Management of concomitant coronary and advanced carotid artery disease

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The high-risk potential for neurological dysfunction following coronary artery bypass grafting (CABG) in patients with concomitant carotid stenosis has always been a challenge. Many surgeons advocate combined CABG with carotid endarterectomy (CEA). However, clinical experience with the concomitant approach is conflicting.[1] Patients with bilaterally diseased carotid artery have a more challenging group. Sixty-five patients underwent both CABG and unilateral CEA (group I) or isolated CABG (group II) was enrolled for this study at Siyami Ersek Thoracic and Cardiovascular Surgery. This retrospective study was initiated with the approval of the institutional review board. All patients had severe bilateral carotid artery disease (CAD) defined as a 50-99% stenosis in conjunction with a >50% stenosis or occlusion in the contralateral carotid artery. Demographic characteristics were comparable between 2 groups. Only a small group of patients (15.5%) had symptomatic carotid artery disease in the whole group. All patients scheduled for CABG underwent carotid color-flow duplex ultrasound examination when a history of transient ischemic attacks, cerebral vascular accidents was present or asymptomatic bruits on physical examination or with an age of >65 years. We excluded patients with previous CABG, concomitant valve replacement, and any other associated procedure or lesions in external carotid artery. We performed CEA procedures either with locoregional anesthesia (6 cases) or general anesthesia (24 cases). The side with symptoms or greater stenosis was generally performed first. We used intraoperative caroted shunt in 2 patients and carotid patch in 2. Coronary artery bypass grafting was performed after completion of the carotid operation. Cerebral protection for our patients during cardiopulmonary bypass included hypothermia and high perfusion flows and pressures. Intermittent tepid blood cardioplegic arrest was primarily used for myocardial protection. Proximal anastomoses were performed during partial aortic cross clamp period. Operative and postoperative data are given in **Table 1**. There were 2 deaths (5.7%) and no stroke in group II and 2 deaths (6.6%) and 4 strokes (13.3%) in group I (p=0.87 and p=0.026). Both deaths in group I were cardiac related. One patient died on the 4th postoperative day due to cardiac arrest and the second died due to low cardiac output syndrome on the 8th postoperative day. Two patients in group II died on the 8th and 34th day postoperative due to multiorgan failure and both patients had neurological and cardiac related complications. Three out of 4 strokes in group I emerged in the early postoperatvie awakening period. The fourth stroke occurred on the 5th postoperative day. Two of these patients died. In 3 patients, the stroke occurred on the side of the ipsilateral hemisphere of the carotid endarterectomy. The last patient died without recovering consciousness due to cerebral ischemia. The other complications were comparable between the 2 groups. Though routine carotid endarterectomy or coronary revascularization can be performed separately in patients without concomitant carotid and coronary disease with minimal morbidity and mortality, the incidence of permanent stroke increased to 6.7% if the contralateral internal carotid artery was >50% narrowed and 11% in the presence of contralateral internal carotid artery occlusion after CABG. Contribution of cardiopulmonary bypass for the stimulation of micro emboli and the activation of multiple components of the inflammatory cascade, resulting in neurological injury and other morbidity has been described previously.[2] On the other hand, beating heart surgery has established a serious ground due to well-documented short and long-term outcomes especially associated with low neurological morbidity rates. We had 21 patients (5 simultaneously operated, and 16 CABG) treated with off-pump myocardial revascularization and only one patient developed hemiplegia that had undergone simultaneous operation. The early beneficial impact of CEA on neurological outcome still needs to be verified. The most recent studies suggested that performing staged or synchronous procedures for stroke prevention especially in asymptomatic patients could gain little or no benefit.[1] Yet patients with bilateral carotid lesions are specific group of patients not encountered frequently. It has been reported that performing a unilateral carotid endarterectomy while ignoring the contralateral diseased carotid in patients who have significant bilateral carotid stenosis may result in increased morbidity and mortality from the uncorrected lesion.[3] In another recently reported document, patients with bilateral carotid artery disease had a 23% incidence of stroke on the untreated contralateral side.[4] Actually these reports do not support concomitant unilateral CEA and CABG operation. We performed isolated CABG in a group of patients in whom bilateral carotid lesion was present and compared early outcomes of this group with concomitantly operated group. In both groups, 2 deaths were present. Although

Table 1 - Operative and postoperative data

Sub-heading	Group I CABG - CEA n=30	Group II CABG n=35	*P*-value
Myocardial preservation (%)			0.13
Beating	5 (14.2)	16 (45.7)	
Arrest	25 (83.3)	19 (54.2)	
CPB time (minute) (mean±SD)	80.4 ± 24	110.8 ± 38.2	0.06
Cross-Clamp time (minute) (mean±SD)	46.7 ± 14.9	80.1 ± 31	0.01
Number of coronary grafts (mean±SD)	2.4 ± 0.8	2.23 ± 0.8	0.43
Mortality (%)	2 (6.6)	2 (5.7)	0.87
Stroke (%)	4 (13.3)	0	0.026
Stroke or mortality (%)	4 (13.3)	2 (5.7)	0.29
Atrial fibrillation (%)	1 (3.3)	4 (11.4)	0.22
Respiratory problems (%)	5 (16.6)	2 (5.7)	0.15
Reentubation (%)	2 (6.6)	2 (5.7)	0.83
Postoperative stay (day) (mean±SD)	3 ± 7.8	1.9 ± 3.4	0.46
Hospital stay (day) (mean±SD)	9 ± 8.6	8.4 ± 4	0.74
Hospital stay >10 days (%)	6 (20)	9 (25.7)	0.58
Maximal carotid stenosis (mean±SD)	81.2 ± 8.4	72.4 ± 13.1	0.03
Side of maximal carotid stenosis			0.6
Right	17	18	
Left	13	17	

CABG - oronary artery bypass grafting, CEA - carotid endarterectomy, CPB - cardiopulmonary bypass

all deaths were cardiac related, this high mortality in both groups is related to severe the coronary vasculature of the patients. However, no patient in group 2 suffered from a perioperative neurological event. Our stroke rate of 13.3% (4 out of 30) in group I was higher than the documented studies.[1] Furthermore, the ipsilateral stroke rate is also higher than expected occurring mainly on the postoperative period associating the stroke event with the carotid endarterectomy procedure. Many factors may have impact for improved early outcomes. Beating heart technique that we have exclusively used in group II patients may canceled the untoward neurological side effects of cardiopulmonary bypass.[5] The patients included in the present study had their procedures performed between 2002 and 2007, and changes in anesthetic, surgical techniques and postoperative care over time could have influenced mortality and morbidity rates. Karmeli et al[6] documented the benefits of locoregional anesthesia especially in bilaterally severely diseased states. Our results suggest that the combined procedure increases the risk of postoperative neurological morbidity in patients with asymptomatic carotid disease in the early perioperative period. Off-pump CABG may probably be better in patients with severe atherosclerotic disease of more than one extracranial vessel. Benefits of local anesthesia by observing the awake patient, or general anesthesia with or without neurological monitoring need to be clarified especially in such complex situation. There is a need for randomized trials to elucidate the need for carotid endarterectomy at the time of coronary artery surgery.

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Investigation of the role of the exogenous *Klebsiella pneumoniae* contaminants in neonatal infections

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Neonatal infections are the major cause of neonatal deaths in the world. These infections can be acquired by exposure to microbes that colonise the maternal genital tract (vertical transmission), or by exposure to unhygienic care practices and environment.[1] Heavily contaminated reservoirs with multiresistant *Klebsiella pneumoniae (K. pneumoniae)* serve as the probable source of infection in developing countries.[1] This present work was conducted between February 2000 to March 2005 under supervision of the Infection control Committee (ICC) of the Istanbul Faculty of Medicine, University of Istanbul, Istanbul, Turkey. Approval from the University of Istanbul was obtained prior to the commencement of the study. We aimed to study the bacterial contaminants of the Neonatal Intensive Care Unit (NICU) and to investigate the role of the exogenous *K. pneumoniae* in the neonatal infections.

For this purpose, a total of 171 swabs were obtained from different environmental sites of the NICU including hands of 45 health care workers (HCWs) and cultured on appropriate media for bacteriological analysis. It was found that 76.9% (10/13) of breast milk collecting containers (BMCCs), 50% (2/4) of eye protecting bands, 44.4% (4/9) of infants ready food, 37.5% (12/32) of respiratory devices, 36.4% (8/22) of infant incubators, 26.7% (12/45) of hands of HCWs, 16.2% (6/37) of intravenous (IV) fluids, and 11.1% (1/9) from most used surfaces, a total of 55 (32.2%) out of 171 environmental cultures were contaminated with 62 contaminants. The distribution of the contaminants were as follows: 16 *K. pneumoniae*, 7 from each of *Pseudomonas species* (4 were *Pseudomonas aeruginosa*), *Acineobacter species* (4 were *Acinetobacter baumannii*), methicillin resistant coagulase negative staphylococci (MRCNS), and *Enterobacter species*, 6 methicillin susceptible *Staphylococcus aureus* (MSSA), 4 from each of *K. oxytoca* and *Serratia marcescens*, 3 *Escherichia coli*, and one alfa-hemolytic streptococci. *Klebsiella pneumoniae* was the most frequent contaminants 16/62 (25.8%) and was responsible for contamination of 16 (29%) out of 55 contaminated environmental sites. *Klebsiella pneumoniae* was the major contaminant in the eye protecting band (50%), IV fluids (50%), and BMCCs (40%). The phenotyping and genotyping relatedness of the 16 exogenous *K. pneumoniae* strains were compared with 9 clinical *K. pneumoniae* strains previously isolated in the same NICU. Of these clinical strains, 8 were from blood and one was from eye secretion. In phenotyping methods, susceptibilities of 25 *K. pneumoniae* strains to 11 antibiotics were performed by disk diffusion methods and production of extended spectrum beta-lactamase (ESBL) was demonstrated by double disk synergyst method (**Table 1**). Both methods were performed according to the Clinical and Laboratory Standards Institute (CLSI) criteria.[2] The strains were also screened for production of siderophores according to the method previously described.[3] In the genotyping methods the plasmid profile analysis (PPA) method was used as previously advised by Kado et al,[4] whereas random amplified polimorphic DNA-polymerase chain reaction (RAPD-PCR) method was performed by adding a 5 µl aliquot of DNA template to 45 µl of PCR mixture [32 µl sterile distilled water, 5 µl 10x PCR buffer with ammonium sulphate, 5 µl 25 mM magnesium chloride, and one µl from each of 10 mM deoxyribonucleotide triphosphate mix, 50 pmol single primer HLWL74 (5'-ACGTATCTGC-3'), and Taq DNA polimerase]. The final solution was employed on a PCR program, initial denaturation (94°C/3 min) followed by 40 cycles of denaturation (94°C/1 min), annealing (35°C/1 min), and final extension (72°C/5 min). Polymerase chain reaction products were analyzed by electrophoresis. The banding patterns were evaluated visually. The concordances of the environment and clinical strains were shown in **Table 1**. Depending on phenotyping and genotyping results it was found that the contaminated

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Table 1 - Phenotyping and genotyping of 25 *Klebsiella pneumoniae* strains.

Isolation date	Specimen	Strain number	RAPD group	Plasmid profile pattern	Antibiotype group*	Siderophore production/ aerobaktin type	ESBL production
18.02.2000	Blood	1	1	g	D	+/-	+
29.11.2000	Blood	5	1	a	A	+/-	+
15.03.2005	Breast milk container	8	1	b	F	+/-	-
13.04.2001	Hand skin HCW	10	1	a	A	+/+	+
09.08.2000	Blood	3	2	a	A	+/+	+
06.02.2004	Breast milk container	12	2	f	C	+/+	-
08.11.2001	Aspirator tip	15	3	h	A	+/+	+
21.11.2003	Infant incubater	19	3	e	C	+/-	+
17.11.2003	Eye bands	17	4	b	F	+/-	-
21.11.2003	Eye secretion	18	4	b	F	+/-	-
09.12.2003	Blood	20	5	c	G	+/-	-
09.12.2003	IV fluid	21	5	c	H	+/-	-
17.07.2001	IV fluid	22	6	d	C	+/-	-
17.07.2001	Blood	23	6	d	C	+/-	+
17.07.2001	Trophamine	24	6	d	C	+/-	+
21.03.2000	Blood	2	V	i	C	+/-	+
20.09.2000	Blood	4	V	a	E	+/-	-
29.11.2000	Blood	6	V	a	B	+/-	+
15.03.2005	Infants incubater	7	V	e	C	+/-	+
13.04.2001	Ready food	9	V	e	C	+/+	+
14.01.2004	Breast milk container	11	V	f	C	+/-	+
24.02.2004	Breast milk container	13	V	f	C	+/-	-
08.11.2001	Aspirator tip	14	V	f	E	+/-	-
16.05.2002	Hand skin HCW	16	V	j	C	+/+	+
13.05.2004	Hand skin HCW	25	V	d	C	+/-	+

Antibiotype groups* - **A**) resistant to aztreonam (ATM 30 µg), cefotaxime (CTX 30 µg), sulbactam/ampicillin (SAM 10/10 µg), cefuroxime sodium (CXM 30 µg), ceftriaxone (CRO 30 µg), ceftazidime (CAZ 30 µg), amoxicillin/clavulanate (AMC 20/10 µg), amikacin (AK 30 µg), netilmicin (NET 30 µg), gentamicin (CN 10 µg), tobramicin (NN 10 µg), **B**) resistant to ATM, CTX, CXM, CRO, CAZ, AMC, AK, NET, NN, **C**) resistant to ATM, CTX, SAM, CXM, CRO, CAZ, AMC, **D**) resistant to ATM, CTX, CXM, CRO, CAZ, AMC, **E**) resistant to ATM, SAM, AMC, **F**) resistant to SAM, AMC, **G**) resistant to CTX, AMC, **H**) resistant to AMC, V - variable, RAPD - random amplified polimorphic DNA, HCW - health care worker, ESBL - extended spectrum beta-lactamase .

hands of HCWs with multidrug resistant *K. pneumoniae* were more likely responsible for contamination of in-house prepared solutions and cross-contamination of different environmental sites (aspirator, infants incubator). The role of the contaminated hands in the neonatal infections could be summarized in 2 points: 1. Contamination of the stock solution (strain no 24) of the nutritional substances (trophamin), might led to contamination of IV fluid (strain no 2), which terminated with sudden onset of septicemia (blood strain no 23) on 17 July 2001, the similar contamination-infection cycle (strains no 20 and 21) occurred on 9 December 2003, 2. Contamination of the eye protection bands (strain no 17), usually used for protection of the eyes of the neonates from UV light during bilirubin therapy, this contamination also resulted in an eye infection (strain no 18) on 17 November 2003. The role of the contaminated BMCCs with neonatal infections was not proved. Some of the concordant strains were not evaluated as of the incompatibility in the date, for example, blood cultures (strains no 1 and 5) were preceded by environmental cultures (strains no 8 and 10) and it is difficult to link between the contamination and infection (**Table 1**). However, highlighting on the characteristics of the isolates has shown that all were siderophore producers (virulence factor), 60% expressing ESBL, and most of them containing large plasmids, varied in sizes between 1.2 kb-54 kb which might harbor resistance genes. These features select the isolates to be potential resistant strains that had an ability to persist in the unit for many years (strains number 1, 3, 5) and circulate via hands of HCWs (strain no 10) to contaminate IV solutions and different environmental sources (strains no 8, 12, 15, 19). The contamination of IV fluids is very critical, their results appear very quick, and most resulted in septicemia (strains no 20 and 23) and even an outbreak. Moore et al[5] reported that 65% of in-use glucose-containing IV fluids were contaminated with *K. pneumoniae*, and they concluded that extrinsically contaminated IV fluids resulted in sepsis and deaths.

This present report has shown that more active surveillance systems in NICU are urgently needed, comprising of systematic educational programs for HCWs and mothers, focusing on hygienic hand washing, and mandatory use of the safety cabinet for preparing of nutritional solutions. These preventions are necessary to control, or at least to decrease the exogenous related nosocomial neonatal infections.

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Comparison of anemia between *Helicobacter pylori* negative and positive adults

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Iron deficiency anemia is a common health problem, and it is estimated to be the most common nutritional deficiency worldwide.[1] Established causes include inadequate iron intake, chronic blood loss, malabsorption, or a combination of them. On the other hand, *Helicobacter pylori (H. pylori)* infection is a common infection, and also is the most prevalent gastric pathogen.[1-4] Recently, there is evidence to suggest a relationship between *H. pylori* gastritis and iron deficiency anemia even in the absence of peptic ulcer disease.[1] It is suggested that the cure for *H. pylori* was also associated with reversal of iron deficiency anemia in adults.[5] The association between *H. pylori* infection and iron deficiency anemia was previously reported. The mechanisms of *H. pylori* related iron-deficiency anemia are still unclear. In a study from Korea, *H. pylori*-seropositive persons were at increased risk for having anemia.[1] The aim of this study was to evaluate the possible effect of *H. pylori* on hemoglobin, and iron indices in adult asymptomatic cases.

A total of 410 cases, 200 males and 210 females (male to female ratio: 0.95), aged 18-43 years old were investigated for hemoglobin, serum ferritin, and serum *IgG* antibodies to *H. pylori*. Cases were consecutive couples presenting for screening for anemia, and undergoing electrophoresis before marriage between June and August 2007, with no major health problems, and cases with no history of chronic hematologic, or disabling diseases, or history of major gastrointestinal problems were included. Cases with a history of known or unknown prolonged gastrointestinal problem, hematologic disease, or any chronic diseases were excluded from the study. All cases and controls were at the same age, and overall condition. Iron deficiency anemia was defined as a low hemoglobin level in the presence of low ferritin level. Hemoglobin was measured using an automated electronic counter, while radioimmunoassay was used to measure serum ferritin. *Helicobacter pylori IgG* antibody concentrations were determined using an ELISA commercial kit. Samples with concentrations >20 U/mL were considered to be positive for *IgG* antibodies to *H. pylori.* Iron deficiency was defined to be a serum ferritin level <15 ng/mL, and the hemoglobin level was less than adjusted values for age and gender, 12 g/dl for females, and 13.6 g/dl for males. Ethical approval for the study was obtained from Ethical Committee of the Tehran University of Medical Sciences. Informed written consent was obtained from each patient involved in the study.

All statistical analysis was performed with SPSS 10 for Windows. Data were expressed as the mean±SD, or median (range) as appropriate degree. A p-value<0.05 was considered statistically significant. Categorical variables were compared using a Chi-square test, and the student t-test was used to compare continuous variables between groups.

There was no significant relationship between age (p>1) and gender (p>0.9) of the 2 studied groups. A total of 268 cases were positive for *H pylori* antibody. Among them, 20.4% had iron deficiency anemia, and among 142 cases without *H. pylori* infection, 8.4% had iron deficiency anemia (p=0.00049, odds ratio: 2.8). Anemia (p=0.00046), and iron deficiency (p=0.0028) were significantly more frequent in the infected group (**Table 1**). There was no relationship between age, gender, ferritin, and hemoglobin level with the level of anti-*H pylori IgG* within each groups (p>0.05 in both groups). Iron deficiency was more frequent in women in both groups (p=0.047). **Table 1** show hematological values, and demographic data of the 2 groups. Mean ferritin level were lower in females of both groups, and it was lower in the infected group, than the non-infected group (**Table 1**).

Table 1 - Hematological values and demographic data of the 2 groups (N=410).

Groups	n (%)	Mean age in years (range)	Gender ratio (Male/female)	Frequency of iron deficiency (%)	Frequency of anemia (%)	Frequency of iron deficiency anemia (%)	Mean serum ferritin (µg/dl) (%)	Mean hemoglobin (g/dl)
		p>0.05	*p*>0.05	*p*=0.0028	*p*=0.00046	*p*=0.00049	*p*=0.00046	*p*=0.0037
Positive group	268 (65.4)	28 (18-43)	130/138	(34)	(28.5)	(20.4)	23± 8	11.8±1.4
Negative group	142 (34.6)	25.6 (18-42)	70/72	(14.2)	(10.8)	(8.4)	31±7	14.6±1.6

Unexplained iron deficiency anemia is often an indication to evaluate the gastrointestinal tract to exclude chronic blood loss secondary to possible malignancies, ulcerations or malabsorptions. However, endoscopic studies and other tests sometimes cannot show the exact cause of iron deficiency, and it remains unexplained.[1] The duodenum plays the most important role in iron absorption, and the stomach participates in this process. Gastric acidity must be adjusted in order to achieve a pH for luminal mucins to be able to bind iron, and keep it in soluble form, available for absorption in the duodenal environment.[1-5] A few theories relating to the effect of *H. pylori* on iron status are described: impairment of iron uptake due to gastric hypoacidity, achievement of iron from transferrin, lactoferrin, and heme by bacteria, dietary non-hemic ferric form of iron needs an acidic intragastric pH to be reduced to ferrous, and be absorbed. This reaction is promoted by ascorbic acid, which is reversibly depleted in the gastric juice of patients with *H. pylori* infection.[2,3,5]

Our study significantly supports the association of *H. pylori* infection, and iron deficiency anemia, and as our cases were asymptomatic, it may be due to microbleeding, and iron uptake by micro-organism leading to deplete iron stores, and finally iron deficiency and iron deficiency anemia, independent of ulcer disease. Our results are in parallel with Seo et al[1] in a study of 753 Korean children, in which *H. pylori* seropositivity was associated with lower serum ferritin, and the relationship between iron deficiency anemia and *H. pylori* infection were reported.[1] Iron deficiency is major health problem affecting general health, immunity, reproduction work performance and psychological status. In our study, 28.5% of infected, and 10.8% of noninfected cases had anemia, and this significant difference may be the result of infection as there is no associated abnormality in their history. As the inclusion or exclusion criteria were only the history of gastrointestinal problem, we could not reliably exclude cases with occult gastrointestinal disorders leading to occult blood loss, and it was the limitation of our study, however, as our subjects were healthy couples presenting for screening before marriage, we could not carry out invasive procedures like colonoscopy.

In conclusion, our results support the proposal that *H. pylori* infection is associated with iron deficiency anemia. Further studies emphasizing the socioeconomic status of cases, strains of *H*. pylori, post treatment measurement of serum iron, and serum ferritin are required, to show whether iron status differs with disappearing of *H. pylori* or not. Due to the simplicity of *H. pylori* diagnosis and treatment, and observed results in the literature, testing for *H. pylori* as a communicable and carcinogenic organism, besides routine investigation for causes of anemia like celiac disease and colon neoplasia in older individuals, and treatment of cases with unexplained iron deficiency anemia appears to be of clinical importance.

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Biphasic insulin aspart 30 treatment improves glycemic control among patients with type 2 diabetes in Saudi Arabia and the Gulf region

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Biphasic insulin aspart 30 (BIAsp 30) is a premixed insulin analog consisting of 30% soluble rapid-acting insulin aspart, and 70% protaminated insulin aspart. The soluble component is rapidly absorbed, and effectively targets postprandial glycemia, while the protaminated component has a prolonged absorption profile, and provides basal insulin coverage.[1] Compared to premixed human insulin, BIAsp 30 offers convenient and flexible meal-time dosing, superior postprandial glycemic control, and a relatively lower risk of hypoglycemia.[1,2] While the efficacy and safety of BIAsp 30 were well-established on randomized controlled clinical trials,[1] information on its use in routine clinical practice was limited and only small numbers of patients were studied in observational studies.[3,4] The physicians' routine evaluation of safety and efficacy of NovoMix® 30 therapy (PRESENT) study, a large clinical experience research involving type 2 diabetes patients from 15 countries worldwide, was conducted to collect data on the use of BIAsp 30 in routine clinical practice.

This was a 6-month, prospective, observational study conducted in 59 centers in Saudi Arabia and the Gulf region, from January to December 2005. There were no specific selection criteria or study-specific interventions. Patients with type 2 diabetes, inadequately controlled on their previous therapy (as diagnosed by their physicians) were eligible for the study. Biphasic insulin aspart 30 treatment (dosing and injection regimen), or discontinuation was entirely at the physicians' discretion. Approval for the conduct of this study was not required, according to the requirements of local regulations.

Of the 2228 patients enrolled, 2226 had baseline data. When stratified according to prior therapy, 51.7% were previously treated with oral hypoglycemic agents (OHAs)-only, 28.2% with insulin-only, and 20.1% were with insulin+OHA(s). Baseline demography was comparable between the groups, except that the diabetes duration was longer among patients on prior insulin treatment, either alone or in combination with OHA(s), compared with the OHA(s)-only group. These groups also had slightly better baseline glycosylated hemoglobin (HbA1c) compared with the OHA(s)-only group. Mean HbA1c was significantly (p<0.001) reduced by 2.61 ± 1.86% points, mean fasting plasma glucose (FPG) by 4.38 ± 3.27 mmol/l, and mean post-prandial plasma glucose (PPPG) by 7.02 ± 4.9 mmol/l at 6 months (**Table 1**). The OHA(s)-only prior treatment group, showed the greatest improvements in HbA1c, FPG, and PPPG compared with the insulin-only, and insulin+OHA(s) groups. The proportion of patients achieving target HbA1c <7% increased from 2.3% at baseline, to 42.8% at 6 months (of which 69.4% did not report hypoglycemia, p<0.001) (**Table 1**) with the insulin-only group showing the largest proportion of patients achieving target HbA1c at the end of 6 months. The mean body weight of the patients showed a decreasing trend from baseline across the groups (**Table 1**). The proportion of patients reporting hypoglycemic episodes, showed a decreasing trend from baseline to 6 months except for the OHA(s)-only group. Throughout the study, most hypoglycemic episodes reported were minor, and diurnal in nature. In the OHA(s)-only group, the overall proportion of patients reporting hypoglycemic episodes increased slightly from 15.5% at baseline, to 17.3% at 6 months. Notably, this increasing trend occurred only in the minor episodes. The insulin-only group reported the greatest reduction in the proportion of patients reporting hypoglycemic episodes, decreasing from 47.8% at baseline to 14.7% at the end of the study.

The results on improved glycemic control were comparable to, or better than trials on BIAsp 30.[3-5] As there was no strict titration algorithm in this study, we believe that aggressive treat-to-target regimen could further improve glycemia, and thus, increase the proportion achieving target. Improvement in glycemia was not accompanied by increase in body weight. The hypoglycemic profile was comparable to the literature.[3-5] Only the OHA(s)-only group reported a slight increase in frequency of hypoglycemic episodes at 3 months, however, this increase appeared to be transient (mostly minor and daytime episodes), and decreased to near baseline level at 6 months. These findings suggest that BIAsp 30 could be used as the initiating insulin in patients previously inadequately controlled on OHA(s). Patients previously treated with insulin also showed significant improvements in glycemic parameters, with reduced frequency of hypoglycemic episodes, and no increase in

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Table 1 - Glycemic parameters and body weight of study population.

Parameters	Total	OHA(s) only	Insulin only	Insulin + OHA(s)
Safety population	**2152**	1112	607	433
HbA1c (%)				
Baseline	**9.72 ± 1.85**	9.97 ± 1.75	9.24 ± 1.87	9.71 ± 1.95
6 months	**7.16 ± 1.20**	7.17 ± 1.17	7.00 ± 1.20	7.36 ± 1.27
Change at 6 months†	**-2.61 ± 1.86***	-2.94 ± 1.79*	-2.25 ± 1.90*	-2.29 ± 1.81*
Proportion achieving HbA1C <7%				
Baseline (%)	**(2.3)**	(0.7)	(4.7)	(3.1)
6 months	**(42.8)**	(41.4)	(48.6)	(38)
FPG (mmol/L)				
Baseline	**11.93 ± 3.50**	12.47 ± 3.26	11.09 ± 3.59	11.68 ± 3.70
6 months	**7.52 ± 1.82**	7.49 ± 1.66	7.53 ± 1.92	7.61 ± 2.02
Change at 6 months†	**-4.38 ± 3.27***	-5.08 ± 3.00*	-3.58 ± 3.42*	-3.90 ± 3.34*
PPPG (mmol/L)				
Baseline	**16.82 ± 4.84**	17.76 ± 4.43	15.55 ± 5.36	16.14 ± 4.60
6 months	**9.80 ± 2.56**	9.78 ± 2.29	9.63 ± 2.65	10.08 ± 2.98
Change at 6 months††	**-7.02 ± 4.90***	-8.11 ± 4.54*	-5.86 ± 5.22*	-6.08 ± 4.69*
Weight (kg)				
Baseline	**85.14 ± 15.33**	87.12 ± 15.72	80.80 ± 14.51	86.24 ± 14.24
6 months	**83.54 ± 13.24**	84.82 ± 12.81	80.65 ± 13.46	84.55 ± 13.33

OHA - oral hypoglycemic agent, FPG - fasting plasma glucose, PPPG - post-prandial plasma glucose, values are mean ± SD, *p<0.001, p-values as compared to baseline, †change from baseline

weight. These may be attributed to the ability of BIAsp 30 to mimic physiological insulin profile,[1] thereby improving PPPG and FPG, and positively impacting the frequency of hypoglycemia and weight.

In conclusion, our study showed that BIAsp 30 is effective and safe among type 2 diabetes patients in Saudi Arabia and the Gulf region. Although this observational study has some inherent limitations, such as uncontrolled design, and lack of standardized laboratory measurements, it provides supportive evidence for the use of BIAsp 30 in routine clinical practice.

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Medical ethics and chronic pain management

Jamil S. Anwari, FFARCS.

For the last 10 years, most of the medical ethics activism in relation to pain management has taken place under the umbrella of the American Pain Society (APS) & the American Academy of Pain Medicine (AAPM).[1,2] As a discipline, both medical ethics and pain management are juvenile fields, about which there is still little awareness amongst healthcare professionals. It is probably not surprising then that the 1997 APS symposium on 'Ethics and Pain' only attracted 4 people.[3] The recent formation of standing ethical committees by the APS & AAPM reflects a growing concern. Simultaneously, an increasing amount of medical ethics literature is being published. The interface between bioethics and pain physicians was written on in a special issue of Pain Medicine (***Pain Medicine*** 2001; 2.). It gave an over view of the field of bioethics, the application of ethical principles to pain medicine and the application of ethics to a specific area of pain medicine. The AAPM Ethics Committee proceeded in their efforts to form an advisory group. Composed of physicians with ethical interests and ethicists with medical expertise the group focused on writing an ethics charter for pain medicine. Their efforts culminated in a 2-day workshop in Chicago in December 2003, which laid the groundwork for a charter. In the following year, the draft charter underwent revisions before the final completed version was presented at the 2005 AAPM annual meeting in Palm Springs.[4] The charter gave recommendations and opinions on ethical issues and dilemmas. In addition to advisory groups, American and British pain societies have a 'special interest group' (SIG), a sub-group of the society, which is interested in ethical issues associated with pain and suffering and the management of such issues.[5,6] The SIGs have annual meetings in which their ideas are discussed and interchanged.

Recently, Frank Brennan, David Carr, and Michael Cousins wrote a landmark review article on "Pain Management: A Fundamental Human Right" which was published in Anesthesia & Analgesia.[7] In this article, pain management as an ethical issue was strategized for the improvement of pain management. It was concluded that we are presently at an "infliction point" in which unreasonable failure to treat pain is universally considered poor medicine, unethical practice, and an abrogation of a fundamental human right. Even when matters are looked at from an ethical lens, further issues can arise. The major problem of making an ethical decision is an ethical dilemma - when 2 ethical principles or obligations appear to conflict with one another. There are several factors, which are integral to the development of ethical dilemmas in chronic pain management. Broadly these factors are categorized under 3 headings a) Characteristics of pain b) Pain patient and c) The system we practice in. Lebovits[3] has outlined the following important factors in the genesis of ethical dilemmas in chronic management:

1. Inherent difficulty of "curing" chronic pain: The very nature of not curing what the patient has come for can lead the doctor and patient to be over aggressive in their approaches. This often leads to significant side effects or iatrogenic injuries.

2. Psychopathology of chronic pain patients: Chronic pain patients might have a significant psychiatric problem, which has existed premorbidly and, which may also be reactive to pain and/or the lack of relief and exacerbated by iatrogenic or traumatic injuries. These patients might not be taken seriously enough and dismissed as "crazy". This might result in them not being treated medically, but just psychiatrically. Alternatively their depression or somatization disorder might amplify their pain resulting in an over aggressive treatment.

3. The patient-physician relationship in chronic pain management can be quite difficult due to the complexity of chronic pain and prior failed attempts at relief. This can lead to anger from the patient and frustration from the provider.

4. Use of unproven methods: Some interventions used by pain centers have not been proved to be efficacious scientifically. Additionally, the growing popularity and acceptance by the medical community for complementary techniques, which are used most often for pain further intensifies the ethical dilemma of using or referring patients for unproven techniques.

5. Vulnerability of patients: These are patients with whom ethical dilemmas are more likely to develop. These include patients who (a) will try anything due to the desperate nature of their pain (b) cannot communicate (infant, elderly, in ICU) (c) are cancer patients (d) are dying patients and (e) are economically disadvantaged patients. The latter group in particular tests the ethical principle of "justice".

6. Litigation: Many chronic patients are in litigation as a result of conditions at the onset of their pain, which frequently is the result of a road traffic accident or an accident on the job. Litigation is a very powerful secondary gain issue, which may consciously or subconsciously reinforce pain, illness behavior, and health care utilization. It often works against the goals of treatment. The ethical dilemma becomes whether/how to treat the patient in the face of such a powerful reinforcer of pain.

7. Increasing economic pressures on pain clinic: The clinician may be under pressure to provide a higher

reimbursement. Patients can be categorized as more, less, or not profitable

In a survey, 1105 members of the APS & AAPM were asked about ethical dilemmas they faced in chronic pain management.[8] The most common reply was pain management at the end of life. The common denominator in this survey was the under treatment of the vulnerable population such as the dying, the elderly, and children. Special reference was made to the under treatment of patients with persistent pain, sickle cell pain, and pain in those with psychiatric disorders or addiction problems. The survey revealed that there is a great desire for guidance through ethical dilemmas in pain management. Furthermore, the results provided a mandate and road map for future study of ethics in pain management. Ranked highest by respondents was to "develop policy statements regarding common ethical dilemmas in pain management."

Specialists in pain management are guided by general ethics, but some issues of particular relevance demand a specific outlook. Therefore, measures are required to increase the awareness among our own community and provide ethical education and guidelines, and also set the professional standards. In order to address these tasks, pain management professionals should show their determination to have a combined effort.

In December 2007, an international symposium on chronic pain management was held at the Riyadh Military Hospital, Riyadh, Kingdom of Saudi Arabia. The issue of medical ethics in relation to chronic pain was discussed. Many speakers expressed the need to create a "Pain society" in the Kingdom of Saudi Arabia, similar to the American, and British Pain Society, which would provide a platform to discuss issues. I strongly support the timely call to form a Saudi Pain Society, and hope this will happen soon.

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Ethical Consent

All manuscripts reporting the results of experimental investigations involving human subjects should include a statement confirming that informed consent was obtained from each subject or subject's guardian, after receiving approval of the experimental protocol by a local human ethics committee, or institutional review board. When reporting experiments on animals, authors should indicate whether the institutional and national guide for the care and use of laboratory animals was followed.