, chronic lung disease, thyroid dysfunction, anemia, malignancy, renal and hepatic insufficiency, chronic inflammatory disease, pregnancy, septicemia, cerebrovascular accident, and thrombocytopenia were excluded from the study. All of the patients were in sinus rhythm and none of them were taking cardioactive medications like antiarrhythmics, antiplatelet, antipsycotics, and antihistaminics. Each patient signed an informed consent form and the local ethics committee approved the study.

For the analysis of MPV, blood samples with K3 EDTA were analyzed after one hour of venipuncture by the Sysmex XT-2000i analyzer (Sysmex, Kobe, Japan).

Echocardiographic Measurements

Two-dimensional, M-mode, pulsed and color flow doppler echocardioagraphic examinations of all subjects were performed by the same examiner with a commercially available machine (Vivid 7 pro, GE , Horten, Norway, 2-5 mHz phased array transducer). During echocardiography, a single-lead electrocardiogram was recorded continuously. M-mode measurements were performed according to the criteria of the American Society of Echocardiography [13,14]. The right atrium , left atrium (LA) diameter, LV end-systolic and end-diastolic diameters were measured. LV ejection fraction (EF) was estimated by Simpson's rule.

Statistical Analyses

The SPSS 16.0 statistical program (SPSS, Chicago, IL, USA) was used for the statistical study. Data were expressed as mean±standard deviation (SD). Student t-test, one-way ANOVA- and chi-square test were used to compare the variables. P value of less than 0.05 was considered significant.

Results

There was no statistically significant difference between patient group and the control with regard to age, gender, diameters of the left atrium, right atrium and the left ventricle, pulmonary artery systolic pressure, body mass index and smoking status (Table 1). Additionally, there were no significant differences between the two groups with regard to lipid profile, fasting glucose levels, creatinine, white and red blood cell and platelet counts. However, MPV was found to be significantly higher in patients with HBV infection (9.2±2.2 fl vs 7.1±1.6 fl, $p<0.001$, Table 2).

Discussion

The present study showed that MPV was significantly higher in patients with chronic HBV infection compared to controls.

Recently, it has been emphasized the importance

Table 1. Comparison of clinical and echocardiographic features of HBV patients and controls group

	Patients (n=50)	Controls (n=50)	*p*
Age (years)	43.0±13.0	39.0±13.0	0.26
Male/female	19/31	22/28	0.20
LA diameter (mm)	33.5±3.5	34.2±3.6	0.69
LV EDD (mm)	45.2±4.2	44.2±4.5	0.24
LV ESD (mm)	23.4±2.1	24.4±2.7	0.61
RA diameter (mm)	37.6±3.8	32.8±3.0	0.48
LVEF (%)	64.0±5.2	64.8±5.9	0.33
BSA (m2)	1.8±0.4	1.8±0.3	0.25
Heart rate (bpm)	78.1±8.2	69.3±8.3	0.12
SPAP (mmHg)	28.8±3.9	25.4±3.4	0.19
SBP (mmHg)	127±25	122.5±24	0.66
DBP (mmHg)	72.5±9	79.3±12	0.88
BMI (kg/m2)	28±4.9	24±3.1	0.52
Smoking	11	12	0.70

BMI=body mass index, BSA=body surface area, DBP=diastolic blood pressure, HBV=hepatitis B virus, LA=left atrium, LVEDD=left ventricular end-diastolic dimension, LVEF=left ventricular ejection fraction, LVESD=left ventricular end-systolic dimension, RA= right atrium, SBP=systolic blood pressure, SPAP= systolic pulmonary artery pressure,

Table 2. Comparison of biochemical and hematological parameters of HBV patients and controls group

	Patients (n=42)	Controls (n=50)	*p*
Glucose (mg/dl)	98.2±13.0	93.5±11.0	0.53
Creatinin (mg/dl)	0.8±0.2	0.75±0.3	0.28
Total cholesterol (mg/dl)	201.0±55.0	195.0±52.0	0.17
Trigliserid (mg/dl)	132.0±25.0	125±23	0.86
HDL- holesterol (mg/dl)	42.0±7.0	44.2±7.5	0.22
White-blood cell count ($x10^3/mm^3$)	7.9±2.8	8.6±2.6	0.23
Hemoglobin (g/dl)	14.1±2.6	13.3±2.2	0.41
Platelet count ($x10^3$)	265.4±63.4	282.3±89.3	0.65
Mean platelet volume (fl)	9.2±2.2	7.1±1.6	<0.001

dl=deciliter, fl=femtolitre, HBV=hepatitis B virus, HDL=high density lipoprotein

of HCV infection in myocarditis and cardiomyopathy. HBV and HCV has been associated with atherosclerosis and HBV sero-positivity in the patients with coronary artery disease was found to be related to cardiac failure and increased mortality [15, 16].

Matsumori *et al.* [6] found anti-HCV positivity in 10.6% of the patients with hypertrophic cardiomyopathy and in 6.3% of the patients with dilated cardiomyopathy. Additionally, they found arrhythmia in 21.5% of anti-HCV positive patients; hence, the authors suggested that HCV might play a role in several cardiac disorders with formerly unidentifiable etiology.

In our previous study, an association was also found between HBV infection and the left and right ventricular dysfunction [17]. There are some conflicting studies in the literature about the relation between HBV/HCV and atherosclerosis and coronary

artery disease [7, 8,18].

Wang *et al.* [19] found higher NT-proBNP levels, increasing with the heart failures in the HBV/HCV patients not having liver failure, in comparison with the control group. Similarly, Kucukazman *et al.* [20] found higher BNP levels in asymptomatic hepatitis B virus positive patients. According to this situation, it is considered that both HBV and HCV infections may increase heart failure. Despite a large number of studies done about the relation between cardiomyopathy, myocarditis and heart failure, the data about cardiac effects of HBV is limited.

Recent studies suggest that MPV is a potentially useful prognostic biomarker in patients with cardiovascular disease such as acute coronary syndrome, valvular heart disease pulmonary and systemic thromboembolism and hypertension [21]. However, relationship between MPV and chronic HBV infection is not defined.

The present study showed that MPV was significantly higher in patients with chronic HBV infection compared to controls. It is known that platelets having dense granules are more active biochemically, functionally, and metabolically and are a risk factor for developing coronary and pulmonary thrombosis, leading to myocardial infarction. In previous studies, increased MPV was demonstrated in acute myocardial infarction [22, 23], mitral and aortic stenosis [9, 10], deep vein thrombosis [11], and hypertension [12].

The Limitation of the Study

The most significant limitation of our study was the insufficient number of patients. The other limitation of our study was the method, so it was not prospective.

Conclusions

In conclusion, our findings show that MPV is increased in patients with chronic HBV infection, compared to controls. The increased MPV may predict the possible increase of the prevalence of cardiovascular events in patients with HBV. Further prospective studies are required to establish the clinical significance of increased MPV and to investigate the role of anti-platelet agents in chronic HBV patients.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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The effect of maternal parameters on umbilical artery blood gas values and neonatal well-being in singleton pregnancies

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ABSTRACT

Objectives. Umbilical cord blood analysis for assessment of the newborn's acid-base status soon after birth is the most objective way of evaluating the fetal metabolic condition at delivery. We researched the effects of maternal age, multiple gestation, fetal heart rate, gestational age, parity, delivery mode and total duration of labor on fetal well-being as assessed by umbilical cord blood gas parameters. ***Methods.*** Prospective study conducted on 67 singleton pregnant women and their off-spring. Maternal age, multiple gestation, fetal heart rate (FHR), gestational age, parity, delivery mode and total duration of labor were recorded. Umbilical artery blood samples were collected at birth. A blood gas analysis was performed on each collected sample. The relationship between maternal parameters and umbilical cord arterial blood gas were investigated. ***Results.*** We found positive correlation between pH and gravida and parity (p=0.026, p=0.049, respectively), whereas negative correlation between total duration of labor and O2 saturation (p=0.033). Base deficit was negatively correlated with gravida and parity (p=0.025, p=0.011, respectively). In linear regression models, FHR and gravida were a significant predictor of pH value (p=0.029 and p=0.040, respectively). ***Conclusions.*** We found no association between maternal age, gestational age, gravida, parity and duration of labor and neonatal acidemia. Thus, maternal age, gestational age, gravida, parity and duration of labor may not be at increased risk of perinatal morbidity. However, the elevation of FHR was related with an increased risk of neonatal morbidity.

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Keywords: Blood gas analysis; umbilical; newborn; outcome; neonatal well-being; maternal parameters

Introduction

Mortality rates in the perinatal period are used to assess the outcome of pregnancy and monitor the quality of perinatal care. The perinatal mortality rate encloses late fetal and early neonatal mortality. Maternal factors that increase the risk of infant mortality include extremes of maternal age, smoking, unmarried status, multiple gestation, prior stillbirth, ethnicity, gestational age, and multi-fetal pregnancies [1-6]. Among term infants, the important causes of neonatal death were asphyxia, infection, congenital

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malformations, prematurity and sudden infant death syndrome (SIDS) [3].

Umbilical cord blood analysis for assessment of the newborn's acid-base status soon after birth is the most objective way of evaluating the fetal metabolic condition at delivery. There is no consensus concerning indications for umbilical cord blood acid-base analysis post delivery.

The effects of maternal parameters on umbilical cord blood gases have been poorly investigated. In this study, we investigated the effects of maternal age, multiple gestation, fetal heart rate (FHR), gestational age, parity, delivery mode and total duration of labor on fetal well-being as assessed by umbilical cord blood gas parameters.

Methods

This prospective study was conducted in the Department of Obstetrics and Gynaecology, Turgut Ozal University, School of Medicine, Ankara, Turkey. The study protocols were approved by the institutional ethics board of Turgut Ozal University and conducted in medical faculty hospital. After informing the patients, informing consent form was obtained. Infants with maternal history of preeclampsia, eclampsia, infection, hypertension, diabetes, congestive heart failure, chronic kidney disease, chronic respiratory disease and prematüre rupture of membranes were not icluded in the study. Infants with hypoxic ischemic encephalopathy, sepsis, respiratory distress syndrome, vacuum extraction delivery, preterm birth and congenital abnormality were excluded from the study. We recorded the following obstetrical characteristics; maternal age, gestational age at birth, birth weight, parity, mode of delivery (vaginal, instrumental, cesarean section), FHR, and total duration of labor. Gestational age was described as the number of completed weeks of gestation based on an ultrasound screening examination conducted between gestational weeks 18 and 20 as identified by the date of the last normal menstrual period. The neonatal mortality rate (NMR) was defined as the number of neonatal deaths during a year, divided by the number of live births during the same year, expressed per 1000 live births. Perinatal mortality rate (PMR) was defined as the sum of fetal deaths (≥20 weeks gestation) plus neonatal deaths (i.e., deaths within the first 28 days of birth) during a year divided by the sum of live births plus late fetal deaths during the same year, expressed per 1000 live births plus late fetal deaths.

The samples were drawn from the umbilical arteries by a 0.9-mm needle puncture with minimal manuplation of the cord. A trained person applied this procedure within 4-5 seconds. Each blood gas sample was collected in individual 2 ml preheparinised plastic syringes prepared and a minimum of 0.5 ml of blood from the umblical artery, immediately transported on ice to the laboratory, was used for analyses of umbilical blood pH, PCO_2, PO_2, bicarbonate (HCO_3^-) and base deficit, in a blood gas analyser (ABL 735; Radiometer A/S, Copenhagen Denmark). All samples were taken by the same investigator and analysed according to the manufacturer's recommendation.

Statistical Analysis

SPSS version 16.0 (SPSS, Chicago, IL, USA) for Windows program was used for statistical analyses. Shapiro-Wilk test was used to determine normal distribution. Descriptive statistics were presented as median (minimum-maximum) for not normally distributed data, and as counts and percentages for categorical data. Mann-Whitney test was used for data not normally distributed. Spearman correlation analysis was used to evaluate relationship between parameters. Linear regression analysis was performed to evaluate whether any maternal parameters could potentially predict blood gas values. Multiple logistic regression analysis was performed to assess whether any maternal parameters could predict pH<7.20 value. The statistical significance level was set at $p<0.05$.

Results

A total 67 pregnant women and their offspring were enrolled in the study. Median age, gravida, parity and gestational age were 26 years (range 17-38 years), 2 (range 1-6), 1 (range 1-4), and 39.4 weeks (range 37.0-41.3 weeks), respectively. In correlation analysis, there was positive moderately correlation between pH and gravida and parity ($p=0.026$, $p=0.049$, respectively), whereas negative correlation between total duration of labor and O_2 saturation ($p=0.033$) (Table 1). Base deficit was negatively correlated with gravida and parity ($p=0.025$, $p=0.011$, respectively). In addition, there was positive correlation between HCO_3^- and parity ($p=0.023$) (Table 1).

In linear regression models, FHR and gravida

Table 1. The correlation analysis results between cord blood gases and obstetric data

		pH	pCO_2	O_2 sat	HCO_3^-	BD
Age	Rho	0.035	0.115	-0.003	0.223	-0.151
	p value	0.781	0.356	0.979	0.087	0.227
Gravida	Rho	**0.274***	-0.066	0.086	0.241	**-0.275***
	p value	**0.026**	0.598	0.501	0.063	**0.025**
Parity	Rho	**0.243***	-0.043	0.091	**0.293***	**-0.311***
	p value	**0.049**	0.729	0.474	**0.023**	**0.011**
Gestational age	Rho	-0.151	0.101	-0.125	-0.076	0.157
	p value	0.252	0.445	0.355	0.587	0.234
FHR	Rho	-0.225	0.161	0.060	0.017	0.043
	p value	0.070	0.197	0.636	0.894	0.734
Total duration of labor	Rho	-0.204	0.093	**-0.302***	-0.159	0.170
	p value	0.151	0.517	**0.033**	0.296	0.234

BD=base deficit, FHR=fetal heart rate, Rho=Sperman's correlation analysis (correlation coefficient)

were a significant predictor of pH (p=0.029 and p=0.040, respectively). Moreover, in linear regression models, an increase in gravida was a predictor of increase in pH value, whereas an increase in FHR was a predictor of decrease in pH. The effect of the other parameters were not significant (p>0.05) (Table 2).

No any factor was found to be effective in predicting patients with pH below 7.20 levels when pH limit is taken as 7.20 (p>0.05) (Table 3). Patients were divided into two groups according to pH values as ≥7.20 and <7.20. There was no significant difference between groups in terms of numerical data (p>0.05) (Table 4). When the investigation carried out with categorical data, no difference were detected between groups with pH above and below 7.20, in terms of induction, type of delivery, the presence of meconium and variability factors (p=0.717, p=0.567, p=0.425 and p=0.417, respectively) (Table 5).

Discussion

The effects of maternal parameters during pregnancy on the fetus have always been worrying. Maternal parameters may cause fetal hypoxia, leading to changes in umbilical arterial blood gas. There are scarce studies that investigating relationship between maternal age, gestational age, gravida, FHR, parity

Table 2. Linear regression analysis results for maternal factors that may affect pH values

	Unstandardized Coefficients		Standardized Coefficients		
	Beta	**SE**	**Beta**	**t**	***p***
Constant	70.849	0.396		190.806	**<0.001**
Age	0.000	0.002	-0.080	-0.435	0.666
Gravida	0.015	0.007	0.292	20.120	**0.040**
Parity	-0.015	0.029	-0.268	-0.533	0.597
Gestational age	-0.004	0.008	-0.079	-0.541	0.591
Total duration of labor	-0.002	0.005	-0.086	-0.516	0.608
FHR	-0.003	0.001	-0.311	-20.254	**0.029**

FHR=fetal heart rate, SE=standard error

Table 3. Logistic regression analysis results for parameters that may affect pH <7.20 levels

	B	SE	*p*	Exp(B)
Group	-0.195	10.112	0.861	0.822
Age	-0.006	0.126	0.963	0.994
Gravida	-0.336	10.403	0.811	0.715
Parity	0.448	10.401	0.749	10.565
Gestational age	-0.372	0.465	0.423	0.689
FHR	-0.116	0.081	0.149	0.890
Labor	-0.951	10.244	0.445	0.386
Total duration of labor	-0.211	0.229	0.356	0.810
Delivery mode	0.707	10.631	0.664	20.029
Constant	10.897	0.438	**<0.001**	60.667

Exp (B)=the ratio of hazard rates, FHR=fetal heart rate, SE=standard error

Table 4. The comparison of groups at pH below and above 7.20 levels

	Age	Gravida	Parity	FHR	Gestational age	Total duration of labor
***p* values**	0.800	0.629	0.649	0.172	0.468	0.847

FHR=fetal heart rate

Table 5. The comparison of categorical data in groups at pH below and above 7.20 levels

		<7.20	≥7.20	*p*				<7.20	≥7.20	*p*
Induction	Count	3	23	0.717	Labor	C/S	Count	1	11	0.567
	%labor	11.5	88.5				%delivery mode	8.3	91.7	
	%pH 7.20	33.3	39.7				%pH 7.20	11.1	19.0	
	% of Total	4.5	34.3				% of Total	1.5	16.4	
Spontaneous	Count	6	35			NSVD	Count	8	47	
	%labor	14.6	85.4				%delivery mode	14.5	85.5	
	%pH 7.20	66.7	60.3				%pH 7.20	88.9	81.0	
	% of Total	9.0	52.2				% of Total	11.9	70.1	

		<7.20	≥7.20	*p*				<7.20	≥7.20	*p*
Meconium (-)	Count	4	34	0.425	Variability	Little	Count	0	4	0.417
	%group	10.5	89.5				%variability	.0	100.0	
	%pH 7.20	44.4	58.6				%pH 7.20	.0	6.9	
	% of Total	6.0	50.7				% of Total	.0	6.0	
Meconium (+)	Count	5	24			Normal	Count	9	54	
	%group	17.2	82.8				%variability	14.3	85.7	
	%pH 7.20	55.6	41.4				%pH 7.20	100.0	93.1	
	% of Total	7.5	35.8				% of Total	13.4	80.6	

C/S=caesarean section, NSVD=normal spontaneous vaginal delivery

and duration of labor and umbilical arterial blood pH, PCO_2, PO_2, bicarbonate and base deficit in an uncomplicated singleton pregnancies. We found positive correlation between pH levels and gravida and parity. In current study, base deficit was negatively correlated with gravida and parity. There was positive correlation between HCO_3^- and parity, whereas negative correlation between total duration of labor

and O_2 saturation. Moreover, an increase in gravida was a predictor of increase in pH value, whereas an increase in FHR was a predictor of decrease in pH value.

Intrapartum evaluation of umbilical cord arterial blood gas values is a decisive method of diagnosis in birth management. Moreover, as a retrospective idea about fetal well-being during delivery, it contributes to the management of the neonatal term and to decisions about possible attempts at neonatal resuscitation in this term. Umbilical cord blood gas measurement conducted at delivery is an objective indicator of fetal acid-base balance, and it is also accepted as the fetal response to birth [7]. When the umbilical cord arterial blood pH value is ≤7.20, the condition is described as fetal acidosis; however, a pH≤7.0 is considered pathological acidosis. In term neonates born with an umbilical cord arterial blood pH>7.0, no increase has been noted in long-term morbidity [8]. The metabolic component of fetal acidemia (base deficit and bicarbonate) is the most important variable for predicting neonatal morbidity. The results of a study showed that moderate and severe newborn encephalopathy, respiratory complications, and composite complication scores >3 were enhanced in newborns with an umbilical artery base deficit greater than 12 to 16 mmol/L compared to those with lower base deficits [9]. A base deficit higher than or equal to 12 mmol/L proposes metabolic acidosis and is related with an elevated risk of neonatal morbidity. Umbilical artery PO_2 and O_2 saturation are not predictive of any neonatal morbidity.

Older maternal age is related with an elevated risk of stillbirth in both nulliparous and multiparous women [10, 11]. Large scale studies propose that an elevated risk of unexplained stillbirth late in pregnancy persists in older women, even after controlling for risk factors such as hypertension, diabetes, placenta previa and multiple gestations [11-13]. Moreover, there seems to be an interaction between first birth and advanced maternal age that places primiparous older women at an elevated risk [11]. In a recent study, a significant relationship was reported between advanced maternal age and an increased likelihood of a caesarean section irrespective of parity [14]. Salem Yaniv *et al.* [15] investigated the perinatal outcomes in elderly nulliparous women and showed a significant linear association between advanced maternal age and adverse perinatal outcome. Prematurity is an important contributor to neonatal and infant mortality. PMR and NMR rise with reducing gestational age in premature infants. Multiple gestations are a powerful risk factor for neonatal mortality.

FHR accelerations and variability are reassuring findings that propose the fetus is neither hypoxemic nor acidotic. The parasympathetic nervous system applies a progressively higher influence on FHR as gestational age advances. FHR variability is infrequently present before 24 weeks of gestation, while the absence of variability is abnormal after 28 weeks of gestation since the parasympathetic nervous system is consistently developed by the third trimester. Absent variability with any of the following FHR changes is predictive of abnormal fetal acid-base status [16].

The Limitations of the Study

Limitations in this study should be noted. This was a cross-sectional study; thus, we were unable to determine effects of maternal parameters on long term neonatal outcomes. Another limiting factor of our study was that a cord venous blood gas analysis was not determined. However, in the case of fetal acidemia and hypoxia, changes first appear in umbilical arterial blood gases. In addition, when umbilical cord venous blood gas values are at normal levels, acidemia may happen in the umbilical artery [17]. Hence, in current study, umbilical arterial blood gas parameters were analyzed.

Conclusions

We found no association between maternal age, gestational age, gravida, parity and duration of labor and neonatal acidemia. Our results suggest that maternal age, gestational age, gravida, parity and duration of labor may not affect fetal well-being in patients with no comorbidities such as gestational diabetes or hypertension. We found that only elevated FHR is related with an increased risk of neonatal morbidity.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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Occupational-related chemical ocular injuries: an analysis of 82 patients

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ABSTRACT

Objectives. To investigate the characteristics of occupational chemical eye injuries. ***Methods.*** Medical records of patients, who were registered to hospital officially as occupational chemical eye injuries between January 2010 and December 2013, were reviewed. The age, gender, injured eye, chemical agent, nature of the chemical, ocular findings, emerging complications and the information whether the patients knew the chemical agent causing the injury was recorded. ***Results.*** One hundred one eyes of 82 patients (2 women, 80 men) were included in the study. The mean age of the patients was 32.9±8.6 years (range: 19-59 years). Injury was bilateral in 19 patients. Chemical agents were not known by 53% of the patients. The most known agents were caustic agents (23%). Sulfuric acid (9%) and calcium hydroxide (4%) were other known chemical agents. The most common injury was superficial punctate epitheliopathy. Ten eyes of 9 patients had corneal edema. This injury was caused by acidic agents in 5 and alkaline agents in 3 patients. Corneoscleral perforation accompanied by chemical injury in one patient with car battery explosion. ***Conclusions.*** Most of the workers, who had eye injuries with chemicals, do not know the nature of chemical agent which caused the injury. Ocular morbidities may be decreased with the education of the workers about chemicals, working environment and protective measures.

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Keywords: Accidents; cccupational; eye injuries; burns; chemical

Introduction

Occupational related ocular injuries are one of main causes of blindness and visual impairment. One of these injuries is chemical burns of the ocular surface [1]. Ocular chemical burns may lead to financial and psycological problems for both individual and society, due to labor force loss besides long period of treatment and rehabilitation [2]. According to data of Turkish Statistical Institue (TSI), 2.3% of the workers had occupational injuries in 2013; and as a result of these injuries 65% of the workers had been away from work, or could not return to work.

A study from middle Anatolia showed that 3% of the patients that referred to the emergency because of

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burns were chemical and all of them were work related [3]. In USA, 2.4% of the all occupational injuries are eye injuries, and 0.045% of them are chemical burns in private sector[4]. A study from Turkey reported that 42% of the amniotic membrane transplantation, and 17% of the penetrating keratoplasty because of corneal perforation were performed in patients with chemical ocular injury [5, 6]. Ocular chemical burns are important public health problems, however in Turkey, this subject has not been studied in detail. In this study, we investigated characteristics of patients, who were registered to hospital officially as occupational chemical eye injury; characteristics of the injuries and chemicals, and knowledge of the patients about chemicals.

Methods

Medical records of patients, who were registered to emergency or ophthalmology department for occupational chemical eye injury between January 2010 and December 2013, were reviewed. One-hundred one chemical ocular injuries were included in the study. Age of patients, gender, chemical agent that caused injury (if the patient knows), ocular findings, ocular complications, knowledge of the patient about chemical and pH that they were exposed to were noted. This retrospective study was conducted in accordance with the Declaration of Helsinki.

Results

Total 82 patients (2 women, 80 men) were included in the study. Ocular chemical burns were 17.2% of all occupational eye injuries. The right eyes were injured in 35 patients, the left eyes in 28 patients, and both eyes in 19 patients. Mean age of the patients was 32.9±8.6 (range: 19-59) years.

In all cases, ocular surface irrigation with saline or ringer lactate solution was performed at emergency department. According to severity of cases, artificial tears, topical antibiotics, cycloplegic drugs and preservative free steroids were prescribed. In severe cases who required hospitalisation, 10% solutions of Na-citrate, Na-ascorbate and N-acetylcysteine were added to the treatment . The patient with corneoscleral perforation underwent primary repair.

Distribution of the patients according to age groups are given in Table 1. Fifty-nine percent of the patients under 30 years old were unaware of the content of the chemical agents. The unawareness of patients about the content of chemical agent was 61% in patients over 60 years old.

Table 1. Distribution of patients according to age groups and the rates of the awareness of patient about the content of chemical agent

Age (year)	n (%)	Awareness rate (%)
< 20	2 (2.5)	50
20-29	32 (39)	59
30-39	30 (36.5)	40
40-49	16 (19.5)	69
50-59	2 (2.5)	100

n=number of the patients

Totally, 35% of the patients did not know how they had been injured, and 52% of them did not know which chemical agent had caused the injury. Mostly known causes for injuries were sodium hydroxide (NaOH) or potassium hydoxide (KOH). The informations about the industrial sectors of the fifty-three patients were avaible. The industrial sectors in which the chemical eye injuries occur are shown in Table 2. The chemical contents of the agents that caused the injury are given in Table 3.

Table 2. Industrial sectors that chemical eye injuries are frequently encountered

Industrial Sector	n (%)
Cleaning	21 (39.6)
Paint and coating	12 (22.6)
Automotive and machine	9 (17)
Gas	6 (11.3)
Construction	3 (5.7)
Food	2 (3.8)

n=number of the patients

Table 3. Chemical contents of agents that caused chemical ocular injury

Chemical content	n (%)
NaOH or KOH	19 (48.7)
H_2SO_4	7 (17.9)
$Ca(OH)_2$	3 (7.7)
HNO_3	2 (5.1)
CN	1 (2.6)
NH_3	1 (2.6)
Organic acid	4 (10.3)
Cyanoacrylate	2 (5.1)

n=number of the patients

The most common ocular findings were superficial punctate epithelyopathy (68%) and conjuctival hyperemia (23%) at initial examination. Two eyes of the 2 patients were injured by battery explosion; one of them had corneoscleral perforation, and the other had hyphema.

Twenty-seven eyes of the 19 patients had conjunctival hyperemia and 14 eyes of the 9 patients had chemosis at initial examination. Seventy eyes of the 56 patients had superficial punctate epitheliopathy or minimal epithelial defect was observed. Nine eyes of 6 patients had total epitheliopathy and 10 eyes of 9 patients had corneal edema.

Discussion

Chemical injuries of the eyes are one of the ophthalmic emergencies and can cause extensive damage. These injuries are mainly encountered in industrial areas [7]. Our department also serves as a reference hospital in one of most important industrial zones of Turkey. In developed countries, the rate of such injuries is low; however in developing countries it is increasing. A study conducted in the United Kingdom, the incidence of serious chemical eye injury was 0.02 per 100 thousand people [8]. Another study from China reported that ocular chemical burns are 1.2-1.7% of all burns, and 33% of the entire chemical burns involved eyes [9]. In a study conducted in Turkey, 2% of severe ocular trauma injuries that require hospitalization are chemical injuries [10]. A study from Singapore noted that 15% of all ocular traumas were chemical burns [1]. In this study, we report that 17.2% of all occupational injuries are ocular chemical burns. Other studies, in accordance with our study, have shown that men were exposed to chemical injury more than women [7, 11, 12].

The most important factor affecting the prognosis in chemical injuries of the eye is the amount and duration of contact of the chemical with the eye [13, 14]. Rapid removal of the chemical and debris from the eye by intensive washing affect outcomes [11]. In this study, it could not be possible to obtain information about duration and amount of the irrigation to the affected eye.

Chemical injuries are two types: acid and alkaline [7]. Alkaline can be found frequently in the context of the detergent used in the home, so usually alkaline injuries are more common than acid injury [12]. We have found that acid and alkaline chemical burn rates are similar in our study. This result may be related with our study group whose injuries were occupation related.

A study in United Kingdom reported that 63% of the chemical eyes injuries are occur in work places. This ratio is 61% in Germany [11, 12]. A recent study from China reported that 86% of the all chemical burns had occurred in work places, and ocular burns had accompanied 10% of them [15].

Sulfuric acid is one of the most common causes of acid burns and usually does not cause very serious damage to the ocular surface. However especially battery explosions may lead to thermal burn besides penetrating trauma of the eye by foreign body [16]. In this study, we noticed that 7 patients were injured with sulfuric acid, and one of them had penetrating eye injury.

The most serious alkaline injury occurs with ammonia. The other agents are potassium hydroxide and sodium hydroxide [16]. While the most important cause of work-related alkaline burn is calcium hydroxide in developed countries, caustic agents are mostly responsible for the burns in developing countries [7, 17, 18]. In our study, injury with ammonia was noted only in one case. However, most frequent injuries were caused by potassium hydroxide and sodium hydroxide.

The age range in which the occupational injuries mostly occur was 18-39 years with the peak at 30-34 years according to 2013 data of the Ministry of Labor and Social Security in Turkey. In our study, the mean age was in accordance with the above data. In previous studies, it has been shown that the ocular chemical burns occur usually between 20-40 years of age [19]. Our study was compatible with the literature with regard to gender and age distribution.

According to our age groups, 59 percent of the patients under 30 years old were unaware of the content of the chemical gents. The unawareness rate was 40% between 30-39 years and 61% for the patients over 60 years old. These findings suggest that the employees do not the content of the chemical agents that they work with. We think that these results may be related to being inexperienced in younger age groups, while it may be related to increased self-confidence in older age groups.

Our study suggests that chemical ocular injuries constitute an important part of work-related injuries. The occupational injuries are not evenly distributed among the regions in Turkey and the registered data are lacking [20]. Since the number of unregistered employees in Turkey according to June 2014 data is 36% and Bursa is the second city after Istanbul in which most of the occupational injuries occur, we estimate that the real number of injuries may be far more than the available data.

Conclusions

The chemical ocular injuries may be prevented by increasing the awareness of the employees about their working conditions, the chemical agents that they work with and preventive measures (mask, goggles etc). Ocular morbidities may be minimised by educating employees about what they should do immediately in case of ocular injury and the the financial and moral burden on individuals and the society may be lessened. The emloyees should be educated about the properties of the chemical agents that they are exposed to. The gain of experience in prevention of the injuries are among the important factors, but extreme self confidence may have a negative impact.

Conflict of interest

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Cardiac surgery in patients with essential thrombocytosis: a report of three cases

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ABSTRACT

Essential thrombocytosis has been classified as a chronic myeloproliferative disorder. Patients with essential thrombocytosis undergoing cardiac surgery are at increased risk for bleeding and thrombosis. However, the incidence and treatment for this condition are not well known. There are profound implications of essential thrombocytosis in patients undergoing cardiac surgery with the use of cardiopulmonary bypass, where heparin is used for anticoagulation. We want to present successful cardiac surgery in three patients with essential thrombocytosis. Patients received hydroxyurea and antiagregant treatment preoperatively and the thrombocyte counts were lowered to reference ranges. There were no cardiac or systemic complications due to essential thrombocytosis during the postoperative period.

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Keywords: Cardiopulmonary bypass; essential thrombocytosis; cardiac surgery

Introduction

Essential thrombocytosis may cause life threatening complications such as thrombosis or bleeding, particularly in older patients or in patients with high cardiovascular risk factors [1]. There are no brief guidelines for patients with essential thrombocytosis undergoing cardiac surgery [2]. Patients with essential thrombocytosis may suffer intraoperative and postoperative thrombosis or postoperative uncontrollable bleeding, however incidence and therapeutic options of these risks are not well known [3]. Therefore, it is a matter of concern for cardiac surgeons to use cardiopulmonary bypass, heparin and anticoagulation in these patients. These concern increases particularly due to the use of warfarin following valve surgery [3]. In this text, we present three cases with essential thrombocytosis, mitral valve replacement was performed in one patient and coronary bypass grafting was performed in two patients.

The presentation of the patients

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Case 1

A 70-year-old female patient with chronic atrial fibrillation, severe mitral valvular stenosis and mitral valvular insufficiency admitted to our institution for mitral valve replacement. The patient had a blood thrombocyte count of 1.100.000/mm^3 and splenomegaly. The patient was being followed by an hematology clinic for two years and she had a history of cerebrovascular disease. The blood levels of uric acid and lactate dehydrogenase (LDH) were 12 mg/dl and 800 U/L respectively. The results of other blood tests including cardiac enzymes, troponins, hepatic and renal function tests and international normalized ratio (INR) were in normal ranges. Hydroxyurea therapy was administered for one week preoperatively after consultation of hematology clinic and blood thrombocyte count was lowered to 350.000/mm^3. Because of not being suitable for mitral valve repair the patient underwent a mitral valve replacement after thrombocyte count reached to the reference range. Mitral valve replacement with a mechanic valve and radiofrequency ablation for chronic atrial fibrillation were applied. The patient who had 650 ml drainage postoperatively and no complications, was followed up with low molecular weight heparin (LMWH) in postoperative period. LMWH was stopped upon INR values reached 2.5 and the patient was discharged with warfarin, hydroxyurea and acetylsalicylic acid therapy on the 7th postoperative day. At 6−year follow-up, the patient showed no signs of thrombohaemorrhagic and microvascular complications.

Case 2

A 66-year-old male patient who admitted with exertional chest pain had a history of smoking, diabetes mellitus, hypertension, hyperlipidemia and positive family history as coronary risk factors. Anterior and apical ischemia was detected in myocardial perfusion scintigraphy. Coronary angiography revealed a 90% stenosis at the left main, 80% stenosis at the circumflex coronary artery and total occlusion at the right coronary artery. On physical examination there was a splenomegaly. The patient had normal regular blood test values including inflammatory markers, however he had thrombocyte count of 1.500.000/mm^3. After the diagnosis of essential thrombocytosis by the haematologist, hydroxyurea therapy was started preoperatively. Blood thrombocyte count of the patient decreased to 400.000/mm^3 following one week of medical therapy. The patient underwent a successful three vessel coronary bypass grafting with cardiopulmonary bypass. The patient had a total drainage of 1000 ml in the first postoperative day. And after aprotinin administration in this patient postoperative course was uneventful . The patients postoperative medication was LMWH and acetylsalicylic acid and was discharged with oral hydroxyurea and acetylsalicylic acid therapies on his 8th postoperative day. At 6−month follow-up, the patient showed no signs of thrombo-haemorrhagic and microvascular complications or angina.

Case 3

A 46-year-old male patient who had obesity and smoking as risk factors admitted to coronary angiography with unstable angina pectoris. Coronary angiography revealed 70% stenosis in the left anterior descending, 60% stenosis in the obtuse marginal branch of circumflex artery and 80% stenosis in the right coronary artery. The patient did not have diabetes mellitus, hypertension, hyperlipidemia or family history of a cardiac event.

The laboratory tests were in normal range except elevated serum LDH, uric acid and blood thrombocyte count was 1.254.000/mm^3. With the diagnosis of essential thrombocytosis by the hematologist clinic, the patient administered hydroxyurea 100 mg/day for a week in order to reduce platelet count to 500.000/mm^3. The patient underwent a successful three vessel on-pump coronary artery bypass grafting. There was a 750 ml drainage postoperatively. Postoperative thrombocyte levels of the patient was over 1.000.000/mm^3. The platelet count was controlled using hydroxyurea 100 mg/day. The patient was dischaeged at 10th day after the surgery with a platelet count of 300.000/mm^3. At one−year follow-up, the patient showed no signs of thrombo-haemorrhagic and microvascular complications or angina.

Discussion

Essential thrombocytosis is a myeloproliferative disorder seen along with permanent and progressive elevation of blood thrombocyte count, thrombohaemorrhagic and microvascular complications.

It is typically characterized with megakaryocytic hyperplasia in bone marrow and splenomegaly [2-5].

The worldwide incidence of this disease is 1.5/100,000 per year [4, 5]. Causes for mortality and morbidity in essential thrombocytosis are thrombosis, bleeding and progression to myelofibrosis or acute leukemia [5]. Only 9.4% myocardial infarction and 9-22% vascular events were reported in patients with essential thrombocytosis [1, 4]. Except a history of thrombosis, risk factors for cardiovascular disease including smoking, hypertension, hyperlipidemia and diabetes are risk factors for thrombosis as well [1, 4]. There are non-endothelial contact, heparin, platelet activating factors and hypercoagulapathy induced by increased thrombin with cardiopulmonary bypass during cardiac surgery. There is a tendency of bleeding due to hemodilution, heparinization, platelet dysfunction and hypothermia as well [6]. Increase in thrombocyte aggregation, platelet dysfunction and von Willebrand factor deficiency were shown in patients with essential thrombocytosis [2, 5]. Therefore, these type of patients who undergo cardiac surgery are at risk of bleeding and thrombosis [1, 6]. Bleeding, thrombosis and neutralization of heparin with protamin become more complex and major bleeding may result in fatality. In general, patients under 40-years of age without any thrombo-haemorrhagic disease are accepted as low-risk group and aspirin therapy is suggested for the treatment of essential thrombocytosis [1, 2, 5]. However, thrombocyte reduction therapy is suggested before surgery to take myeloproliferation under control and reduce the risk of bleeding in patients with extreme thrombocytosis [2]. Drugs such as hydroxycarbamide, anagrelide, interferon-a and hydroxiurea are suggested to reduce thrombocyte count to normal range in the preoperative period [2, 5]. Reduction of platelet count to normal levels would also lower the risks of thrombocyte aggregation and microemboli during cardiopulmonary bypass [4, 7].

Our patients underwent cardiac surgery with reduction of thrombocyte count to normal levels and there were no complications afterwards. Hydroxyurea was started in our patients for thrombocyte reduction therapy and the reference levels were reached after approximately one week treatment. Preoperative usage of hydroxiurea that lowered the thrombocyte count seems likely to influence postoperative outcomes positively which should be examined in further studies. Immune suppression with these drugs has been worrisome regarding postoperative infections. Although hydroxyurea is cytotoxic, it is also shown for this drug has no a negative effect on antimicrobial functions of the leukocytes [8]. Postoperative bleeding occurred in one of our patients for whom complete neutralization of heparin couldn't be obtained even with full dose of protamin. 1000 ml of drainage occurred in this patient in the first postoperative day. This patient was given aprotinin, which significantly reduced the bleeding. Aprotinin was reported to provide significant reduction in postoperative bleeding in patients with thrombocyte dysfunction [9]. Off-pump operations are recommended for hematologic diseases to avoid adverse effects of cardiopulmonary bypass and surgical complications of extreme bleeding or thrombosis [5]. Risk factors evaluation should be made individually for thrombohaemorrhagic complications under cardiopulmonary bypass. Smoking, obesity, hypertension and high blood thrombocyte count are shown as risks for thrombohaemorrhagic complications [2]. Risk of bleeding and thrombosis are higher particularly for patients over 60 years of age and in patients with thrombocyte counts over 1.500.000/mm³ [1, 2, 5, 8]. Our patients were also at high risk; thrombocyte levels were reduced to reference range preoperatively with hydroxyurea and aspirin therapies regarding recommendations of the hematologist and postoperative changes in life style (such as weight loss for obese patients, to give up smoking for smokers etc.) were suggested. Catastrophic hemorrhagic complications may occur during warfarin therapy particularly in patients at high risk group who have essential thrombocytosis, where a much aggressive therapy (such as chemotherapy or bone marrow transplantation) may be necessary.

Nevertheless, therapeutic attempts to stop bleeding may result in valve thrombosis [2]. For this reason, bioprosthetic valves should be preferred to avoid a lifetime warfarin therapy. However, metallic valves may be chosen for young patients with low risk of essential thrombocytosis [2]. For our mechanic valve replaced patient, necessity of warfarin usage due to chronic atrial fibrillation and history of a thromboembolic event made us prefer a mehanical valve.

Conclusion

In conclusion, special attention is necessary in patients with essential thrombocytosis undergoing open cardiac surgery to go on with the precise balance

between the risk of bleeding and tendency of thrombosis. Preoperative usage of hydroxiurea reduces the thrombocyte count and seems likely to influence postoperative outcomes positively. There are open cardiac surgical operations of patients with essential thrombocytosis in current literature. However, there is not yet sufficient data for optimal therapy for these patients, requires further studies in large patient populations.

Informed consent

Written informed consent was obtained from the patients for the publication of this case report.

Conflict of interest

The authors declared that there are no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Percutaneous drainage in treatment for spontaneous rectus abdominis hematoma due to rivaroxaban usage

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ABSTRACT

Rivaroxaban is currently used to prevent stroke in patients with atrial fibrillation. Like all anticoagulants, rivaroxaban carries a risk of bleeding. There is a single reported case of rectus abdominis hematoma due to rivaroxaban use in the literature. We present an 82-year-old female patient presented to our outpatient clinic with sudden pain and swelling in the abdominal region. The patient had been treated with rivaroxaban for three months without warfarin. Computed tomography scanning showed a 25x10x15 cm long acute hematoma in the left rectus abdominis. Rivaroxaban was replaced with enoxaparin for thromboembolus prophylaxis. We performed percutaneous drainage in order to reduce pain and recovery time by decreasing the hematoma size. Catheter drainage was used in the third day to minimize rivaroxaban activity. We did not come across any literature date on percutaneous drainage treatment of spontaneous rectus abdominis hematoma. We report a case of hematoma of the rectus abdominis muscle that occurred following rivaroxaban use and was successfully treated with percutaneous drainage.

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Keywords: Rivaroxaban; spontaneous rectus abdominis hematoma; treatment; percutaneous drainage

Introduction

Rivaroxaban is currently used to prevent strokes in patients with atrial fibrillation. It offers several advantages compared with standard agents, including rapid onset of action, fixed dosing, and no requirement for routine coagulation monitoring. However, like all anticoagulants, rivaroxaban carries a risk of bleeding [1-3]. Hematomas of the rectus abdominis muscle are commonly reported complications of systemic anticoagulation treatment [4]. There is a single reported case of rectus abdominis hematoma due to rivaroxaban use in the literature [5]. We did not come across any literature date on percutaneous drainage treatment of spontaneous rectus abdominis hematoma. We report a case of hematoma of the rectus abdominis muscle that occurred following rivaroxaban use and was successfully treated with percutaneous drainage.

Case Presentation

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An 82-year-old female patient presented to our outpatient clinic with sudden pain and swelling in the abdominal region. She had a history of previous coronary artery bypass surgery, heart failure, hypertension, diabetes mellitus, and atrial fibrillation. Her medical treatment consisted of diltiazem, furosemide, rosuvastatin, valsartan and rivaroxaban. The CHA2DS2-VASC and HAS BLED scores were 7 and 2 respectively. The patient had been treated with rivaroxaban for three months without warfarin because of the difficulty of dosing warfarin in elderly patients. Physical examination revealed a mass in the left side of the umbilicus. Laboratory results were hemoglobin (Hb):12 gr/dl, platelets: 178000 K/uL, prothrombin time: 14.2 sec, international normalization ratio (INR): 1.12, and serum creatinine: 0.81 mg/dl, with normal liver function test results.

Computed tomography (CT) scanning showed a

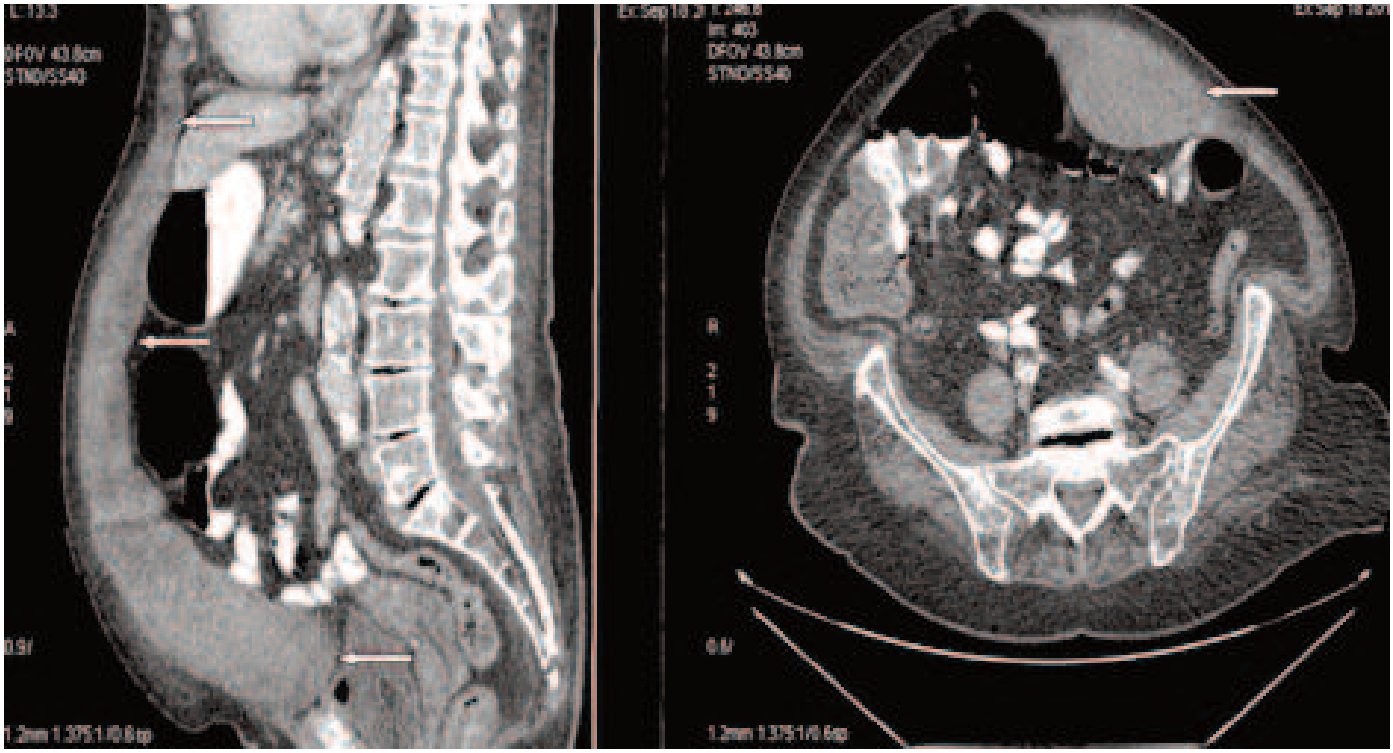

Figure 1. Computed tomography showing long acute hematoma in the left rectus abdominis (Arrows)

25x10x15 cm long acute hematoma in the left rectus abdominis (Figure 1). In history, there was no surgical intervention or trauma which cause hematoma. Rivaroxaban was replaced with enoxaparin for thromboembolic prophylaxis. The hb level was 9.8 gr/dl on the first day and she was administered 2 units of erythrocyte suspension. Hb values remained stable at follow-up. However patient had severe abdominal pain resulting in hypotension and abdominal discomfort. Therefore, we decided for percutaneous drainage instead of spontaneous resorption. On the third day, an ultrasound-guided percutaneous drainage catheter (12 F drainage catheter Skater, Angiotech) was implanted to the hematoma region under local anaesthesia to accelerate the resorption of the hematoma. Partial drainage of the hematoma was performed by manual aspiration and then free drainage was allowed. Adequate drainage was provided and the catheter was removed on the 3rd postoperative day. Abdominal pain and patients discomfort ceased after the successful drainage of the hematoma. The patient was discharged on the clopidogrel and acetylsalicylic acid combination because of the refusal of rivaroxaban use by the patient and her relatives. The rectus muscle hematoma was almost completely resorbed at the third month follow-up CT (Figure 2).

Discussion

Rivaroxaban is an oral anticoagulant agent that directly inhibits Factor Xa and interrupts both the intrinsic and extrinsic pathways. It is currently indicated for atrial fibrillation and prophylaxis of deep venous thrombosis. It does not require INR monitoring like warfarin [5].

Real-world data on bleeding with rivaroxaban are limited, but trial sub-analyses are available. In the Rivaroxaban Once-daily, Oral, Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for

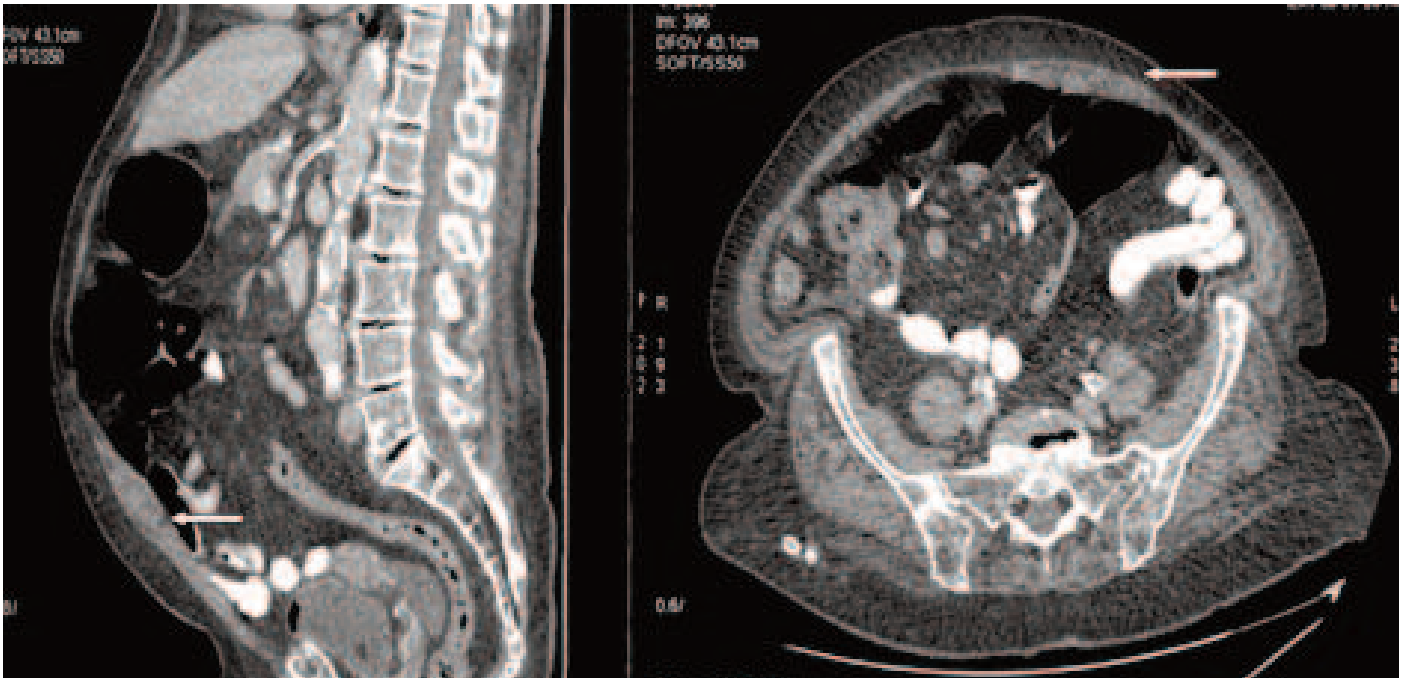

Figure 2. The rectus muscle hematoma is almost completely resorbed at the third month follow-up CT scan (Arrows)

Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET AF Trial) study, predictors of major bleeding with rivaroxaban included older age, male sex, increased body mass index, diabetes, chronic obstructive lung disease, and worsening renal function. Risks of major adverse outcomes including death following a major bleeding event were similar in patients treated with rivaroxaban and warfarin in the ROCKET AF Trial [1-3].

Rectus hematoma is considered an uncommon bleeding complication that can occur spontaneously after trauma or as a result of anticoagulation therapy. Management of a rectus hematoma is usually conservative [4]. Invasive treatment is only indicated if the rectus hematoma is progressive or if the patient is hemodynamically unstable [6]. We performed percutaneous drainage in order to reduce pain and recovery time by decreasing the hematoma size. Catheter drainage was used in the third day to minimize rivaroxaban activity.

Conclusion

Rectus abdominis hematoma should be considered in patients who complain of abdominal pain/swelling while using rivaroxaban. The hematoma may occur without surgery or trauma especially in older patients. Large muscle hematomas can be drained percutaneously in order to terminate abdominal pain, which may cause vagal reactions and to accelerate patients' recovery.

Informed consent

Written informed consent was obtained from the patient for the publication of this case report.

Conflict of interest

The authors declared that there are no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Incidentally observed 15-meter-long tapeworm during surgery in a patient with newly diagnosed gastric cancer

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ABSTRACT

Parasitic infestations are mostly encountered in underdeveloped or developing countries. *Taenia saginata* is the most frequently found genus in Turkey and cases occur particularly in the Southeastern Anatolian Region. A 57-year-old woman admitted to hospital with the complaints of weakness, weight lose and abdominal pain. Gastroscopy was performed and a tumoral mass was observed. Pathologic evaluation of the endoscopic biopsies was reported as signet ring cell gastric carcinoma. Tapeworm was incidentally observed when the incision was made for jejunal bypass. Fifteen-meter-long parasite was extracted. There are not enough studies and case reports that questioned the relationship between *taeniasis* and cancer.

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Keywords: Taenia saginata; gastric cancer; asymptomatic; surgery.

Introduction

Parasitic infestations are mostly encountered in underdeveloped or developing countries. The natural definitive host of these tapeworms (*Taenia solium* and *Taenia saginata*) is human small intestine. Pig and Cattle being intermediate hosts for *T. solium* and *T. saginata* respectively [1]. *T. saginata* is the most frequently found genus in Turkey and cases occur particularly in the Southeastern Anatolian Region. There are very few cases of *T. solium* due to prohibition of pork consumption by the religion in Turkey.

T. saginata is transmitted to humans through uncooked or improperly cooked beef. While most cases are asymptomatic patients may have cramp-like abdominal pain, diarrhea or constipation. Taenia-related surgical complications include complications include Meckel's, acute appendicitis, cholecystitis, liver abscess, pancreatitis, obstruction and perforation of the intestine, and anastomotic leakage [2].

We report an interesting case of 15-meter-long tapeworm, which is diagnosed during surgery of the newly diagnosed gastric cancer.

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Case Presentation

A 57-year-old woman admitted to hospital with the complains of weakness, weight lose and abdominal pain. Physical examination is normal except mild epigastric tenderness. Her hemoglobin was 12.2 g per 100 ml, total leucocyte count was 8,200 cells per cubic millimeter (mm3) of blood, with a differential count revealing 68.9% neutrophils, 1.6% eosinophils, 21 % lymphocytes and 6.9% monocytes. The platelet count was 407,000/mm3. Erythrocyte sedimentation rate was 19 mm/hr.

Gastroscopy was performed due to epigastric findings and reflux symptoms. A passage narrowing tumoral mass was identified at the point that Z line should be existed. The mass that fills the stomach lumen was extending through the distal corpus at the greater curvature side. Multiple endoscopic biopsy was performed.

Staging tests were performed due to endoscopic findings. Tumor markers including carcinoembryonic antigen (CEA), cancer antigen 125 (CA 125), CA 15-3, CA 19-9 and alfa-fetoprotein (AFP) was all negative. Kidney (urea, creatinine and urinalysis) and liver (AST, ALT, ALP, GGT, Bilirubin and PT, INR) function tests were within normal limits. In complete abdominal tomography (CAT), at the thickest part, 22 mm nodular thickening was observed at the level of cardia, greater and small curvature. No lymph node, liver or distant metastasis was noted in thorax and CAT scan.

Pathologic evaluation of the endoscopic biopsies was reported as signet ring cell carcinoma. The patient was discussed at the gastrointestinal oncology council and it was decided to do surgery.

Total gastrectomy was performed. Tapeworm was observed when the incision was made for jejunal bypass 35 cm below the Treitz ligament. Fifteen-meter-long parasite was extracted from 1 cm incision. Remaining part of tapeworm was extracted from the secondary incision 35 cm prior the caecum (Figure 1).

Postoperative pathological evaluation reveals signet ring cell carcinoma of 9x7 cm diameter and 1 cm depth. Subserosa was infiltrated by the tomor. One

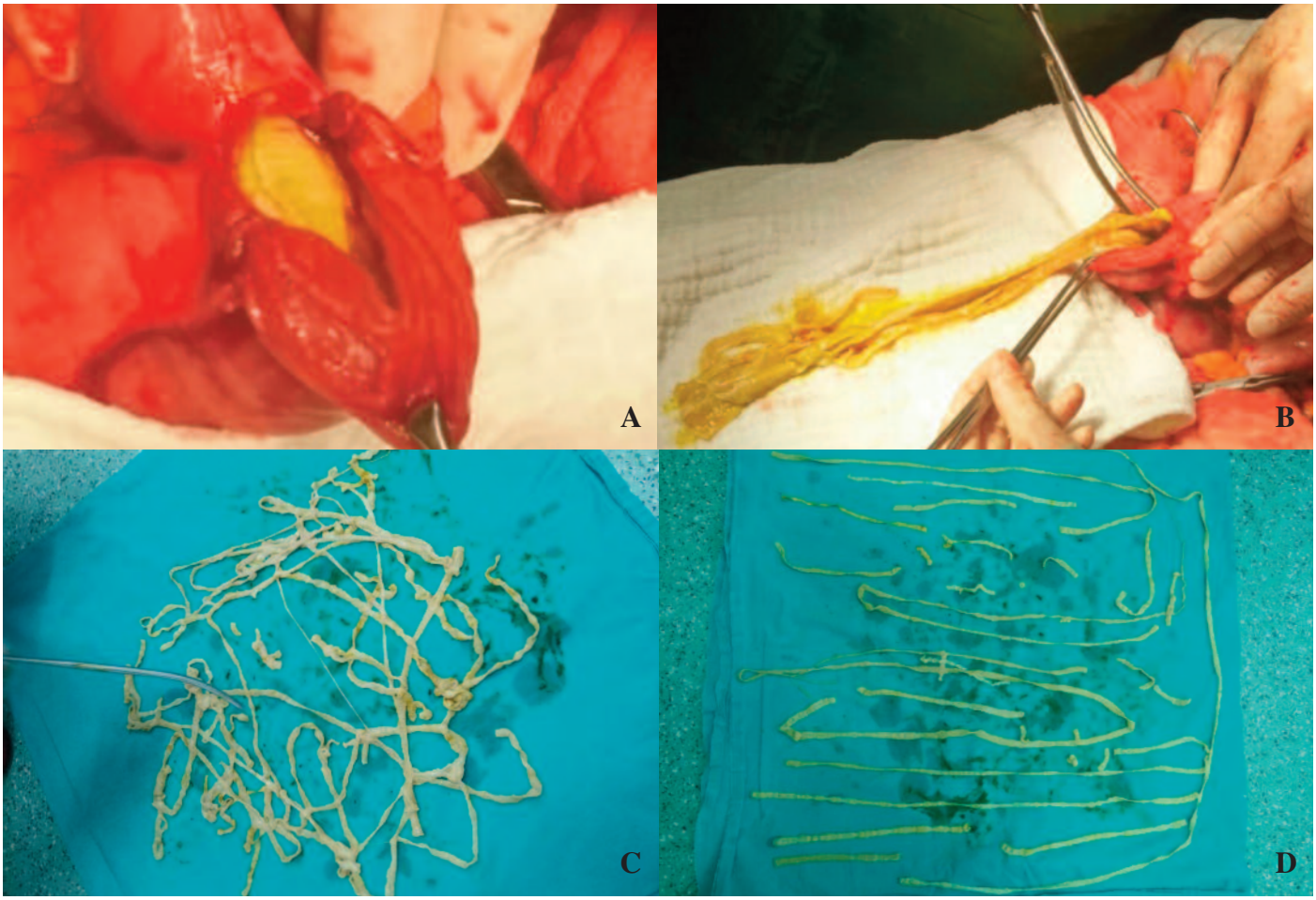

Figure 1. Appearance of tapeworm from 1-cm incision that was made for jejunal bypass 35 cm below the Treitz ligament (A), extraction of the tapeworm (B), and removed *Taenia saginata* (C, D).

lymph node and 2 omental tumor implantation was observed. Pathological staging was $PT_{2b}N_1$ tumor.

Discussion

T. saginata infestations are usually asymptomatic for a long period of time. Abdominal pain, weight loss, nausea, vomiting, constipation or diarrhea and intestinal obstruction are the symptoms that can be seen in some patients. It is usually treated with a single dose of Praziquantel or Niclosamide.

Surgery is recommended only for the treatment of complications [2]. There are only a few cases describing surgery requiring tapeworm complications. Gall bladder perforation [3], colonic anastomotic leakage following a right hemicolectomy procedure related to *T. saginata* infestation [2], emerging of a tapeworm from the eviscerated midline incision in a post-surgery patient [4] and a case report describing a *T. solium* peritonitis with multiple ileal perforations [1] were reported in the literature.

The effects of parasites are not clear in gastric tumor progression [5]. Serologically, toxocaris infestation was detected in gastric and colorectal cancer patients [6]. Microfilaria was reported in a patient with gastric carcinoma [7]. Although the association is considered to be low, *Tropheryma whippelii* has been strongly associated with gastric adenocarcinoma [8].

Inflammation and cancer relationship is well established. Interactions between various immune cells, and other mediators can lead to signaling toward tumor cell proliferation, growth, and invasion [9]. Chronic tapeworm infestation may increase inflammatory response.

Our case reveals that tapeworm infestations can be asymptomatic although it is 15-meter long. Dural *et al.* [4] removed 2.4-meter-long taenia in a patient with stage IV gastric cancer. There are not enough studies and case reports that questioned the relationship between taeniasis and cancer.

Conclusion

The relationship between taeniasis and gastric cancer should be enlightened with the detailed retrospective analysis and prospective studies. The underlying mechanism of tumor development still needs to be investigated.

Informed Consent

Written informed consent was obtained from the patient for the publication of this case report.

Conflict of interest

The authors declared that there are no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Fahr's disease: a rare diagnosis requiring admission to the emergency department

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ABSTRACT

Fahr's disease is a rare degenerative neurological disorder characterized by the presence of abnormal calcium deposition and associated cell loss in the areas of the brain that control movement, including the basal ganglia and cerebral cortex. Clinical findings associated with Fahr's disease include parkinsonism, dystonia, chorea, ataxia and psychiatric symptoms. Fahr's disease may result from metabolic disorders, especially parathyroid disorders. We report our experience with 4 patients admitted to our emergency department with complaints such as convulsions, hand spasms, loss of consciousness, and weakness. Computed tomography of all patients showed calcification in the bilateral basal ganglia. The purpose of this paper is to draw attention to a rare disorder involved in the etiology of elderly patients admitted to the emergency department for seizure and/or unconsciousness..

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Keywords: Fahr's disease; hypocalcemia; intracranial calcification; seizure; unconsciousness

Introduction

Fahr's disease (FD) is an inherited neurological disorder characterized by calcification of the basal ganglia and other areas of the brain, parkinsonism, and neuropsychiatric symptoms, which was first described in 1930 [1]. Fahr's disease may result from metabolic disorders, especially parathyroid disorders [1]. Fahr's syndrome (FS) is a general term including Fahr's disease as well as other conditions presenting with secondary calcification of the basal ganglia.

Frequent clinical findings in patients with FD including parkinsonism, dystonia, chorea, ataxia, dementia, and mood disorders [1]. Intracerebral calcifications are usually accompanied by disorders in calcium and phosphorus metabolism. More rarely, FD may occur during the course of other metabolic disorders, familial diseases, or in the absence of abnormalities in calcium metabolism [2-4]. Neuropsychiatric, extrapyramidal and cerebellar symptoms, as well as speech disorders and dementia, may also occur. Some patients are asymptomatic despite the widespread accumulation of calcium. Typically, age at onset of clinical symptoms is 40–60 years, although these symptoms have also been observed in children [1-4].

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The aim of this paper is to report our experience with four patients admitted to our emergency department for complaints such as convulsions, hand spasms, loss of consciousness, and weakness, who were diagnosed with FD.

The Presentation of the Patients

Patient 1

An 82-year-old woman was transported via ambulance to the emergency department with convulsions and hand spasms. She was reported to have experienced a convulsion two months earlier. Her vital signs were stable at admission. Family members reported that, during the previous few years, she demonstrated remarkable impairments in memory functions and daily activities, including difficulties incommunication and self-care. Serum analysis showed a calcium concentration of 6.3 mg/dl (normal: 8.4-10.2 mg/dl), phosphorus concentration of 5.3 mg/dl (normal: 2.3-4.7 mg/dl), and a parathyroid (PTH) concentration of 1.5 pg/ml (normal: 15-65 pg/ml). Computed tomography (CT) scans showed symmetrical calcifications in the bilateral cerebellar hemispheres at the bulbar and periventricular levels, in the bilateral internal capsule and caudate nucleus, and on both sides at the level of the centrum semiovale (Figure 1). The patient was diagnosed with FD associated with idiopathic hypoparathyroidism. After calcium replacement therapy, the patient was discharged from the hospital for outpatient follow-up.

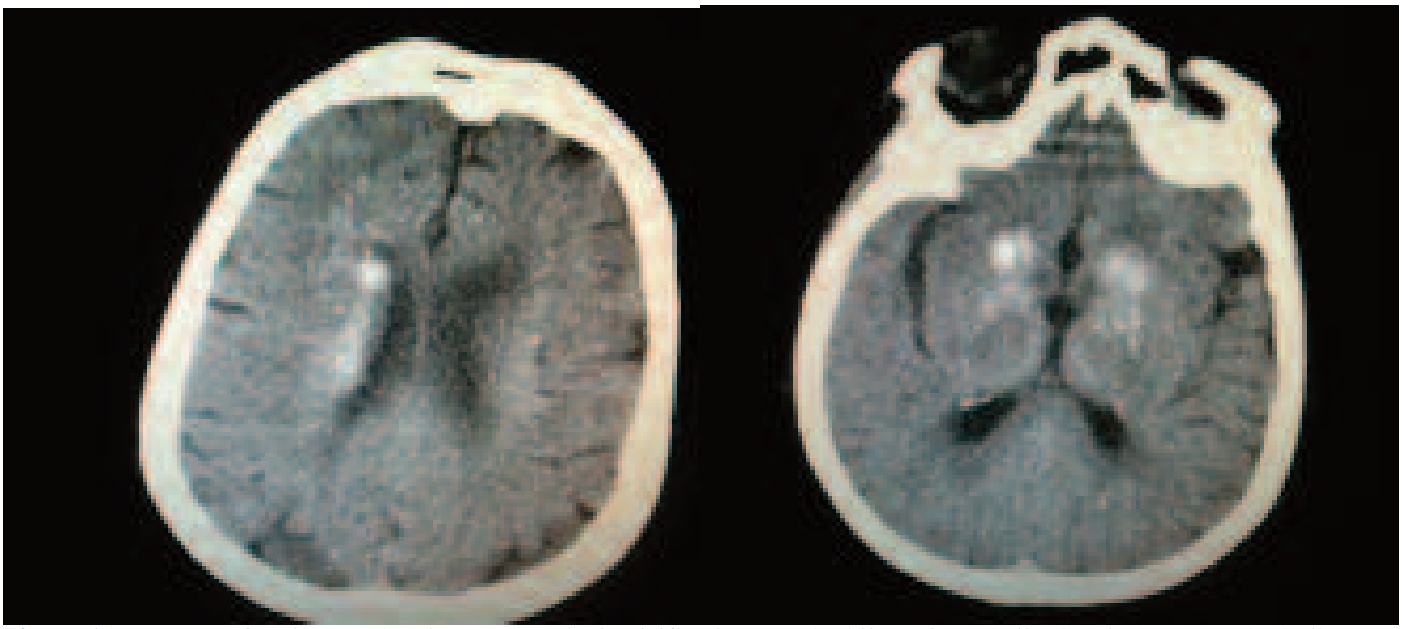

Figure 1. CT scans of patient 1, showing symmetrical calcifications on the bilateral cerebellar hemispheres, at the bulbar and periventricular levels, the bilateral internal capsule and caudate nucleus and on both sides at the level of the centrum semiovale.

Patient 2

A 40-year-old male was admitted to our hospital for general body fatigue and muscle cramps and numbness in the arms. Upon physical examination, the patient was conscious, alert, oriented and had stable vital signs. His medical history showed no evidence of any comorbid diseases, drug use or allergy. He had been occasionally referred to a doctor for these symptoms and found to have low calcium levels, for which he received oral calcium therapy, but he was not followed-up. At admission, this patient showed evidence of neuromuscular hyperexcitability, with positive Chvostek and Trousseau signs, with blood tests showing serum calcium, phosphorus and PTH concentrations of 4.08 mg/dl (normal: 8.4-10.2 mg/dl), 5.4 mg/dl (normal: 2.3-4.7 mg/dl) and 6.5 pg/ml (normal: 15-65 pg/ml), respectively. CT showed hyperdense patchy calcifications at the posterior fossa level, the dentate nucleus of both cerebellar hemispheres, the basal ganglia, the thalamus, and at the levels of the frontal, parietal and occipital lobes of the deep subcortical area extending to the white matter (Figure 2). The patient was diagnosed with FD associated with idiopathic hypoparathyroidism. Calcium replacement therapy increased his serum calcium levels, resulting in the resolution of his symptoms.

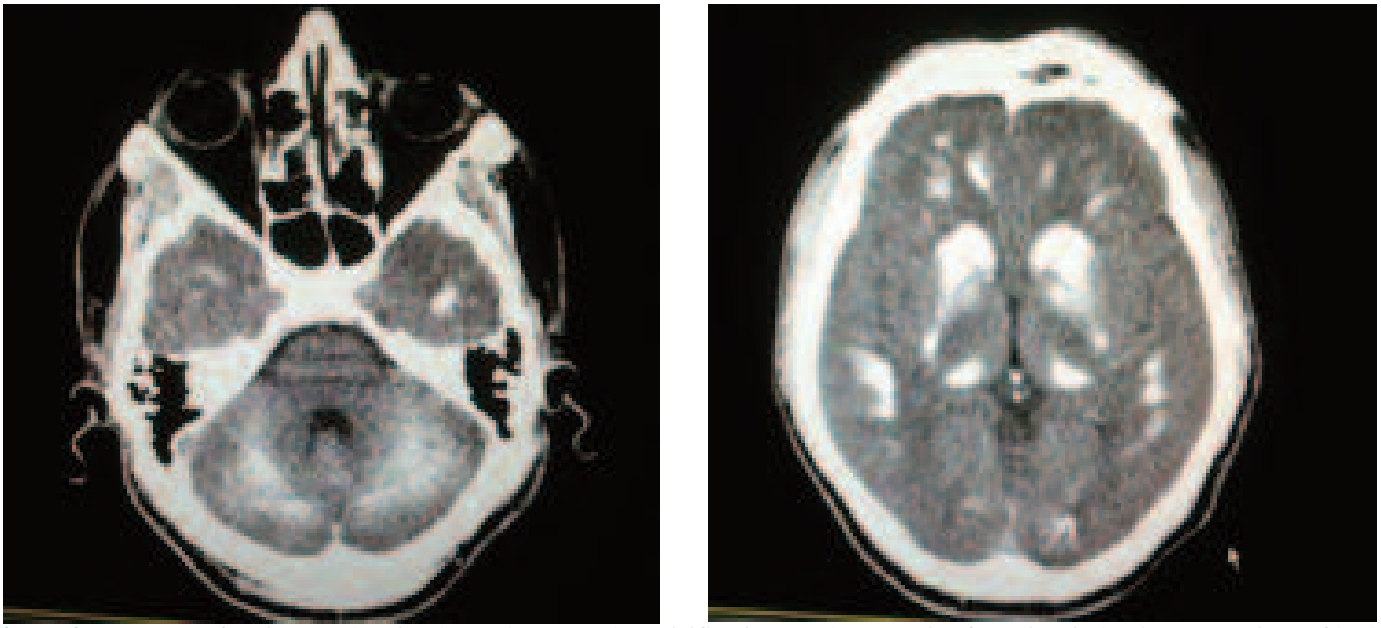

Figure 2. CT scans of patient 2, showing hyperdense patchy calcifications at the posterior fossa level, the dentate nucleus of both cerebellar hemispheres, the basal ganglia, the thalamus, and at the levels of the frontal parietal and occipital lobes of the deep subcortical area extending to the white matter.

Patient 3

A 56-year-old male with seizures was admitted to the emergency department. His medical history showed increasing dementia, but he had not been diagnosed with epilepsy. His family regarded his condition as age-related. His serum calcium, phosphorus, and PTH concentrations were 6.47 mg/dl (normal: 8.4-10.2 mg/dl), 4.5mg/dl (normal: 2.3-4.7 mg/dl) and 17 pg/ml (normal: 15-65 pg/ml). He was started on intravenous calcium gluconate therapy. CT showed massive calcification of the bilateral basal ganglia, the periventricular white matter of the thalamus, the centrum semiovale, the posterior fossa and the bilateral cerebellar hemispheres (Figure 3). The patient was diagnosed with FS.

Patient 4

A 30-year-old male with generalized tonic-clonic seizures was brought to the emergency service by ambulance. This patient had no previous history of epilepsy, trauma, drug use, alcohol abuse, smoking or previous surgery. Physical examination revealed no pathology. His serum calcium, phosphorus, and PTH concentrations were 9.3 mg/dl (normal: 8-10.2 mg/dl), 4.1 mg/dl (normal: 2.3-4.7 mg/dl) and 22 pg/ml

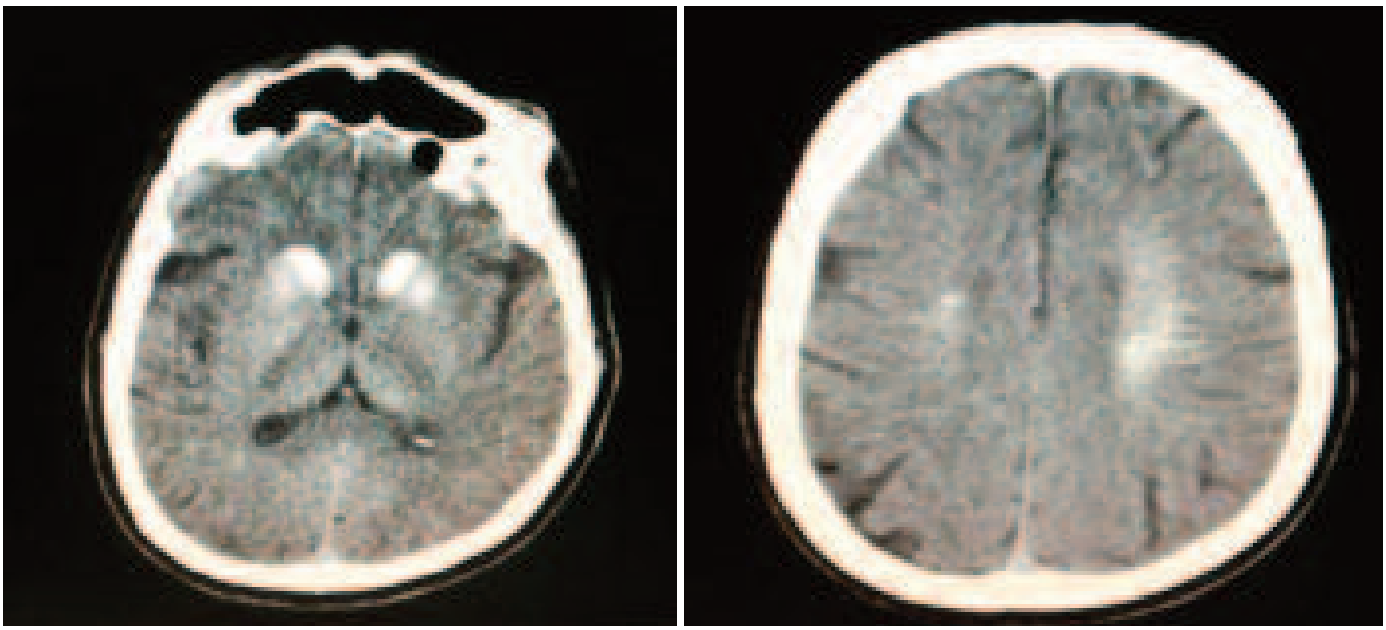

Figure 3. Brain CT scans of patient 3, showing massive calcifications of the bilateral basal ganglia, the periventricular white matter of the thalamus, the centrum semiovale, the posterior fossa and the bilateral cerebellar hemispheres.

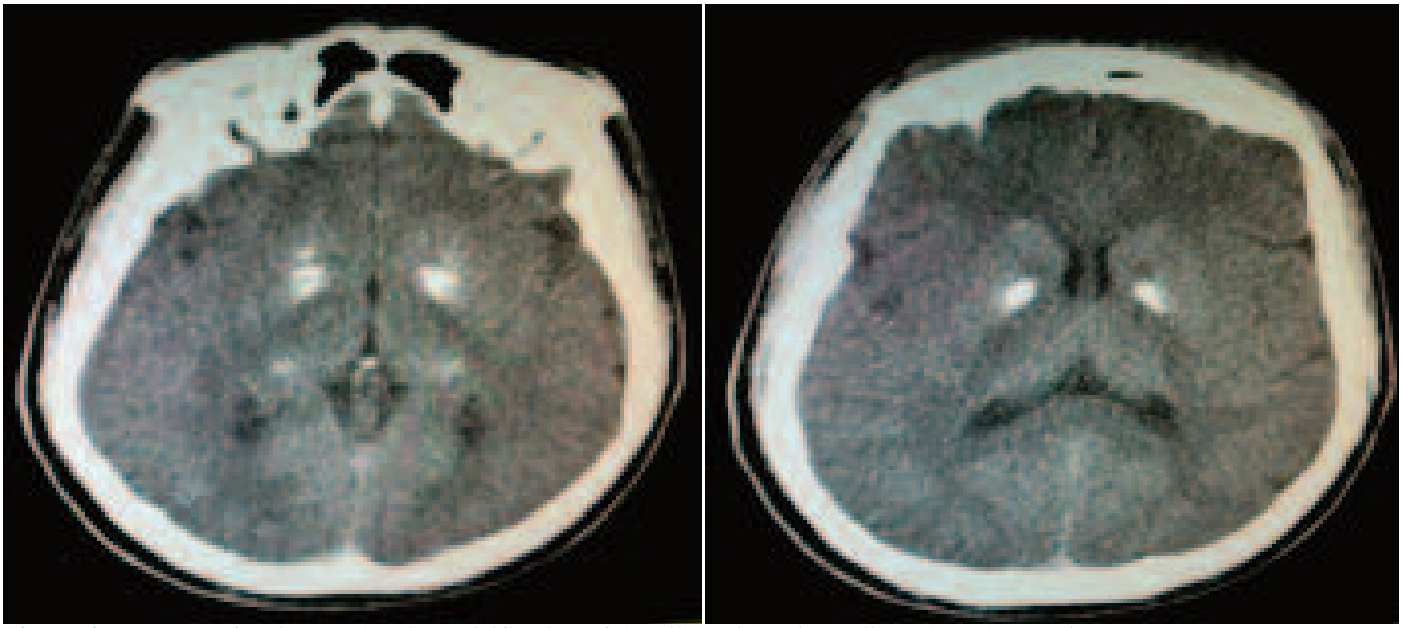

Figure 4. CT scans of patient 4, showing calcification of the bilateral basal ganglia and caudate nucleus.

(normal: 15-65 pg/ml), respectively. His hemogram, serum electrolytes, liver function tests and renal function tests were all within normal limits. Serological tests showed that he was negative for hydatid, toxoplasma, cysticercosis, cryptococcosis, cytomegalovirus and human immunodeficiency virus (HIV). CT of the brain revealed extensive calcification involving the bilateral basal ganglia and caudate nucleus (Figure 4). There was no family history of a similar illness. The patient was diagnosed with FS. Due to his young age and for his clinical well-being, the patient was discharged and followed up as an outpatient.

Discussion

FS is a condition characterized by symmetrical calcifications of the basal ganglia and cerebellar regions [1]. FD is a type of FS. Although the etiological factors of FS are not clearly understood, it has been associated with disorders of calcium metabolism, degenerative congenital developmental abnormalities and genetic disorders, systemic inflammatory diseases, and toxic effects on anoxic brain interactions. Clinical diagnosis of this condition is based on clinical features, the results of brain imaging, and the exclusion of other causes of intracranial calcification. The most common method used to diagnose FS is CT [5, 6]. Imaging results showing symmetric and extensive calcification are usually observed, as in our four patients. Two of these patients were diagnosed with FS and two with FD, depending on the intensity and location of the calcifications.

FD/FS can develop secondary to toxic and anoxic effects, congenital degenerative development anomalies, systemic diseases and previous inflammatory events [7-9]. Although most frequently associated with hypoparathyroidism and hypocalcemia [3], the method by which hypoparathyroidism leads to intracranial calcification has not been determined [6]. Initially asymptomatic patients may become symptomatic over time [10].

Manyam et al. [11] reported movement disorders in 56% and seizures in 22% of cases in a review of 213 patients with this disorder. Three of our patients were admitted to the hospital with seizures, with a calcium metabolism disorder diagnosed after detailed examination. Findings in two of three patients show that hypoparathyroidism can result in generalized seizures. The incidence of basal ganglia calcification increases as the duration of hypocalcemia increases, with symptoms of calcification emerging after about 30 years [11]. Replacement of calcium and vitamin D improves metabolic abnormalities and delays clinical progression [12, 13].

Forty percent of patients with basal ganglia calcifications presents with psychiatric symptoms at the beginning of the disease. Among these; cognitive and psychotic disorders are most prominent [14-16]. Our first patient during the previous few years demonstrated remarkable impairments in memory functions and daily activities, including difficulties

incommunication and self-care.

Conclusion

In conclusion, FS/FD should be considered in the differential diagnosis of patients admitted to the emergency department with neuropsychiatric symptoms, a history of undiagnosed seizures, and symptoms of hypocalcemia.

Informed Consent

Written informed consent was obtained from the patients for the publication of these case series.

Conflict of interest

The author declared that there are no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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