



Strategies for the Prevention of Hepatitis B, Hepatitis C and Human Immunodeficiency Virus infection in the Paediatric Population of Developing Countries page 33

From the Editor

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In this issue of the journal the third paper on evidence based medicine is presented. The paper is about Critical Reading of an Article about Therapy. The main objective of this paper is to understand the process of assessing the quality of a therapy article and how to apply its results to clinical practice. Specifically, the learners are expected to be able to: Assess the validity of a therapy paper; Determine the importance of the results of a valid therapy paper; and Determine how a valid and important evidence from therapy paper be applied to patient care.

A retrospective study was carried out at KFCH over an 11-years period from 1994 to 2005. All patients (3287), age of 12 years and above referred for endoscopy unit were enrolled in this study. The objectives of this study were to identify the common indications and findings of upper gastrointestinal (GI) endoscopy in patients presenting to King Fahd Central Hospital (KFCH) in Gizan town Southwest Saudi Arabia, and to furthermore, determine the associations between and the common endoscopic findings and some selected clinical and demographic variables. A total of 3287 patients were included in the study with a mean age of 45.3 years (SD ± 18.4), Indications for upper GI endoscopy included upper gastrointestinal (GI) bleeding (23.3%), with a significant difference between males and females (p-value = 0.000), Epigastric pain (15.7%), Acid Peptic Disease (APD) (14.4%), Dyspepsia (7.5%) and regular follow-up (6.5%). The results of the study suggested that UGI bleeding was the main indication

for UGI E in the vast majority of our patients. In addition to that three common diseases; Oesophageal Varices, Gastritis and Oesophagitis were the main findings of the UGI E among study population. Preventive measures should be adopted to cope with the situation and to prevent complications of esophageal and gastritis diseases among Gizan population.

A paper from Pakistan looked at the Strategies for the Prevention of Hepatitis B, Hepatitis C and Human Immunodeficiency Virus infection in the Paediatric Population of Developing Countries. After a brief background about the epidemiology of Hepatitis B, C and HIV, strategies for their prevention are discussed in the paediatric population of developing countries. These strategies are focused on mother to child transmission, misuse of injections, use of infected needles, myths and use of material infected with the hepatitis positive patient such as a comb, tooth brush etc. Malnutrition and its relationship with Tuberculosis and HIV infection are discussed. World Health Organization (WHO) guidelines on the management of malnutrition, Tuberculosis and HIV are discussed briefly. A real scenario highlighting the existence of HBV, HCV and HIV is described. Finally role of policy makers, NGO, WHO and local governments in the prevention of HBV, HCV and HIV in the paediatric population is discussed.

A cross sectional descriptive study was conducted in MOH hospitals and PHCC sectors and private hospitals and dispensaries in Jeddah. Self administered questionnaires were distributed to 210 general managers and medical directors of MOH governmental and private hospitals plus MOH PHCC supervisors and only medical directors of private dispensaries. Data were collected by 3 trained data collectors. It was entered and analyzed using SPSS version 16. Ethical considerations were ensured. The current study aim at identifying enabling factors and determine barriers among health policy makers toward utilization of national medical research' recommendations in Jeddah city, Saudi Arabia, 2010.

There is concern for the international community that research findings are not being utilized in the implementation of research future wise. 19% of

the respondents addressed that they received recommendation from the previously conducted research while only 12.4% indicated that there was previous research conducted in their institution. The authors concluded that among the interviewed health policy-makers there was a gap between the perceived importance of the research from one side and its conduction and utilization of its recommendations on the other side. The reported barriers were mainly remediable as being attributed chiefly to modifiable subjective factors driven from the lack of knowledge and experience about research methodology. In addition, the insufficient time perceived as a barrier reflects the vision of the studied institute which were not focusing in part of it on conduction of research and incorporating it in its plan and regular routine work.

A paper from Turkey looked at Chronic obstructive pulmonary disease as one of the terminal endpoints of the sickle cell diseases. All patients with the SCDs were taken into the study. The study included 411 patients with the SCDs (199 females and 212 males). There were 60 patients (14.5%) with the COPD. Mean age of the patients was significantly higher in the COPD group (33.0 versus 29.5 years, P=0.005). The male ratio was significantly higher in the COPD group, too (80.0% versus 46.7%, P<0.001). Smoking was also higher in the COPD group, significantly (36.6% versus 9.9%, P<0.001). Parallel to the smoking, alcoholism was also higher among the COPD cases, significantly (3.3% versus 0.8%, P<0.05). The authors concluded that SCDs are chronic catastrophic processes on vascular endothelium particularly at the capillary level, and terminate with accelerated atherosclerosis induced end-organ failures in early years of life. COPD may be one of the terminal endpoints of the diseases.

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Indications and findings of upper gastrointestinal endoscopy (UGIE) in patients of Gizan, Saudi Arabia: A retrospective study

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Abstract

Objectives: The objectives of this study were to identify the common indications and findings of upper gastrointestinal (GI) endoscopy in patients presenting to King Fahd Central Hospital (KFCH) in Gizan town Southwest Saudi Arabia, and to furthermore, determine the associations between them and the common endoscopic findings and some selected clinical and demographic variables.

Patients and Methods: This was a retrospective study carried out at KFCH over an 11 year period from 1994 to 2005. All patients (3287), age of 12 years and above referred for endoscopy unit were enrolled in this study. Standardized form (sheet) was used to collect all relevant data including age, gender, and indications for the procedure, clinical examination and endoscopic findings.

Results: A total of 3287 patients were included in the study with a mean age of 45.3 years (SD \pm 18.4); males patients comprised 70.1%. Indications for upper GI endoscopy included upper gastrointestinal (GI) bleeding (23.3%), with a significant difference between males and females (p-value = 0.000), Epigastric pain (15.7%), Acid Peptic Disease (APD) (14.4%), Dyspepsia (7.5%) and regular follow-up (6.5%). Among patients who underwent UGI E, (21.3%) had normal endoscopic findings.

Three common findings were; Oesoph Varices (15.2%), Gastritis (14.0%) and Oesophagitis (10%). Gender and age of patient were associated with a significantly high risk of Oesoph. Varices (OR=3.43 and 1.95 respectively; p-value< 0.001 for all).

Conclusion: The results of the study suggested that UGI bleeding was the main indication for UGI E in the vast majority of our patients. In addition to that three common diseases; Oesophageal Varices, Gastritis and Oesophagitis were the main findings of the UGI E among the study population. Preventive measures should be adopted to cope with the situation and to prevent complications of esophageal and gastritis diseases among the Gizan population.

Key words: Dyspepsia, indications, Gizan, Oesophageal Varices, Gastritis, Oesophagitis

Introduction

Upper gastrointestinal endoscopy (UGIE), or oesophagogastroduodenoscopy (EGD) is a simple procedure that is often performed with the patient lightly sedated [1&2]. The procedure provides significant information with high diagnostic value upon which specific treatment can be given. In certain cases, therapy can be administered directly through the endoscope. Serious complications rarely occur from upper gastrointestinal endoscopy [3-5].

UGIE is indicated for the evaluation of patients with upper abdominal symptoms that persist despite an adequate trial of therapy, as well as, in cases associated with other signs or symptoms that suggest serious organic disease such as weight loss, in patients who are over the age of 50 years [6]. Upper GI endoscopy is also indicated for the evaluation of dysphagia, odynophagia, and Oesophageal reflux that is persistent or recurrent despite adequate therapy, persistent vomiting of an unknown cause, or diarrhea [6]. The procedure is also common for screening patients for gastric cancer [7-9].

Gastrointestinal disorders are among the common causes of visiting health care facilities in Saudi Arabia and the number of patients attending endoscopy units for various gastro symptoms is increasing [10-13]. Dyspepsia was considered among the most common indications for upper gastrointestinal endoscopy [14-16], while other causes are also overwhelming [17-19].

The objectives of this study were to identify the common indications and findings on Upper endoscopy in patients presenting to King Fahd Central Hospital (KFCH) in Gizan, Southwest Saudi Arabia, and to study the associations between common endoscopic findings and some selected demographic and clinical variables.

Patients and Methods

This was a retrospective study carried out at King Fahd Central Hospital over a 11 year period from 1994 to 2005. King Fahd Central hospital is a tertiary hospital that serves Jazan region which is populated with nearly 1.5 million people. The endoscopy unit provides an open-access service and receives patients from outpatient clinics and other hospitals in the region. All patients (3287), age 12 years and above referred for endoscopy unit were enrolled in this study.

Standardized form (sheet) was used for extracting data from medical record department that includes; clinical data, demographic characteristics, indications for UGIE and findings for all patients undergoing upper endoscopy were recorded. Indications for UGI E were classified as; upper gastrointestinal bleeding; anemia; reflux symptoms heartburn and/or regurgitation; dysphagia, weight loss, anorexia, dyspepsia and other symptoms. In case of multiple indications the predominant one was chosen.

Data entry and statistical analyses were carried out with SPSS 17. Descriptive statistics based on frequency distributions and percentages were used for presenting the results. Chi-square tests/Fisher exact test were used to compare categorical variables and to assess some associations; two-proportion z-test was also utilized to compare some proportions. Logistic regression model was also used to evaluate factors associated with the common findings of UGIE. A p -value < 0.05 was considered to be statistically significant.

As per international guidelines and KFCH endoscopy guidelines, an informed written consent [20-21] was obtained from all adults. An informed written consent was obtained from guardians of all patients less than 18 years enrolled, as per ethical guidelines regulations in Saudi Arabia. Purpose, potential risk and benefits of the endoscopy have been communicated in Arabic language and consent was documented for all participants. The ethical approval for the current study was obtained from the ethical committee at the Faculty of Medicine, Jazan University. It should be noted that the study was based on the secondary data collected from the patient's files during the study period, so it does not deal with any personal data, since it was anonymous.

Results

A total of 3287 UGIE's were performed over the 11 year period of the study. Table 1 (next page) illustrates some background characteristics of the study population. The mean age of the participants was 45 years (SD=18.4). Around 38.7% of study participants were less than 40 years old, followed by 34.8% of participants who were in the age group 40 to 59 years old. The majority of study participants were Saudi 86.1%, compared to 13.9% who were non-Saudi. Only 5.8% of study subjects reported tobacco use. Male participants constituted 61.1%, of the study participants while those females were 38.9%.

According to Table 2, (page 6) the commonest indications for endoscopy among study participants were UGI bleeding (23.3%), with a significant difference between males and females (p -value=0.000), (29.2%) and (14.3%) respectively. Epigastric pain was the second indication (15.7%) also with a significant difference between male and female patients (p -value=0.000). Acid Peptic Disease (APD) was the third indication for UGIE (14.4%), followed by Dyspepsia (7.5%) and regular follow-up (6.5%). Other causes were Reflux Oesophagitis (5.5%), Dysphagia (4.3%), Abdominal pain (3.8%), Pers. Nausea/Vomiting(3.6%) and Anemia (3.2%).

Table 3 presents results on findings of upper GI endoscopy among the studied patients according to gender and age groups. The table suggests that endoscopic diagnoses revealed normal findings in 21.3% of patients. Normal findings for females were (31.0%) significantly higher than for male patients (15.5%), p -value = 0.000. Normal findings also differ significantly according to age groups (p -value =0.000), and show a decreasing trend with increase in patient's age. Table 3 further confirmed that pattern of

Table 1: Age distribution, nationality and Tobacco use among study participants

| Characteristics | Males No % | Females No % | Total No % |
|---------------------------|--------------------|--------------------|--------------------|
| Age Groups | | | |
| <i>Less than 40 years</i> | 692(34.4) | 580(45.4) | 1272(38.7) |
| <i>40-59</i> | 761(37.9) | 384(30.1) | 1145(34.8) |
| <i>60 and above</i> | 557(27.7) | 313(24.5) | 870(26.5) |
| <i>Mean</i> | 47.0 | 42.7 | 45.3 |
| <i>Median</i> | 45.0 | 40.0 | 44.0 |
| <i>Mode</i> | 40.0 | 40.0 | 40.0 |
| <i>SD</i> | 17.9 | 18.8 | 18.4 |
| Nationality | | | |
| <i>Saudi</i> | 1643(81.7) | 1187(93.0) | 2830(86.1) |
| <i>Non-Saudi</i> | 367(18.3) | 90(7.0) | 457(13.9) |
| Tobacco use | | | |
| <i>Users</i> | 186(9.3) | 6(0.50) | 192(5.8) |
| <i>Not users</i> | 507(25.2) | 478(37.4) | 985(30.0) |
| <i>Not stated</i> | 1317(65.5) | 793(62.1) | 2110(64.2) |
| Total | 2010(100.0) | 1277(100.0) | 3287(100.0) |

Table 2: Causes of referral of the studied patients to the upper endoscopy unit according gender

| Indications | Gender | | | Total No % |
|----------------------------------|------------------|------------------|----------------|------------------|
| | Males No % | Females No % | <i>P-value</i> | |
| <i>UGI bleeding</i> | 587 (29.2) | 182(14.3) | 0.0000 | 769(23.3) |
| <i>Epigastric pain</i> | 282(14.0) | 235(18.4) | 0.0000 | 517(15.7) |
| <i>APD (Acid Peptic Disease)</i> | 259(12.9) | 213(16.7) | 0.0025 | 472(14.4) |
| <i>Dyspepsia</i> | 115(5.7) | 132(10.3) | 0.6455 | 247(7.5) |
| <i>Follow-up</i> | 103(7.8) | 36(4.5) | 0.0000 | 139(6.5) |
| <i>Reflux Oesophagitis</i> | 119(5.9) | 63(4.9) | 0.0000 | 182(5.5) |
| <i>Dysphagia</i> | 80(4.0) | 60(4.7) | 0.3221 | 140(4.3) |
| <i>Abdominal pain</i> | 75(3.7) | 49(3.8) | 0.8728 | 124(3.8) |
| <i>Pers. Nausea/Vomiting</i> | 50(2.5) | 69(5.4) | 0.0000 | 119(3.6) |
| <i>Anemia</i> | 57(2.8) | 47(3.7) | 0.1770 | 104(3.2) |
| <i>Chr. liver disease</i> | 56(2.8) | 12(0.9) | 0.0003 | 68(2.1) |
| <i>Oesophageal varices</i> | 50(2.5) | 5(0.4) | 0.0000 | 55(1.7) |
| <i>Malignancy</i> | 24(1.8) | 11(1.4) | 0.3628 | 35(1.6) |
| <i>Oesophageal stricture</i> | 23(1.1) | 18(1.4) | 0.5028 | 41(1.2) |
| <i>Heartburn</i> | 6(0.3) | 5(0.4) | 0.6527 | 11(0.3) |
| <i>Anorexia</i> | 2(0.1) | 2(0.2) | 0.6455 | 4(0.1) |
| <i>Other indications</i> | 122(2.9) | 138(8.6) | 0.0000 | 260(5.2) |
| Total | 2010(100) | 1277(100) | | 3287(100) |

Table 3: Findings of upper endoscopy among the studied patients according to gender and age groups

| Findings | Gender | | Age groups | | | P-value | Total* No % |
|----------------------------------|---------------|-----------------|------------|-------------|---------------|-----------|----------------|
| | Males No % | Females No % | P-value | <40 No % | 45-59 No % | | |
| Normal | 398(15.5) | 478(31.0) | 0.0000 | 454(30.3) | 274(18.6) | 148(12.9) | 876(21.3) |
| Oesophagitis | 235(9.1) | 172(11.1) | 0.03662 | 169(11.3) | 123(8.4) | 115(10.0) | 407(10.0) |
| Oesoph. Varices | 509(19.8) | 115(7.4) | 0.0000 | 137(9.1) | 321(21.8) | 166(14.4) | 624(15.2) |
| Oesoph. Stricture | 47(1.8) | 44(2.8) | 0.03078 | 61(4.1) | 6(0.4) | 24(2.1) | 91(2.2) |
| Oesoph. Mass | 18(0.7) | 21(1.4) | 0.034 | 6(0.4) | 10(0.7) | 23(2.0) | 39(0.9) |
| Oesoph. Ulcer | 67(2.6) | 30(1.9) | 0.0000 | 24(1.6) | 27(1.8) | 46(4.0) | 97(2.4) |
| Hiatus hernia | 151(5.9) | 111(7.2) | 0.09296 | 69(4.6) | 89(6.1) | 104(9.1) | 262(6.4) |
| Gastritis | 340(13.2) | 237(15.3) | 0.05614 | 204(13.6) | 193(13.1) | 180(15.7) | 577(14.0) |
| Gastric Varices | 31(1.2) | 4(0.3) | 0.00138 | 9(0.6) | 14(1.0) | 12(1.0) | 35(0.9) |
| Hypertensive Gastropathy (HG) | 73(2.8) | 21(1.4) | 0.00214 | 13(0.9) | 58(3.9) | 23(2.0) | 94(2.3) |
| Gastric Ulcer | 108(4.2) | 45(2.9) | 0.03486 | 40(2.7) | 55(3.7) | 58(5.0) | 153(3.7) |
| Gastric Mass | 41(1.6) | 26(1.7) | 0.82588 | 18(1.2) | 12(0.8) | 37(3.2) | 67(1.6) |
| Duodenitis | 163(6.3) | 81(5.2) | 0.15272 | 98(6.5) | 97(6.6) | 49(4.3) | 244(5.9) |
| Duodenal Ulcer | 286(11.1) | 83(5.4) | 0.0000 | 127(8.5) | 132(9.0) | 110(9.6) | 369(9.0) |
| Gastric Erosion | 46(1.8) | 23(1.5) | 0.47152 | 23(1.5) | 15(1.0) | 31(2.7) | 69(1.7) |
| Duodenal Erosion | 40(1.6) | 37(2.4) | 0.0536 | 33(2.2) | 28(1.9) | 16(1.4) | 77(1.9) |
| Hyperemia of GE. J. | 11(0.4) | 8(0.5) | 0.67448 | 8(0.5) | 9(0.6) | 2(0.2) | 19(0.5) |
| Gastric Atrophy | 8(0.3) | 7(0.5) | 0.4654 | 5(0.3) | 6(0.4) | 4(0.3) | 15(0.4) |
| Malignancy | 1(0.0) | 1(0.1) | 0.71138 | 0(0.0) | 1(0.1) | 1(0.1) | 2(0.0) |

* Some patients have more than one disease.

endoscopic diagnoses shows the persistence of three common diseases; Oesoph Varices (15.2%), Gastritis(14.0%) and Oesophagitis(10%). Oesoph. Varices was significantly higher among males than females, and also significantly different among the three different age groups (p-value =0.0000). Gastritis increases with increase in age but with no significant differences between the different three age groups and gender. Regarding the other findings, Duodenal Ulcer was diagnosed in (9%) of

the patients and was significantly higher in males than females. Gastric Ulcer disease was diagnosed in only (3.7%) of the patients.

The results of logistic regression analyses for potential risk factors of three common endoscopic findings are shown in Table 4. The analysis revealed that gender, and patient's age was associated with a significantly high risk of Oesoph. Varices (OR=3.43 and 1.95 respectively and

Table 4: Logistic Regression Analyses for potential risk factors of common UGI findings among the study patients

| Category | Oesoph. Varices | | | Gastritis | | | Oesophagitis | | |
|-----------------------|-----------------|------------|---------|-----------|------------|---------|--------------|-----------|---------|
| | OR | 95% C.I. | P-value | OR | 95% C.I. | P-value | OR | 95% C.I. | P-value |
| Gender | | | | | | | | | |
| Female* | 1 | | | 1 | | | 1 | | |
| Male | 3.43 | 2.76 -4.25 | 0.000 | 0.89 | 0.74-1.07 | 0.227 | 0.851 | 0.68-1.05 | 0.132 |
| Age groups | | | | | | | | | |
| Less than 40* | 1 | | | 1 | | | 1 | | |
| 40-59 | 1.95 | 1.53-2.50 | 0.000 | 1.36 | 1.09- 1.70 | 0.006 | 1.0 | 0.77-1.28 | 0.964 |
| 60 and above | 0.60 | 0.49-749 | 0.000 | 1.28 | 1.02- 1.61 | 0.028 | 1.27 | 0.97-1.66 | 0.089 |
| Smoking status | | | | | | | | | |
| No* | 1 | | | 1 | | | 1 | | |
| Yes | 0.73 | 0.48-1.09 | 0.128 | 2.786 | 1.75-4.44 | 0.000 | 1.34 | 0.80-2.22 | 0.265 |
| NSAID USE | | | | | | | | | |
| Yes* | 1 | | | 1 | | | 1 | | |
| No | 2.8 | 0.65-11.5 | 0.165 | 4.284 | 1.02-17.9 | 0.046 | 1.16 | 0.40-3.30 | 0.785 |

*Reference Category

P-value< 0.001 for all). The table also suggested that the most important independent predictors of Gastritis were patients' age, smoking status and NSAID use (OR = 1.36, 12.8, 2.786 and 4.284 respectively, p-value< 0.05 for all coefficients). None of the variables mentioned in the table were a significant predictor of Oesophagitis (p-value>0.05 for all).

Discussion

Gastrointestinal (GI) diseases are sources for substantial morbidity and mortality in developing as well as in developed countries [22]. Gastrointestinal disorders are among the common causes of visiting health care facilities in Saudi Arabia [10-13]. These types of diseases affect patients' quality of life; cause a significant reduction in work productivity and increased economic burden [23&24].

This is the first study that has dealt with UGI E in Gizan region. Previously published work on UGI endoscopy in Gizan investigated Barrett's oesophagus and oesophageal cancer [25]. The present study attempted to study the common indications and findings of upper endoscopy in patients in Gizan patients presenting to King Fahd Central Hospital. A total of 3287 UGI endoscopy were performed over the 11 year period of the study. The results of the study suggested that UGI bleeding was the indication for UGIE in the vast majority of our patients. Such a high proportion has not been reported before by the studies conducted in KSA [26, 27], while a similar trend can be observed from other West African and East African studies [28-29]. From this study, the next most common indication for UGI is Epigastric pain, which is also different from studies conducted in other parts of KSA[26, 27].

The differences in the commonest indication may be due to differences in the terminologies used. Epigastric pain is localized to the region of the upper abdomen. It is a common symptom of gastroesophageal reflux disease (GERD) or heartburn. On the other hand Acid Peptic Disease (APD) was reported as the third indication for undergoing UGIE. APD is a collective term used to include many conditions such as gastro-esophageal reflux disease (GERD), gastritis, gastric ulcer, duodenal ulcer, esophageal ulcer and Zollinger Ellison Syndrome (ZES). Other common reasons for UGIE among our patients were Dyspepsia, Reflux Oesophagitis, dyspepsia GERD symptoms, recurrent vomiting and anemia. Only 1.6% of our patients underwent UGIE for Malignancy. Although Dyspepsia is less encountered in our studies, it accounts for 15-77.5% of indications for UGIE in Saudi Arabia and other studies elsewhere [26, 30-34].

This study documented three common diseases reported by upper endoscopy procedures which are; OesophVarices, Gastritis and Oesophagitis. The results suggest that esophageal disease is common in Jazan region. Other studies in Saudi Arabia indicate the low prevalence of such diseases [12,26]. The finding that the prevalence of esophageal varices in Gizan differs from other parts of Saudi Arabia [26] draws question whether it is linked to schistosomiasis, which may be the underlying

cause of esophageal varices in the region, during the study time. Similar prevalence was reported in Sudan in which schistosomiasis is prevalent [35]. Suliman et al, 2010 attributed the increase of esophageal disorders to the changes in life style and nutritional habits in Saudi Arabia[33].

Gastritis is a well known heterogeneous pathological condition that is responsible for the incidence of many gastrointestinal diseases. Literature suggests that the prevalence of gastritis among adults in the Western world is estimated at 62%[36]. In the present study, Gastritis was the commonest pathology reported in our patients with prevalence of 14%, which is similar to other studies in Saudi and other Arabian countries [12,26, 35]. The difference between our results and western countries' prevalence regarding Gastritis may be attributed to life style and alcohol use, which is not prevalent in Saudi Arabia.

In the present study normal endoscopy was reported more commonly in females (31.2%) as compared to males (15.3%) showing that more females suffer from gastrointestinal symptoms in our setup. Although the rate of normal endoscopy is similar to other Saudi studies conducted during the past 20 years [10-12], it calls for more in-depth investigation, when compared to more recent Saudi and regional studies [26&35].

In this article an effort was made to document the reasons for and outcome of upper gastrointestinal endoscopy in Gizan region for the first time. The limitations of this study are that subjects were studied in a single hospital only. In addition, the fact that the study was based on a retrospective study design may not allow for proper causal inferences and study variables were limited to what was available in patients' files.

Conclusion

In conclusion the results of the study suggested that UGIE bleeding was the main indication for UGIE in the vast majority of our patients. In addition to that three common diseases; Oesophageal Varices, Gastritis and Oesophagitis were the main findings of the UGIE among the study population. Preventive measures should be adopted to cope with the situation and to prevent complications of esophageal and gastritis diseases among the Gizan population.

Acknowledgement:

I would like to thank the nursing and medical staff of the endoscopic unit of the King Fahad Central Hospital, Jazan Region KSA.

Abbreviations

| | |
|--------|---|
| KSA | Kingdom of Saudi Arabia |
| UGIE | Upper gastrointestinal endoscopy |
| GI | Gastrointestinal |
| EGD | Oesophagogastroduodenoscopy |
| KFCH | King Fahd Central Hospital |
| APD | Acid Peptic Disease |
| Oesoph | Oesophageal |
| SD | Standard Deviation |
| HG | Hypertensive gastropathy |
| GERD | Gastro-esophageal reflux disease |
| ZES | Zollinger Ellison Syndrome |
| CI | Confidence Interval |
| SPSS | Statistical Package for Social Sciences |
| NSAIDS | Nonsteroidal anti-inflammatory drugs |
| GE. J. | Gastroesophageal Junction |

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Chronic obstructive pulmonary disease may be one of the terminal endpoints of the sickle cell diseases

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Abstract

Background: Sickle cell diseases (SCDs) are chronic destructive processes on vascular endothelium initiating at birth all over the body. We tried to understand whether or not there is an association between chronic obstructive pulmonary disease (COPD) and severity of the SCDs.

Methods: All patients with the SCDs were taken into the study.

Results: The study included 411 patients with the SCDs (199 females and 212 males). There were 60 patients (14.5%) with the COPD. Mean age of the patients was significantly higher in the COPD group (33.0 versus 29.5 years, $P=0.005$). The male ratio was significantly higher in the COPD group, too (80.0% versus 46.7%, $P<0.001$). Smoking was also higher in the COPD group, significantly (36.6% versus 9.9%, $P<0.001$). Parallel to the smoking, alcoholism was also higher among the COPD cases, significantly (3.3% versus 0.8%, $P<0.05$). Beside these, transfused red blood cell units in their lives (69.1 versus 32.9, $P=0.001$), priapism (10.0% versus 1.9%, $P<0.001$), leg ulcers (26.6% versus 11.6%, $P<0.001$), digital clubbing (25.0% versus 7.1%, $P<0.001$), coronary heart disease (26.6% versus 13.1%, $P<0.01$), chronic renal disease (16.6% versus 7.1%, $P<0.01$), and stroke (20.0% versus 7.9%, $P<0.001$) were all higher among the COPD cases, significantly.

Conclusion: SCDs are chronic catastrophic processes on vascular endothelium particularly at the capillary level, and terminate with accelerated atherosclerosis induced end-organ failures in early years of life. COPD may be one of the terminal endpoints of the diseases.

Key words: Sickle cell diseases, chronic obstructive pulmonary disease, chronic endothelial damage

Introduction

Chronic endothelial damage induced atherosclerosis may be the major cause of aging and death by causing disseminated tissue ischemia all over the body. For example, cardiac cirrhosis develops due to the prolonged hepatic hypoxia in patients with pulmonary and/or cardiac diseases. Probably the whole afferent vasculature including capillaries are involved in the process. Some of the well-known accelerators of the inflammatory process are physical inactivity, weight gain, smoking, and alcohol intake for the development of irreversible endpoints including obesity, hypertension (HT), diabetes mellitus (DM), cirrhosis, peripheral artery disease (PAD), chronic obstructive pulmonary disease (COPD), chronic renal disease (CRD), coronary heart disease (CHD), mesenteric ischemia, osteoporosis, and stroke, all of which terminate with early aging and death. They were researched under the title of metabolic syndrome in the literature, extensively (1, 2). Similarly, sickle cell diseases (SCDs) are chronic catastrophic processes on vascular endothelium, particularly at the capillary level. Hemoglobin S (HbS) causes loss of elastic and biconcave disc shaped structures of red blood cells (RBCs). Probably, loss of elasticity is the major problem, since sickling is rare in the peripheral blood samples of the SCDs patients associated with thalassemia minors, and human survival is not so affected in hereditary spherocytosis or elliptocytosis. Loss of elasticity is probably present in whole lifespan, but exaggerated with increased metabolic rate and various stresses of the body. The hard cells induced prolonged endothelial inflammation, remodeling, and fibrosis mainly at the capillary level terminate with disseminated tissue hypoxia all over the body (3, 4). On the other hand, obvious vascular occlusions may not develop in greater vasculature due to the transport instead of distribution function of them. We tried to understand whether or not there is an association between COPD and severity of SCDs in the present study.

Material and Methods

The study was performed in Medical Faculty of the Mustafa Kemal University between March 2007 and July 2015. All patients with the SCDs were studied. The SCDs are diagnosed with the hemoglobin electrophoresis performed via high performance liquid chromatography (HPLC) method. Medical histories including smoking habit, regular alcohol consumption, painful crises per year, transfused RBC units in their lives, surgical operations, priapism, leg ulcers, and stroke were learnt. Patients with a history of one pack-year were accepted as smokers, and one drink-year were accepted as drinkers. Cases with acute painful crises or any other inflammatory event were treated at first, and then the laboratory tests and clinical measurements were performed on the silent phase. A check up procedure including serum iron, iron binding capacity, ferritin, creatinine, liver function tests, markers of hepatitis viruses A, B, and C and human immunodeficiency virus, a posterior-anterior chest x-ray film, an electrocardiogram,

a Doppler echocardiogram both to evaluate cardiac walls and valves and to measure the systolic blood pressure (BP) of pulmonary artery, an abdominal ultrasonography, a computed tomography of brain, and a magnetic resonance imaging (MRI) of hips was performed. Other bones for avascular necrosis were scanned according to the patients' complaints. So avascular necrosis of bones was diagnosed by means of MRI (5). Stroke is diagnosed by the computed tomography of brain. Acute chest syndrome is diagnosed clinically with the presence of new infiltrates on chest x-ray film, fever, cough, sputum production, dyspnea, or hypoxia in the patients (6). An x-ray film of abdomen in upright position was taken just in patients with abdominal distention or discomfort, vomiting, obstipation, or lack of bowel movement. The criterion for diagnosis of COPD is post-bronchodilator forced expiratory volume in one second/forced vital capacity of less than 70% (7). Systolic BP of the pulmonary artery of 40 mmHg or higher is accepted as pulmonary hypertension (8). CRD is diagnosed with a persistent serum creatinine level of 1.3 mg/dL in males and 1.2 mg/dL in females. Cirrhosis is diagnosed with findings of physical examination, hepatic function tests, ultrasonographic findings, and histologic procedure in case of indication. Digital clubbing is diagnosed with the ratio of distal phalangeal diameter to interphalangeal diameter which is greater than 1.0 and with the presence of Schamroth's sign (9, 10). Associated thalassemia minors are detected with serum iron, iron binding capacity, ferritin, and hemoglobin electrophoresis performed via HPLC method. An exercise electrocardiogram is just performed in cases with an abnormal electrocardiogram and/or angina pectoris. Coronary angiography is taken just for the exercise electrocardiogram positive cases. So CHD was diagnosed either angiographically or with the Doppler echocardiographic findings as the movement disorders in the cardiac walls. Rheumatic heart disease is diagnosed with the echocardiographic findings, too. Ileus is diagnosed with gaseous distention of isolated segments of bowel, vomiting, obstipation, cramps, and with the absence of peristaltic activity of the abdomen. Ophthalmologic examination was performed according to the patients' complaints. Eventually, cases with COPD and without were collected into the two groups, and they were compared in between. Mann-Whitney U test, Independent-Samples t test, and comparison of proportions were used as the methods of statistical analyses.

Results

The study included 411 patients with the SCDs (199 females and 212 males). There were 60 patients (14.5%) with the COPD. Mean age of patients was significantly higher in the COPD group (33.0 versus 29.5 years, $P=0.005$). The male ratio was significantly higher in the COPD group, too (80.0% versus 46.7%, $P<0.001$). Smoking was also higher among the COPD cases, significantly (36.6% versus 9.9%, $P<0.001$). Parallel to the smoking, alcoholism was also higher among the COPD cases, significantly (3.3% versus 0.8%, $P<0.05$). Prevalence of associated thalassemia minors were similar in both groups (71.6% versus 66.6% in the COPD group and other, respectively, $P>0.05$) (Table

Table 1: Characteristic features of the study cases

| Variables | Cases with COPD* | P-value | Cases without COPD |
|------------------------|----------------------------|------------------|---------------------------|
| Prevalence | 14.5% (60) | | 85.4% (351) |
| Male ratio | 80.0% (48) | <0.001 | 46.7% (164) |
| Mean age (year) | 33.0 ± 10.0 (13-58) | 0.005 | 29.5 ± 10.1 (5-59) |
| Thalassemia minors | 71.6% (43) | Ns† | 66.6% (234) |
| Smoking | 36.6% (22) | <0.001 | 9.9% (35) |
| Alcoholism | 3.3% (2) | <0.05 | 0.8% (3) |

*Chronic obstructive pulmonary disease †Nonsignificant (P>0.05)

Table 2: Associated pathologies of the study cases

| Variables | Cases with COPD* | P-value | Cases without COPD |
|------------------------------|----------------------------|------------------|----------------------------|
| Painful crises per year | 6.3 ± 8.7 (0-36) | Ns† | 5.1 ± 8.4 (0-52) |
| Transfused RBC‡ units | 69.1 ± 89.1 (0-434) | 0.001 | 32.9 ± 39.8 (0-250) |
| Priapism | 10.0% (6) | <0.001 | 1.9% (7) |
| Ileus | 5.0% (3) | Ns | 3.4% (12) |
| Cirrhosis | 6.6% (4) | Ns | 3.7% (13) |
| Leg ulcers | 26.6% (16) | <0.001 | 11.6% (41) |
| Pulmonary hypertension | 11.6% (7) | Ns | 12.8% (45) |
| Digital clubbing | 25.0% (15) | <0.001 | 7.1% (25) |
| CHD§ | 26.6% (16) | <0.01 | 13.1% (46) |
| CRD¶ | 16.6% (10) | <0.01 | 7.1% (25) |
| Rheumatic heart disease | 8.3% (5) | Ns | 5.1% (18) |
| Avascular necrosis of bones | 20.0% (12) | Ns | 24.2% (85) |
| ACS** | 1.6% (1) | Ns | 3.9% (14) |
| Stroke | 20.0% (12) | <0.001 | 7.9% (28) |
| Mortality | 8.3% (5) | Ns | 6.2% (22) |

*Chronic obstructive pulmonary disease †Nonsignificant (P>0.05) ‡Red blood cell §Coronary heart disease Chronic renal disease **Acute chest syndrome

Table 3: Peripheral blood values of the study cases

| Variables | Cases with COPD* | P-value | Cases without COPD |
|------------------------|--|---------|---|
| Mean WBC+ counts (/µL) | 15.796 ± 6.374 (6.600-36.900) | Ns† | 14.879 ± 6.670 (1.580-48.500) |
| Mean Hct§ values (%) | 22.8 ± 6.0 (10-35) | Ns | 23.7 ± 5.0 (8-42) |
| Mean PLT¶ counts (/µL) | 433.071 ± 177.283 (113.000-1.142.000) | Ns | 457.538 ± 236.171 (48.800-1.827.000) |

*Chronic obstructive pulmonary disease †White blood cell ‡Nonsignificant (P>0.05) §Hematocrit ¶Platelet

1). On the other hand, transfused RBC units in their lives (69.1 versus 32.9, $P=0.001$), priapism (10.0% versus 1.9%, $P<0.001$), leg ulcers (26.6% versus 11.6%, $P<0.001$), digital clubbing (25.0% versus 7.1%, $P<0.001$), CHD (26.6% versus 13.1%, $P<0.01$), CRD (16.6% versus 7.1%, $P<0.01$), and stroke (20.0% versus 7.9%, $P<0.001$) were all higher among the COPD cases, significantly (Table 2). The differences according to the mean white blood cell (WBC) counts, hematocrit (Hct) value, and platelet (PLT) counts of peripheric blood were nonsignificant ($P>0.05$) between the two groups (Table 3). Beside these there were three patients with sickle cell retinopathy, all of them were found in cases without the COPD. There were 27 mortality during the nine-year follow up period, and 14 of them were males. The mean ages of mortality were 33.6 ± 9.5 (range 19-47) in females and 30.8 ± 8.9 years (range 19-50) in males ($P>0.05$). Additionally, there were four patients with HBsAg positivity (0.9%) but HBV DNA was positive in none of them by polymerase chain reaction (PCR) method. Although antiHCV was positive in 25 (6.0%) of the study cases, HCV RNA was detected as positive just in four patients by PCR method.

Discussion

Chronic endothelial damage induced atherosclerosis may be the most common type of vasculitis, and the leading cause of morbidity, mortality, and aging in human beings. Although it is much more common in the elderly, chronic inflammatory processes including SCDs, rheumatologic disorders, cancers, and chronic infections decrease the age of involvement. Probably the whole afferent vasculature including capillaries are involved in the process. Much higher BP of the afferent vasculature may be the major underlying cause, and efferent vascular endothelium are probably protected due to the much lower BP in them. Secondary to the chronic endothelial damage, inflammation, and fibrosis, vascular walls become thickened, their lumens are narrowed, and they lose their elastic natures which reduce the blood flow and increase BP further. Although early withdrawal of the causative factors including physical inactivity, weight gain, smoking, and alcohol intake may prevent terminal consequences, after development of cirrhosis, COPD, CRD, CHD, PAD, or stroke, the endothelial changes may not be reversed completely due to the fibrotic nature of them (11).

SCDs are life-threatening genetic disorders nearly affecting 100,000 individuals in the United States (12). As a difference from other causes of atherosclerosis, the SCDs probably keep vascular endothelium particularly at the capillary level (13), since the capillary system is the main distributor of the hard RBCs to the tissues. The hard cells induced chronic endothelial damage, inflammation, and fibrosis build up, an advanced atherosclerosis in much younger ages of the patients. As a result, lifespans of the patients with SCDs were 48 years in females and 42 years in males in the literature (14), whereas they were 33.6 and 30.8 years in the present study, respectively. The great differences may be secondary to delayed initiation of hydroxyurea therapy and inadequate RBC supports in

emergencies in our country. On the other hand, longer lifespan of females with the SCDs (14) and longer overall survival of females in the world (15) can not be explained by the atherosclerotic effects of smoking or alcohol alone, instead it may be explained by more physical power requiring role of male sex in life that may terminate with an exaggerated sickling and/or atherosclerosis all over the body (16).

COPD is the third leading cause of death with differing causes, pathogenic mechanisms, and physiological effects, worldwide (17). It is an inflammatory disease that may mainly affect the pulmonary vasculature, and aging, smoking, and excess weight may be major causes. As also observed in the present study, regular alcohol consumption may also take place in the inflammatory process. Similarly, COPD was one of the most frequent diagnoses in patients with alcohol dependence in another study (18). Additionally, 30-day readmission rate was higher in COPD patients with alcoholism (19). Probably the accelerated atherosclerotic process is the main structural background of functional changes characteristic of the COPD. The inflammatory process of endothelium is enhanced by release of various chemicals by inflammatory cells, and it terminates with fibrosis, atherosclerosis, and pulmonary losses. Although COPD may mainly be an accelerated atherosclerotic process of the pulmonary vasculature, there are several reports about coexistence of an associated endothelial inflammation all over the body (20, 21). For example, there may be a close relationships between COPD, CHD, PAD, and stroke in a previous study (22). Similarly, two-thirds of mortality were caused by cardiovascular diseases and lung cancers, and CHD was the most common one among them in a multi-center study performed on 5,887 smokers (23). When the hospitalizations were researched, the most common causes were the cardiovascular diseases again (23). In another study, 27% of all mortality was due to the cardiovascular causes in the moderate and severe COPD patients (24). As also shown in a previous study (25), COPD may be one of the terminal endpoints of SCDs due to the higher prevalences of priapism, leg ulcers, clubbing, CHD, CRD, and stroke in the group with COPD in the present study.

Smoking may have a major role in systemic atherosclerotic processes such as COPD, digital clubbing, cirrhosis, CRD, PAD, CHD, stroke, and cancers (11, 26). Its atherosclerotic effects are the most obvious in Buerger's disease and COPD. Buerger's disease is an inflammatory process terminating with obliterative changes in small and medium-sized vessels, and it has never been reported in the absence of smoking. Smoking induced endothelial damage probably affects pulmonary vasculature much more than the other organs due to the higher concentration of its products in the respiratory system. But it may even cause cirrhosis, CRD, PAD, CHD, stroke, and cancers with the transport of its products in the blood. COPD may also be accepted as a localized Buerger's disease of the lungs. Although its strong atherosclerotic effects, smoking in human beings and nicotine administration in animals may be associated with some weight loss (27), there may be an increased

energy expenditure during smoking (28), and nicotine may decrease caloric intake in a dose-related manner (29). Nicotine may lengthen intermeal time, and decrease amount of meal eaten (30). Body mass index (BMI) seems to be the highest in former, the lowest in current, and medium in never smokers (31). Similarly, smoking may also show the weakness of volition to control eating, and prevalences of HT, DM, and smoking were the highest in the highest triglyceride having group as a significant parameter of the metabolic syndrome (32). Additionally, although CHD were detected with similar prevalences in both sexes (26), smoking and COPD were higher in males against the higher prevalences of BMI and its consequences including dyslipidemia, HT, and DM in females. Probably tobacco smoke induced acute inflammation on vascular endothelium all over the body is the major cause of loss of appetite, since the body doesn't want to eat during fighting. On the other hand, when we thought of some antidepressant properties of smoking and alcohol, the higher prevalences of them may also indicate some additional stresses on male sex in life and shortened survival of them.

Regular alcohol consumption may also cause an endothelial inflammation all over the body (33). Similar to the tobacco smoke, alcohol leads to an increased proinflammatory cytokine secretion and reactive oxygen species (ROS) production by tissue macrophages that damage organs via oxidative stresses, and these effects lie far beyond lung and liver. Against harmful effects of the ROS, there are enzymatic and non-enzymatic antioxidants in the body. Enzymatic ones include catalase, superoxide dismutase, glutathione reductase, and glutathione peroxidase and non-enzymatic ones include glutathione, carotene, bilirubin, tocopherol, uric acid, and metal ions (34). In a previous study, both tobacco smoke and ethyl alcohol resulted in a change of glutathione levels in serum and tissues in rats, and tobacco smoke had the strongest effect on protein nitrosylation in the brain (34). Ethyl alcohol had effects on glutathione level in serum, kidney, and brain, and superoxide dismutase activity in the brain (34). Chronic endothelial effects of alcohol may even be seen in the absence of a significant liver disease. For example, erectile dysfunction was significantly higher among aborigines with the risk of alcohol dependence in another study (35). There was a significant increase in leukocyte adhesion after chronic alcohol exposition in pancreas, and histological changes and cytokine levels correlated with the duration of exposition in rats in another study (36). Probably, cirrhosis is also a capillary endothelial inflammation terminated with disseminated hepatic destruction (37), and it may even be accepted as a localized Buerger's disease of the liver caused by alcohol. Stromal cells including hepatic stellate and endothelial cells have been proposed to control the balance between hepatic fibrosis and regeneration, but chronic damage eventually leads to progressive substitution of hepatic parenchyma by scar tissue resulting with cirrhosis (38). Although atherosclerotic effects of alcohol are the most obvious on liver due to the highest concentrations of its products via the portal blood flow (33), alcohol may even

cause COPD, digital clubbing, CRD, PAD, CHD, stroke, and cancers like other atherosclerotic endpoints by the transport of its products within the blood.

Digital changes may help to identify some systemic disorders within the body. For example, digital clubbing is characterized by loss of normal $<165^\circ$ angle between the nailbed and fold, increased convexity of the nail fold, and thickening of the whole distal finger (39). Some authors found clubbing in 0.9% of all patients admitted to the department of internal medicine (9), whereas the prevalence was 4.2% in both sexes in our university (11). The exact cause and significance is unknown but chronic tissue hypoxia induced vasodilation and secretion of growth factors have been proposed (40-43). In the above study, only 40% of clubbing cases turned out to have significant underlying diseases while 60% remained well over the subsequent years (9). But according to our experiences, digital clubbing is frequently associated with smoking and pulmonary, cardiac, and/or hepatic disorders that are featuring with chronic tissue hypoxia since lungs, heart, and liver are closely related organs that affect their functions in a short period of time. Similarly, digital clubbing may be an indicator of disseminated atherosclerosis particularly at the capillary level in the SCDs, and we observed clubbing in 9.7% of all patients with the SCDs in the present study. In addition to the SCDs, the higher prevalences of smoking ($P<0.001$) and clubbing ($P<0.001$) in the COPD group may also indicate some additional roles of smoking and COPD on clubbing.

Leg ulcers are seen in 10 to 20% of patients with the SCDs (44), and the ratio was 13.8% in the present study. The incidence increases with age, and they are also common in males and sickle cell anemia (HbSS) cases (44). Similarly, leg ulcers were found as 19.3% in males versus 8.0% in females ($P<0.001$) in the present study. Beside that, mean ages of the patients with leg ulcers were significantly higher than the others (34.8 versus 29.2 years, $P<0.000$). The leg ulcers have an intractable nature, and around 97% of healed ulcers relapse in a period of one year (45). As an evidence of their atherosclerotic natures, the leg ulcers occur in distal areas with less collateral blood flow in the body (45). Chronic endothelial damage particularly at the capillary level due to the hard RBCs may be the major cause in the SCDs (44). Prolonged exposure to the hard RBCs due to the blood pooling in the lower extremities by the effect of gravity may also explain the leg but not arm ulcers in the SCDs. As also observed in venous ulcers of the legs, venous insufficiencies may also accelerate the process by causing pooling of causative hard RBCs in the legs. Probably pooling of blood in the lower extremities is also true for the diabetic ulcers, Buerger's disease, digital clubbing, varicose veins, and onychomycosis. Beside the hard RBCs of the SCDs, smoking and alcohol may also have some additional roles for the leg ulcers since both of them are much more common in males, and their atherosclerotic effects are obvious particularly in COPD, Buerger's disease, and cirrhosis (44). According to our nine-year experiences, prolonged resolution of ulcers with hydroxyurea may also suggest that the ulcers may

be secondary to increased WBC and PLT counts induced disseminated endothelial edema particularly at the capillary level.

Stroke is also a common complication of the SCDs (47). Similar to the leg ulcers, it is higher in the HbSS cases (48). Moreover, a higher WBC count is associated with a higher incidence of stroke (49). Sickling induced endothelial injury and activations of WBC and PLTs may terminate with chronic endothelial inflammation, edema, remodeling, and fibrosis in the brain (50). Stroke of the SCDs may not have a macrovascular origin, instead disseminated endothelial inflammation and edema may be much more important at the capillary level. Infection, inflammation, and various stresses may precipitate stroke, since increased metabolic rate may accelerate sickling and secondary endothelial edema. Similar to the leg ulcers, a significant reduction of stroke with hydroxyurea may also suggest that a significant proportion of stroke is secondary to increased WBC and PLT counts induced disseminated endothelial edema in the SCDs (13, 51).

As a conclusion, SCDs are chronic catastrophic processes on vascular endothelium particularly at the capillary level, and terminate with accelerated atherosclerosis induced end-organ failures in early years of life. COPD may be one of the terminal endpoints of the diseases.

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Enabling Factors and Barriers among Health Policy Makers toward Utilization of National Medical Research' Recommendations in Jeddah, 2010

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Abstract

Background: There is concern for the international community that research findings are not utilized by health policy-makers to the extent that they could be. The review of literature revealed that most of the findings from this field are based on studies from developed countries, and relatively little is known about these factors in developing countries. Moreover, although a considerable number of health related research is conducted in Jeddah Governorate every year, less is put into consideration. This situation might have negative implications on the implementation of research in the future.

Objectives: The current study aimed at identifying enabling factors and determining barriers among health policy makers toward utilization of national medical research' recommendations in Jeddah city, Saudi Arabia, 2010.

Methods: A cross sectional descriptive study was conducted in MOH hospitals and PHCC sectors and private hospitals and dispensaries. Self administered questionnaires were distributed to

210 general managers and medical directors of MOH governmental and private hospitals plus MOH PHCC supervisors and only medical directors of private dispensaries. For convenience, two versions of the questionnaire were used; Arabic & English. It included 3 parts: socio- demographic data, enabling factors and potential barriers for utilization of research' recommendations. Data were collected by 3 trained data collectors. It was entered and analyzed using SPSS version 16. Ethical considerations were ensured.

Results: 19% of the respondents addressed that they received recommendations from previously conducted research while only 12.4% indicated that there was previous research conducted in their institution. Moreover, 23.3% pointed out that they find solutions for their problems in the received recommendations. It was noted that 51.9% of the respondents shared in previous research, and an equal percentage reported that they conducted research. Although 95.7% of the respondents believe that conduction of research is important, nevertheless, a lower percentage (83.8%) of them expressed that they wish to conduct research. The top three barriers reported by the respondents included a pile of situations pertinent to the staff working in the institute such as lack of

their awareness to research, being isolated from knowledgeable colleagues with whom they wish to discuss the research and lack of support from other staff in implementation. On the other side, it was remarked that the least potential barriers for conducting research perceived by the respondents were related to difficulty in understanding statistical analyses, methodological design and inability to justify conclusions drawn from the research.

Conclusion: Among the interviewed health policy-makers there was a gap between the perceived importance of the research from one side and its conduction and utilization of its recommendations

on the other side. The reported barriers were mainly remediable as being attributed chiefly to modifiable subjective factors driven from the lack of knowledge and experience about research methodology. In addition, the insufficient time perceived as a barrier reflects the vision of the studied institute which were not focusing in part of it on conduction of research and incorporating it in its plan and regular routine work.

Key words: enabling factors, barriers, research recommendations, Saudi Arabia

Introduction

A strong emphasis should be given to improving the linkages between researchers and policy-makers.(1) Policy makers can be defined as Individuals responsible for the development of policy and supervision of the execution of plans and functional operations.(13) On the other hand, research utilization has been defined simply as the implementation of research findings in practice.(2)

Research, practice and policy in the health care sector focus on improving the organization, delivery and outcomes of care.(3) It is clear that policy-makers have a vital role to play in supporting the research/policy interface by creating space and time for engagement with researchers.(4) On the other hand, most health researchers would like to believe that the work they produce is influencing practice and policy and consequently leading to actual improvements in health care delivery.(5)

However, there is concern that research findings are not being utilized by health policy-makers to the extent that they could be. (5) This gap between research findings and practice has been, and continues to be, a concern for the international community.(6) It has a new term called "know-do gap".(14)

Recognition of the importance of bridging the "know-do" gap is increasing around the world and has resulted in an emergence of various institutions involved in analyzing this problem and promoting the transfer of knowledge to practice and policy. (15)

To bridge this gap a commonly suggested strategy is to identify barriers for changing practice and then implement interventions to reduce identified barriers.(7) Most of the findings from this field are based on studies from developed countries, and relatively little is known about these factors in developing countries.(8)

Rationale

1- The researcher believes that research is time and effort consuming, that's why his concern is regarding the barriers among health policy makers toward utilization of national medical research' recommendations.

2- Up to the researcher's knowledge, no similar study has been done in Saudi Arabia.

Aim of the Study

To promote utilization of national medical research' recommendations among health policy makers.

Objectives

1. To identify enabling factors for utilization of national medical research' recommendations among MOH health policy makers in Jeddah city, KSA 2010.
2. To determine barriers among MOH health policy makers toward utilization of national medical research' recommendations in Jeddah city, KSA 2010

Literature Review

Health policy-makers have been the focus of studies. Some can involve health policy-makers, for example in mental health, being shown research papers describing evaluations of programmes and then asked how useful they would find such research. Others examine the policy-makers' use of research in general.(9)

In Canada in 1999 one study interviewed 25 executive directors and held a focus group with a group of other directors to examine the use and transfer of research in these organizations. A number of central issues were identified by the directors that affect the contribution of research to the delivery of their programs and services. A conceptual model for developing 'locally-based research transfer' was subsequently outlined that could serve as the basis for

enhanced research use and research transfer in other local area contexts.(10)

In Mexico in 1999 the results of a descriptive study of the relationship between health research and policy in four vertical programmes (AIDS, cholera, family planning, immunization) were reported. 67 researchers and policy-makers from different institutions and levels of responsibility were interviewed. Then interviewee responses looking for factors that promoted or impeded exchanges between researchers and policy-makers were analyzed. These were, in turn, divided into emphases on content, actors, process, and context. Many of the promoting factors resembled findings from studies in industrialized countries. Some important differences across the four programmes, which also distinguish them from industrialized country programmes, included extent of reliance on formal communication channels, role of the mass media in building social consensus or creating discord, levels of social consensus, role of foreign donors, and extent of support for biomedical versus social research. Various ways were recommended to increase the impact of research on health policy-making in Mexico. Some of the largest challenges include the fact that researchers are but one of many interest groups, and research but one input among many equally legitimate elements to be considered by policy-makers. Another important challenge in Mexico is the relatively small role played by the public in policy-making. Further democratic changes in Mexico may be the most important incentive to increase the use of research in policy-making.(19)

In Poland in 1999 a national postal survey was conducted and supplemented with information collected during focus groups, semi-structured interviews and through analysis of relevant policy documents. The main aim of the described study was to obtain data describing the needs, preferences and limitations of healthcare managers as information users, and to identify environmental factors influencing their information behaviour. The target population included hospital chief executives, medical directors, head nurses and directors of the institutions responsible for health services planning and purchasing. Target institutions were drawn systematically from official lists, stratified by regions of the country and hospital reference level. The interviews were conducted with primary care unit managers and with Ministry of Health officials. National health strategy and directives, cost-effectiveness analyses of interventions and clinical practice guidelines emerged as information of primary importance to respondents. The main barriers to effective information behavior were found to be: attitudes towards research activity, lack of appropriately processed data, lack of skills enabling information seeking and appraisal, inappropriate format of publications, ineffective dissemination of information and absence of services facilitating access to evidence. The current information environment of healthcare managers, together with their attitude towards information and deficiencies in information skills, appear to serve as a barrier to evidence-based practice in the Polish healthcare system.(20)

In 2002, physicians from secondary and tertiary hospitals in six cities located in China, Thailand, India, Egypt and Kenya were enrolled in a cross-sectional questionnaire survey. The primary outcome measures were scores on a Likert scale reflecting stated likelihood of changing clinical practice depending on the source of the research or its publication. Results revealed that overall, local research and publications were most likely to effect change in clinical practice, followed by North American, European and regional research/publications respectively, although there were significant variations between countries. The impact of local and regional research would be greater if the perceived research quality improved in those settings. It was concluded that conducting high quality local research is likely to be an effective way of getting research findings into practice in developing countries.(11)

In 2004, a survey of more than 550 policy-makers and almost 1,900 researchers in 13 low- and middle-income countries found that, on average, a greater proportion of policy-makers than researchers reported that more resources should be spent on health systems research such as health policy, service delivery, financing and surveillance as the best means of meeting the objectives of the national health research system.(12)

In 2007, in Mali, a study of the selection and updating of Mali's national essential medicines list was undertaken using qualitative methods. In-depth semi-structured interviews and a natural group discussion were held with national policy-makers, most specifically members of the national commission that selects and updates the country's list. The resulting text was analyzed using a phenomenological approach. A document analysis was also performed. Results showed several factors emerged from the textual data that appear to be influencing the utilization of health research findings for these policy-makers. These factors include: access to information, relevance of the research, use of research perceived as a time consuming process, trust in the research, authority of those who presented their view, competency in research methods, priority of research in the policy process, and accountability. It was concluded that improving the transfer of research to policy will require effort on the part of researchers, policy-makers, and third parties. This will include: collaboration between researchers and policy-makers, increased production and dissemination of relevant and useful research, and continued and improved technical support from networks and multi-national organizations. Policymakers from developing countries will then be better equipped to make informed decisions concerning their health policy issues. (5)

Up to the researcher's knowledge there is no similar study in KSA, hence our study will be of great importance.

Material and Methods

3.1 Study Area:

Jeddah is a Saudi city located in the middle of the Eastern coast of the Red Sea known as the 'Bride of the Red Sea' and is considered the economic and tourism capital of the country. Its population is estimated around 3.4 million and it is the second largest city after Riyadh.(16)

The study was conducted in Jeddah Health Affairs involving all governmental and non governmental health institutions. Governmental health institutions included MOH (Ministry Of Health) hospitals (n= 9) plus PHCC (Primary Health Care Center) sectors (n= 7) each supervisory sector includes 6-7 centers .While non-governmental health institutions included all private hospitals (n=31) and private dispensaries (n=181). (data were obtained from Jeddah Health Affairs)

3.2 Study Population:

Target population was constituted of those who fulfill definition of policy makers (individuals responsible for the development of policy and supervision of execution of plans and functional operations).

Governmental

- PHCCs: 7 supervisory sectors.
- Hospitals: 9 hospitals

Private:

- In private hospitals: all general managers and medical directors
- In private dispensaries: medical directors.

3.3 Study Sample:

- Sector supervisors (n=7)
- General managers & medical directors in MOH governmental hospitals (9*2) (n=18)
- Private hospitals (31*2) (n=62)
- Medical directors in private dispensaries (n=118)

So, total was 210 after adding 5 administrative directors at Jeddah Health Affairs to the population sample.

3.4 Study Design:

A cross-sectional descriptive study.

3.5 Data collection tool:

Validated questionnaire published in several studies(15),(17),(18) for administrators, clinicians, nurses and librarians & revised by epidemiologist and public health consultant for further adaptation and modification for policy makers. It was bilingual (2 versions English & Arabic) (see appendix); the English version was translated into Arabic then it was back translated to ensure lexical equivalence.

The questionnaire included 3 parts: Socio-demographic data, enabling factors and barriers.

The first part was about enabling factors of utilization of research' recommendations (19 questions plus 8 research related questions) using a 5 point Likert scale

in which 5=strongly agree while 1=strongly disagree; the second part was about barriers to utilization of research' recommendations (27 questions) using the same scale and the third part included socio-demographic data (7 items).

3.6 Data collection technique:

Selfadministered questionnaire was used for data collection. Questionnaires were distributed by the researcher and 3 well trained data collectors during regular day working hours over a 3 month period using different methods. The first was by visiting the hospital and meeting directly with the Director of the hospital who filled out the form; the second method was to put a file that contains a form with a letter from the Health Affairs Director and return at a later date to receive it and the third method was through sending the form via fax or e-mail attached with a letter after talking with the director and explaining the purpose of the research The majority of data were collected through direct meetings. Regular meetings and contact between researcher and data collectors and monthly written reports for progress of data collection were done. All the data were verified by hand then were coded and entered into a personal computer.

3.7 Data entry and analysis:

Data were entered and analyzed using SPSS version 16. Categorical variables were presented as frequency and percentage.

3.8 Pilot study:

A pilot study was conducted in Makkah among 10 health policy makers from different health institutions to test the validity of the questionnaire. Modifications were done accordingly.

3.9 Ethical considerations:

- Written permission from Joint Program of Family & Community Medicine was obtained before conduction of the research.
- Written permission from the concerned authority in MOH was obtained too.
- Individual consent was considered as a prerequisite for data collection. It was written on the front page of the questionnaire that answering the questionnaire implied agreement to participate in the study).
- All information was kept confidential and was not accessed except for the purpose of scientific research

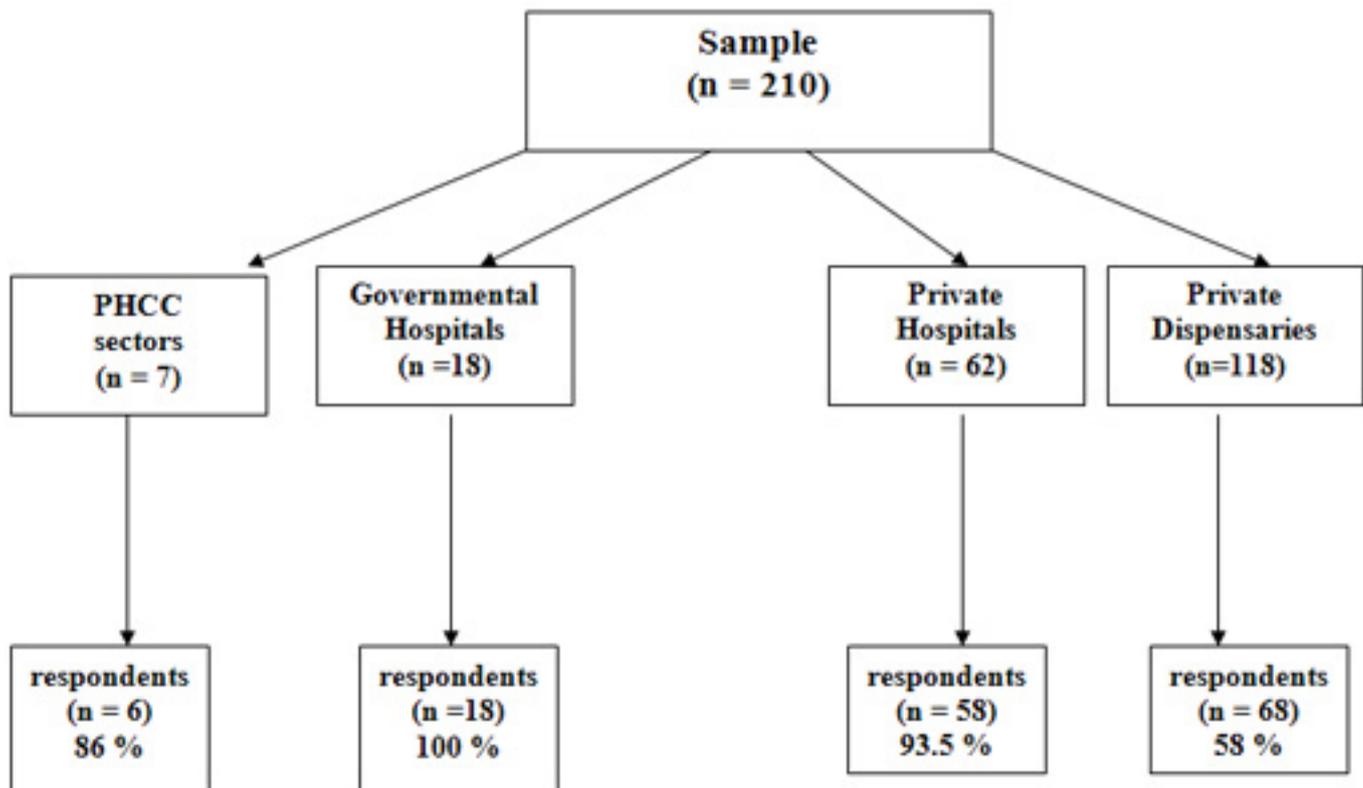
3.10 Budget:

The research is self funded.

Results

The current study aims at identifying enabling factors and determining barriers among health policy makers toward utilization of national medical research' recommendations in Jeddah Governorate. Accordingly the respondents were 210; response rate is shown in Figure 1 and compensation of non respondents were by medical directors of large poly clinics and administrative directors.

Figure 1: response rate of the participants in the study



1. Characteristics of the study group:

Demographic characteristics of the study group

Table 1: Demographic characteristics of the study group (n=210)

| Characteristics | No. | % |
|-------------------------------------|-----|------|
| Age group | | |
| <40 years | 33 | 16.3 |
| 40-<50 years | 72 | 35.4 |
| 50+ years | 98 | 48.3 |
| Gender | | |
| Males | 193 | 91.9 |
| Females | 17 | 8.1 |
| Nationality | | |
| Saudi | 63 | 30.0 |
| Non Saudi | 147 | 70.0 |
| Qualification | | |
| Bachelor | 44 | 21.0 |
| Master Degree | 11 | 5.2 |
| Board | 102 | 48.6 |
| PhD | 53 | 25.2 |
| Type of job | | |
| Medical | 195 | 92.9 |
| Administrative | 15 | 7.1 |
| Experience in the job | | |
| <5 years | 87 | 45.3 |
| 5+ years | 105 | 54.7 |
| Type of the health institute | | |
| Governmental | 31 | 14.8 |
| Private | 179 | 85.2 |

The table shows that the majority of the participants 170 (83.7%) were in their 5th decade or above, and the overwhelming majority 193 (91.9%) are males. The Saudis constituted 63 (30%) of the policy makers in the involved health institute, and those who have postgraduate qualifications amounted to be 166 (79%) who have mainly Board 102 (48.6%) or PhD degrees 53 (25.2%). The majority of the participants have medical jobs 195 (92.9) and slightly more than one half of them 105 (54.7%) have experience in their job of five years or more.

The participants in the governmental health institutes accounted for 31(14.8%).

Table 2: Previous and current participation in research and opinion about conduction of research

| | No. | % |
|---|-----|------|
| Previous research done in the institution | | |
| Yes | 26 | 12.4 |
| No | 184 | 87.6 |
| Received recommendations from research | | |
| Yes | 40 | 19.0 |
| No | 170 | 81.0 |
| Finding solutions for problems from research | | |
| Yes | 49 | 23.3 |
| No | 161 | 76.7 |
| Sharing in previous research | | |
| Yes | 109 | 51.9 |
| No | 101 | 48.1 |
| Conducted research | | |
| Yes | 109 | 51.9 |
| No | 101 | 48.1 |
| Think that conduction of research is important | | |
| Yes | 201 | 95.7 |
| No | 9 | 4.3 |
| Wish to conduct research | | |
| Yes | 176 | 83.8 |
| No | 34 | 16.2 |

The table shows that only 12.4% of the respondents indicated that there was previous research conducted in their institution while 19% addressed that they received recommendations from the previously conducted research. Moreover, 23.3% pointed out that they find solutions for their problems in the received recommendations. It was noted that 51.9% of the respondents shared in previous research, and an equal percentage reported that they conducted research (Figure 2). On the other hand, it was remarked that although 95.7% of the respondents believe that conduction of research is important (Figure 3), nevertheless, a lower percentage (83.8%) of them expressed that they wish to conduct research (Figure 4).

Figure 2: Previous research done in the institution

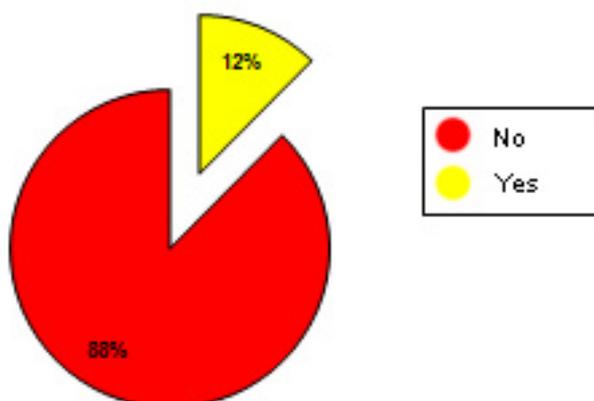


Figure 3: Conducted research

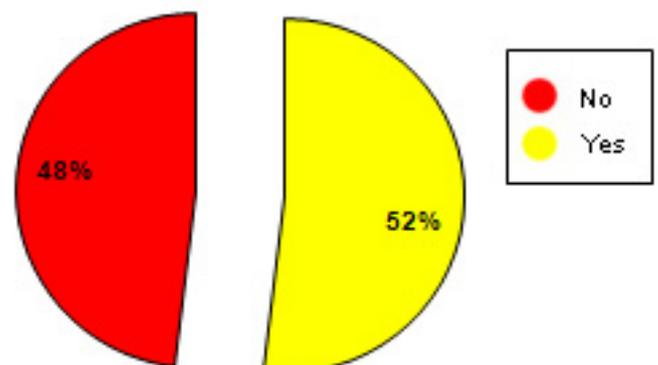


Figure 4: Think that conduction of research is important

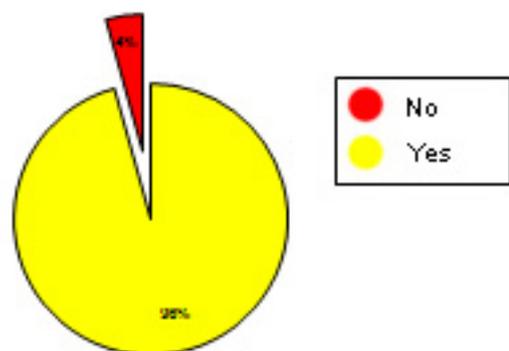


Figure 5: Wish to conduct research

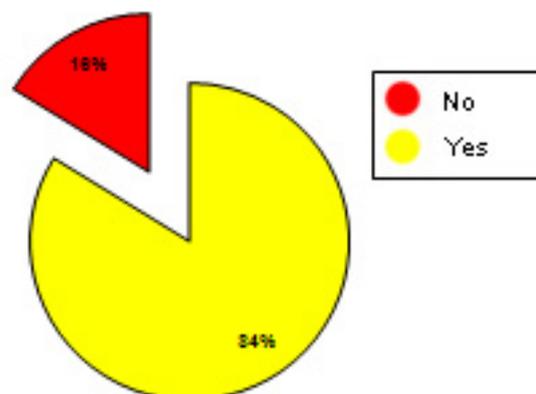


Table 3: Agreement of the respondents to the items representing enabling factors for research

| Enabling factor | Strongly disagree | Disagree | Neutral | Agree | Strongly agree |
|---|-------------------|------------|------------|------------|----------------|
| Research quality | -- | 7(3.3%) | 14(6.7%) | 162(77.1%) | 27(12.9%) |
| Agreement of both researchers and policy makers to give more attention to biomedical than social | 2(1.0%) | 4(1.9%) | 21(10.0%) | 155(73.8%) | 28(13.3%) |
| Specificity, concreteness and cost-effectiveness | 4(1.9%) | 1(0.5%) | 14(6.7%) | 155(73.8%) | 36(17.1%) |
| Both researchers and policy makers identify priority together | 3(1.4%) | 4(1.9%) | 28(13.3%) | 148(70.5%) | 27(12.9%) |
| National support | 1(0.5%) | 5(2.4%) | 4(1.9%) | 129(61.4%) | 71(33.8%) |
| Official research organizations e.g. research department | 3(1.4%) | 3(1.4%) | 12(5.7%) | 128(61.0%) | 64(30.5%) |
| Informal ties | 16(7.6%) | 53(25.2%) | 38(18.1%) | 83(39.5%) | 20(9.5%) |
| Balanced interests | -- | 31(14.8%) | 59(28.1%) | 105(50.0%) | 15(7.1%) |
| Formal communications | -- | 5(2.4%) | 15(7.1%) | 152(72.4%) | 38(18.1%) |
| Political stability | -- | -- | 19(9.0%) | 118(56.2%) | 73(34.8%) |
| Homogeneity of research community | 2(1.0%) | 7(3.3%) | 19(9.0%) | 135(64.3%) | 47(22.4%) |
| Policy-makers' access to information | 2(1.0%) | 5(2.4%) | 21(10.0%) | 148(70.5%) | 34(16.2%) |
| Relevance of research findings | 3(1.4%) | 45(21.4%) | 38(18.1%) | 92(43.8%) | 32(15.2%) |
| Perception that utilizing research findings is time-consuming | 64(30.5%) | 128(61.0%) | 10(4.8%) | 7(3.3%) | 1(0.5%) |
| Policy-makers' competency in research methods | 2(1.0%) | 3(1.4%) | 32(15.2%) | 142(67.6%) | 31(14.8%) |
| Trust policy-makers place on research | 1(0.5%) | 6(2.9%) | 47(22.4%) | 123(58.8%) | 33(15.7%) |
| Authority of those who present their view | 3(1.4%) | 39(18.6%) | 80(38.1%) | 73(34.8%) | 15(7.1%) |
| Relative importance or priority of research findings compared with other sources of information in the policy-process | -- | 23(11.0%) | 91(43.3%) | 87(41.4%) | 9(4.3%) |
| Uncertainty of who is responsible or accountable for accessing, locating, and providing research findings to address the policy-decisions | 11(5.2%) | 74(35.2%) | 101(48.1%) | 22(10.5%) | 2(1.0%) |

Table 3 demonstrates the agreement of the participants about the statements representing the enabling factors for research. It shows that the majority of them agree about the research quality being an enabling factor (90%), and an almost equal percentage (91.1%) agree about concern in biomedical rather than social research, and 90.9% agree about the importance of specificity, concreteness and cost effectiveness. Moreover, it was found that 95.2% of the respondents assert their agreement about the importance of national support as an enabling factor, and 90.5% pointed to the formal communications in addition to 91% who addressed political stability as enabling factors.

On the other hand, it was noted that the great majority of the participants (91.5%) disagree about the assumption that utilizing research findings is time consuming.

Table 4 (next page) illustrates the response of the participants to the items representing barriers for conducting research arranged in descending order according to the overall agreement for each item. Based on this ranking, it was evident that the top ten barriers included a pile of situations pertinent to the staff working in the institute such as lack of their awareness to research, being isolated from knowledgeable colleagues with whom to discuss the research and lack of support from other staff in its implementation. The other pile of barriers are related to the quality of the research, where it was found that there is high agreement on the ambiguous reporting of the research, being not readily available, vague implication on practice in addition to late publication are potential barriers for conducting research. Moreover, two of the top ten barriers are conceptualized around the time factor, where it was found that 60% of the respondents perceive that there is not sufficient time on the job to implement

new ideas, in addition to 58.6% who see that there is not sufficient time to read research. Finally, the factor which is related to the institute in general was represented by the availability of facilities, where it was found that 76.7% of the participants consider the inadequate facilities in the institute as a crucial barrier for implementing research.

On the other hand, it was remarked that the least potential barriers for conducting research perceived by the respondents were related to fine details of the research, for example: difficulty to understand statistical analyses, inadequacy of the methodological design and unjustified conclusions drawn from the research.

Discussion

Making the best use of available research studies is a priority goal in most countries, developed or developing, and what was promising in our study was that the majority of participants had a positive attitude toward research conduction although little research was conducted by participants and few of them were useful in practice in comparison with Polish managers where only 15% of respondents thought that research results had significant influence on practice in health care, and only 3.2% perceived developments in scientific knowledge as having an input in their area of decision making.(20)

Trosle et al(19) looked for factors that promoted or impeded exchanges between researchers and policy makers. These were in turn divided into emphasis on content, actors, process, and context. They finally recommended improving communication between researchers and policy makers via training of both parties: assisting researchers to communicate their findings in an understandable and

Figure 6: Agreement of the respondents to the items representing top ten barriers for research conduction

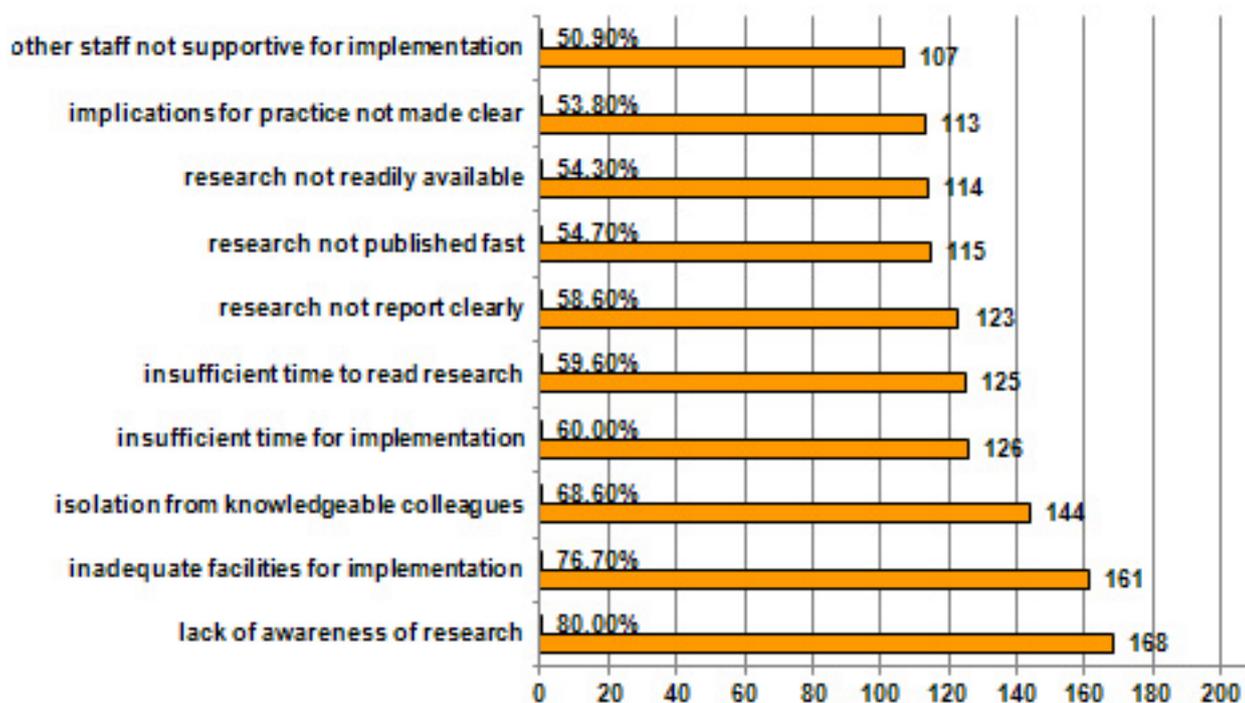


Table 4: Agreement of the respondents to the items representing barriers for research

| Barriers | Strongly disagree | Disagree | Neutral | Agree | Strongly agree |
|--|-------------------|------------|------------|------------|----------------|
| Lack of awareness of the research | 5(2.4%) | 28(13.3%) | 9(4.3%) | 136(64.8%) | 32(15.2%) |
| Inadequate facilities for implementation | 8(3.8%) | 15(7.1%) | 26(12.4%) | 119(56.7%) | 42(20.0%) |
| Being isolated from knowledgeable colleagues with whom to discuss the research | 7(3.3%) | 41(19.5%) | 18(8.6%) | 123(58.6%) | 21(10.0%) |
| Insufficient time on the job to implement new ideas | 13(6.2%) | 52(24.8%) | 19(9.0%) | 99(47.1%) | 27(12.9%) |
| Insufficient time to read research | 8(3.8%) | 56(26.7%) | 21(10.0%) | 98(46.7%) | 27(12.9%) |
| The research is not reported clearly and readably | 4(1.9%) | 55(26.2%) | 28(13.3%) | 96(45.7%) | 27(12.9%) |
| Research reports/articles are not published fast enough | -- | 39(18.6%) | 56(26.7%) | 96(45.7%) | 19(9.0%) |
| Research reports/articles are not readily available | 4(1.9%) | 64(30.5%) | 28(13.3%) | 88(41.9%) | 26(12.4%) |
| Implications for practice are not made clear | -- | 53(25.2%) | 44(21.0%) | 100(47.6%) | 13(6.2%) |
| Other staff not being supportive of implementation | 2(1.0%) | 45(21.4%) | 56(26.7%) | 92(43.8%) | 15(7.1%) |
| Staff not cooperating with implementation | 8(3.8%) | 40(19.0%) | 57(27.1%) | 83(39.5%) | 22(10.5%) |
| Research has not been replicated | 4(1.9%) | 34(16.2%) | 67(31.9%) | 98(46.7%) | 7(3.3%) |
| Feeling the benefits of changing practice will be minimal | 5(2.4%) | 85(40.5%) | 24(11.4%) | 82(39.0%) | 14(6.7%) |
| Uncertainty about the believability of the results of the research | 2(1.0%) | 50(23.8%) | 62(29.5%) | 79(37.6%) | 17(8.1%) |
| Administration not allowing implementation | 11(5.2%) | 58(27.6%) | 48(22.9%) | 79(37.6%) | 14(6.7%) |
| The relevant literature is not compiled in one place | -- | 40(19.0%) | 80(38.1%) | 83(39.5%) | 7(3.3%) |
| Research results not generalizable to own setting | 7(3.3%) | 53(25.2%) | 61(29.0%) | 75(35.7%) | 14(6.7%) |
| Not feeling capable of evaluating the quality of the research | 3(1.4%) | 79(37.6%) | 40(19.0%) | 78(37.1%) | 10(4.8%) |
| The research is not relevant to the practice | 9(4.3%) | 80(38.1%) | 41(19.5%) | 59(28.1%) | 21(10.0%) |
| Seeing little benefit for self | 11(5.2%) | 97(46.2%) | 23(11.0%) | 68(32.4%) | 11(5.2%) |
| Literature reports conflicting results | 3(1.4%) | 40(19.0%) | 93(44.3%) | 64(30.5%) | 10(4.8%) |
| Not perceiving a need to change practice | 16(7.6%) | 96(45.7%) | 26(12.4%) | 63(30.0%) | 9(4.3%) |
| Unwillingness to change/try new ideas | 12(5.7%) | 113(53.8%) | 19(9.0%) | 50(23.8%) | 16(7.6%) |
| Not setting the value of research for practice | 37(17.6%) | 87(41.4%) | 22(10.5%) | 50(23.8%) | 14(6.7%) |
| Statistical analyses are not understandable | 2(1.0%) | 54(25.7%) | 96(45.7%) | 52(24.8%) | 6(2.9%) |
| Methodological inadequacies of the research | 4(1.9%) | 38(18.1%) | 119(56.7%) | 41(19.5%) | 8(3.8%) |
| Conclusions drawn from the research are not justified | 4(1.9%) | 68(32.4%) | 94(44.8%) | 37(17.6%) | 7(3.3%) |

stimulating way, or synthesizing policy makers on the usefulness of research results as an input to decision making. They also recommended that research should be evaluated in terms of its cost and effectiveness before being considered as the basis for a policy or program. However, this type of evaluation is still underdeveloped internationally. (19)

While in a Mali study (5) the factors influencing the use of research findings were Policy-makers' access to information, relevance of research findings, perception that utilizing research findings is time-consuming, policy-makers' competency in research methods, trust policy-makers place on research, authority of those who present their view, relative importance or priority of research findings compared with other sources of information in the policy-process and uncertainty of who is responsible or accountable for accessing, locating, and providing research findings to address the policy-decisions. In our study the participants point of views were comparable except for the perception that utilizing research findings is time-consuming, where the majority disagreed. On the other hand two of the top ten barriers are conceptualized around the time factor, where it was found that 60% of the respondents perceive that there is not sufficient time on the job to implement new ideas, in addition to 58.6% who see that there is not sufficient time to read research and this could be explained in the way of utilization of research findings will outweigh the time consumed for research conduction i.e efficiency will mask real time consuming.

Moreover, it was found that the other top barriers included a pile of situations pertinent to the staff working in the institute such as lack of their awareness to research, being isolated from knowledgeable colleagues with whom to discuss the research and lack of support from other staff in its implementation. The other pile of barriers are related to the quality of the research, where it was found that there is high agreement on that the ambiguous reporting of the research, being not readily available, vague implications on practice, in addition to late publication, are potential barriers for conducting research. Finally, the factor which is related to the institute in general was represented by the availability of facilities, where it was found that 76.7% of the participants consider the inadequate facilities in the institute is considered as a crucial barrier for implementing research.

Conclusion

The current study revealed that among the interviewed health policy-makers there was a gap between the perceived importance of the research from one side and its conduction and utilization of its recommendations on the other side. The reported barriers are mainly remediable as being attributed chiefly to modifiable subjective factors driven from the lack of knowledge and experience about research methodology. In addition, the insufficient time perceived as a barrier reflects the vision of the studied institute which are not focusing in part of it on conduction of research and incorporating it in its plan and regular routine work.

Recommendations

- Encouragement of conduction of research in different health institutions through real and pragmatic support.
- Incorporate any executive directors, planners or managers who are subjected to trainer course for administration to be fortified by a research methodology course
- Deliberate efforts should be made to legislate provision of incentives for research implementation.

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Appendix

(pdf versions of the Arabic and English appendices can be found at www.mejfm.com/????)

بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ
السَّلَامُ عَلَيْكُمْ وَرَحْمَةُ اللَّهِ وَبَرَكَاتُهُ

Dear health policy maker:

I would like to have your active participation in my research, which is about **(Enabling Factors and Barriers among Health Policy Makers toward Utilization of National Medical Researches Recommendations in Jeddah, KSA, 2010)**

A questionnaire is attached to this paper. It is about enabling factors and barriers toward utilization of recommendations of national medical research.

Answering the questionnaire means that you are agree to participate in the study. Be sure please, that all data submitted to us will be treated confidentially

Thank you for giving us part from your valuable time to support our new research area.

For any comments feel free to contact me,

Dr. Mahmoud Abdullah Al-Zahrani

Family Medicine Physician

dr.mahmoud1402@hotmail.com

Mobile : 0503619407

Part 1: Enabling Factors

Using the following scale, please circle your response to each of the following statements regarding
Strongly disagree = 1, Disagree = 2, Neutral = 3, Agree = 4, Strongly agree = 5

| Enabling Factors | Strongly disagree | Disagree | Neutral | Agree | Strongly agree |
|---|-------------------|----------|---------|-------|----------------|
| 1. Research quality | 1 | 2 | 3 | 4 | 5 |
| 2. Agreement of both researchers and policy makers to give more attention to biomedical than social | 1 | 2 | 3 | 4 | 5 |
| 3. Specificity, concreteness and cost- effectiveness of research recommendations | 1 | 2 | 3 | 4 | 5 |
| 4. Both researchers and policy makers identify priority together | 1 | 2 | 3 | 4 | 5 |
| 5. National support | 1 | 2 | 3 | 4 | 5 |
| 6. Official research organizations e.g. research department | 1 | 2 | 3 | 4 | 5 |
| 7. Informal personal ties | 1 | 2 | 3 | 4 | 5 |
| 8. Balanced interests (i.e. research recommendations are not conflictive with feasibility) | 1 | 2 | 3 | 4 | 5 |
| 9. Formal communications | 1 | 2 | 3 | 4 | 5 |
| 10. Political stability | 1 | 2 | 3 | 4 | 5 |
| 11. Homogeneity of research community | 1 | 2 | 3 | 4 | 5 |
| 12. Policy-makers' access to information | 1 | 2 | 3 | 4 | 5 |
| 13. Relevance of research findings | 1 | 2 | 3 | 4 | 5 |
| 14. Perception that utilizing research findings is time-consuming | 1 | 2 | 3 | 4 | 5 |
| 15. Policy-makers' competency in understanding the full meaning of the research . | 1 | 2 | 3 | 4 | 5 |
| 16. Trust policy-makers place on research | 1 | 2 | 3 | 4 | 5 |
| 17. Authority of researcher who present their view to policy-makers . | 1 | 2 | 3 | 4 | 5 |
| 18. Relative importance or priority of research findings compared with other sources of information in the policy-process | 1 | 2 | 3 | 4 | 5 |
| 19. Uncertainty of who is responsible or accountable for accessing, locating, and providing research findings to address the policy-decisions | 1 | 2 | 3 | 4 | 5 |

Part 2: Barriers

Using the following scale, please circle your response to each of the following statements regarding enabling factors

Strongly disagree = 1, Disagree = 2, Neutral = 3, Agree = 4, Strongly agree = 5

| Barriers | Strongly disagree | Disagree | Neutral | Agree | Strongly agree |
|---|-------------------|----------|---------|-------|----------------|
| 1. Lack of awareness of the research | 1 | 2 | 3 | 4 | 5 |
| 2. Being isolated from knowledgeable colleagues with whom to discuss the research | 1 | 2 | 3 | 4 | 5 |
| 3. Not feeling capable of evaluating the quality of the research | 1 | 2 | 3 | 4 | 5 |
| 4. Feeling the benefits of changing practice will be minimal | 1 | 2 | 3 | 4 | 5 |
| 5. Seeing little benefit for self | 1 | 2 | 3 | 4 | 5 |
| 6. Unwillingness to change/try new ideas | 1 | 2 | 3 | 4 | 5 |
| 7. Not perceiving a need to change practice | 1 | 2 | 3 | 4 | 5 |
| 8. Not seeing the value of research for practice | 1 | 2 | 3 | 4 | 5 |
| 9. Insufficient time on the job to implement new ideas | 1 | 2 | 3 | 4 | 5 |
| 10. Staff not cooperating with implementation | 1 | 2 | 3 | 4 | 5 |
| 11. Administration not allowing implementation | 1 | 2 | 3 | 4 | 5 |
| 12. Other staff not being supportive of implementation | 1 | 2 | 3 | 4 | 5 |
| 13. Research results not generalizable to own setting | 1 | 2 | 3 | 4 | 5 |
| 14. Inadequate facilities for implementation | 1 | 2 | 3 | 4 | 5 |
| 15. Insufficient time to read research | 1 | 2 | 3 | 4 | 5 |
| 16. Research has not been replicated | 1 | 2 | 3 | 4 | 5 |
| 17. Uncertainty about the believability of the results of the research | 1 | 2 | 3 | 4 | 5 |

| | | | | | |
|---|---|---|---|---|---|
| 18. Literature reports conflicting results | 1 | 2 | 3 | 4 | 5 |
| 19. Methodologic inadequacies of the research | 1 | 2 | 3 | 4 | 5 |
| 20. Research reports/articles are not published fast enough | 1 | 2 | 3 | 4 | 5 |
| 21. Conclusions drawn from the research are not justified | 1 | 2 | 3 | 4 | 5 |
| 22. Statistical analyses are not understandable | 1 | 2 | 3 | 4 | 5 |
| 23. The relevant literature is not compiled in one place | 1 | 2 | 3 | 4 | 5 |
| 24. Implications for practice are not made clear | 1 | 2 | 3 | 4 | 5 |
| 25. Research reports/articles are not readily available | 1 | 2 | 3 | 4 | 5 |
| 26. The research is not reported clearly and readably | 1 | 2 | 3 | 4 | 5 |
| 27. The research is not relevant to the practice | 1 | 2 | 3 | 4 | 5 |

Part 3: Socio-demographic

Please; Fill the space or mark the proper answer

| | |
|--|--|
| 1. Age | |
| 2. Gender | Male <input type="checkbox"/> Female <input type="checkbox"/> |
| 3. Nationality | Saudi <input type="checkbox"/> Non-Saudi <input type="checkbox"/> |
| 4. Qualification | Medical <input type="checkbox"/> Non-Medical <input type="checkbox"/> |
| 5. your highest degree | <input type="checkbox"/> Master <input type="checkbox"/> Bachelor <input type="checkbox"/> Ph.D <input type="checkbox"/> Board <input type="checkbox"/> Other |
| 6. How many months/ years in your current position | |

| | |
|---|--|
| 7. your institution (choose all applicable please) | <input type="checkbox"/> a- Governmental <input type="checkbox"/> Private <input type="checkbox"/> b- MOH <input type="checkbox"/> Non-MOH <input type="checkbox"/> c- Hospital <input type="checkbox"/> Dispensary <input type="checkbox"/> Sector <input type="checkbox"/> Others(specify)..... |
| | |

بسم الله الرحمن الرحيم

السلام عليكم ورحمة الله وبركاته

عزيزي المسؤول في المنشأة الصحية

أقدر مشاركتك لي في بحثي ، والذي هو عبارة عن

(عوامل التمكين والحواجز بين رسمي السياسات الصحية نحو الاستفادة من توصيات البحوث الطبية الوطنية في جدة ، السعودية ،
2010)

الاستبيان مرفق بهذه الورقة. وهو يتألف من عوامل التمكين والحواجز أمام الاستفادة من توصيات البحوث الطبية.

إجابتك على هذا الاستبيان تعتبر موافقة منك بالمشاركة في البحث.

يرجى التقيد من أن جميع البيانات المقدمة لنا سوف تعمل بسرية تامة.

أشكركم على إتاحة جزء من وقتكم الثمين لدعم جهودنا في مجال الأبحاث الجديدة.

في حال وجود أي ملاحظات أو استفسارات يمكنكم التواصل عن طريق الايميل أو الجوال في أي وقت

الدكتور محمود عيد الله الزهراتي

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Strategies for the Prevention of Hepatitis B, Hepatitis C and Human Immunodeficiency Virus infection in the Paediatric Population of Developing Countries

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Abstract

After a brief background about the epidemiology of Hepatitis B, C and HIV, strategies for their prevention are discussed in the paediatric population of developing countries. These strategies are focused on mother to child transmission, misuse of injections, use of infected needles, myths and use of material infected with the hepatitis positive patient such as a comb, tooth brush etc. Malnutrition and its relationship with Tuberculosis and HIV infection are discussed. World Health Organization (WHO) guidelines on the management of malnutrition,

Tuberculosis and HIV are discussed briefly. A real scenario highlighting the existence of HBV, HCV and HIV is described. Finally role of policy makers, NGO, WHO and local governments in the prevention of HBV, HCV and HIV in the paediatric population is discussed.

Key words: Hepatitis B; Hepatitis C; Human Immunodeficiency Virus infection; Paediatric population

Background

At global level, HBV, HCV and HIV infected population stands at 370, 130 and 40 million respectively. HIV and HBV co-infection are 2-4 million, while HIV and HCV co-infection are 4-5 million(1). Transmission of these infections varies and is dependent upon the geographic region and local practices e.g. in some areas of the world where men who have sex with men, these infections are more common. Hepatitis infections HBV and HCV are endemic in some of the developing countries(1).

Among persons with HBV, HCV and HIV co infections, the presenting features are different. They are dependent upon the epidemiology of the infection in a particular geographical region. As the epidemiology of an infection changes over time, surveys are needed which will detect these epidemiological changes over time and hence can help in developing strategies to prevent these infections in a particular region or communities(2).

HBV is caused by a DNA virus, while HCV by a RNA virus. These viruses cause acute and chronic liver disease worldwide, leading to cirrhosis and hepatocellular carcinoma (HCC). There is difference in the clinical presentation, pathology and outcome in patients with HCC depending upon whether the cause is HBV or HCV. This difference affects the cure rate and the prognosis(3). HBV and HCV are blood borne viruses; however, HBV can be transmitted by both percutaneous and mucosal exposures and HCV by percutaneous exposure(4). Transmission of these viruses most commonly occurs in developing countries by misuse of infected syringes and rarely by vertical transmission(5, 6) child abuse and possible risk of co-existence of HBV, HCV and HIV infection in garbage scavengers from poor communities(7) (Figure 1) tattooing in older children, drug abuse, and needle piercing(8, 9).

HBV prevention is achieved by immunization for all children according to the Expanded Program for Immunization (EPI) (10, 11). Some centers are giving a booster dose of hepatitis B vaccine, 11-15 years after the primary vaccination. A study done in China indicates that in those children with a low level (0.1-0.9 and <0.1mIU/mL) of the anti-HBs titer, prior to the booster vaccine may need more than one booster dose vaccination. While in those children with a higher level of pre-booster anti-HBs titer of 1-9.9mIU/mL, additional booster vaccination dose is not required. Hence, the protective levels of the HBs antibody decrease more rapidly in those with low titers(11, 12).

The vaccine for HCV is not available, even though trials on the vaccine development are being conducted(12). Lack of availability of the vaccine against HCV is a serious concern as there will be an upsurge of HCV infections compared to HBV infection, leading to more cases of HCC. Adolescent children are more prone to infections related to drug abuse and sexual intercourse(13).

HIV infection numbers in Southeast Asia was 320,000 in the year 2001, but has now declined to 210,000 in the year 2010. The countries of the WHO Southeast Asia Region

(SEAR) (14) include Bangladesh, Bhutan, South Korea, India, Indonesia, the Maldives, Myanmar, Nepal, Sri Lanka, Thailand, and Timor-Leste. The largest numbers of cases are from Indonesia, where the number of HIV infections is increasing. In the remaining countries of SEAR region, the number of HIV positive cases is decreasing. The maximum number of cases reported from SEARS after Indonesia is from India, which has the second highest number of cases in the region due to heterosexual intercourse(14).

Some older children practice anal intercourse that may also result in HIV infections(15). HIV positive men are more likely to have sexual abuse with children than HIV negative men(16). Knowledge of the children is inadequate regarding HIV infection transmission and they represent the vulnerable group(17).

Prevention strategies for HIV infection in children are the same as for hepatitis viruses and focus on mother-to-child transmission of HIV from an HIV-infected woman to her child during pregnancy, childbirth (also called labor and delivery), or breastfeeding. Mother-to-child transmission is the most common way that children become infected with HIV(18).

Pregnant women infected with HIV are given medications for the HIV infection during pregnancy and at childbirth. Elective Cesarean section may be done to prevent HIV infection from mother to child. A baby born to a mother with HIV infection will receive HIV medication for 6 weeks after birth. The medications will reduce the risk of HIV infection transmitted from the mother to the newborn baby(18).

HIV can be transmitted via breast milk. Hence women in the USA are advised not to breast feed their babies if they are suffering from HIV infection. In such cases formula milk is a safe and healthy alternative to breast milk(19).

However, breast-feeding is promoted in developing countries regardless of HBV, HCV or HIV infection in mother. In developing countries, due to risk of malnutrition in children, the morbidity and mortality is high. Approximately half of the deaths, which occur in children under five years of age, are due to malnutrition. This results in loss of 3 million deaths every year, which could have been prevented. Recurrent infections in children with malnutrition leads to a vicious cycle with delayed recovery and makes the child more prone to susceptible infections leading to death(20). In babies, who are not breast fed, milk is given to them in contaminated bottles and water used is not consumable for health, hence it is advised to continue breast-feeding in these areas. Thus in countries with poor socio-economic backgrounds, with mothers infected with HBV or HCV or HIV, exclusive breastfeeding is recommended. Breast feeding in HIV-infected mothers is continued for the first six months of life, unless replacement feeding is acceptable, feasible, affordable, sustainable and safe for their infants(19, 20).

In areas with poor social and health sector development, incidence of HCV and HIV is high. Drug addicts have to

cope not only with their addiction but also with the process of social exclusion. To the greatest extent possible, any course of action for such a group should be built into integrated, coordinated plans that take a broad approach to the main issues involved(21).

Co-infection of tuberculosis (TB) and HIV

Both children and adults may be co-infected with HIV and tuberculosis. In children, data available on TB and HIV co-infection is rare. However, a strong suspicion of HIV must be kept in mind for HIV when TB is diagnosed in any child, especially if HIV is endemic in that particular region or the child is immunocompromised. Hence the awareness among paediatricians when managing children with severe malnutrition and in case of history of contact with a TB patient, the child must be investigated for HIV also after appropriate counseling of the parents. This may occur in Multi drug resistant cases of tuberculosis (MDR TB) and co-existing HIV infections. WHO has suggested a special team, which can manage these patients (22). Since HIV infection can occur in immuno-compromised children, with tuberculosis, prevention of tuberculosis in developing countries should focus on curtailing the epidemic of TB and HIV especially in endemic areas. Strict control of the vaccination program, protection of children from exposure to infected individuals with TB and prevention of patient transfer with active transfer from one country to another should be monitored(23).

Diagnosis of HIV/TB co-infection in children is challenging. Paediatric TB and HIV(22,23) have overlapping clinical manifestations, which could lead to missed or late diagnosis.

HBC, HCV and Hepatitis D (HDV) Co-infection

HBV and HDV co-infection or HBV and HCV co-infection have a worse prognosis than these infections alone. HDV infection will only occur in the presence of HBV infection and eradication of HDV infection is difficult(24). These co-infections are related to misuse of infected needles and lack of immunization for HBV, a preventable infection, hence, parents should be counseled and law should be passed that every child follows the immunization program of the respective country especially in areas where HBV and HCV is endemic.

Strategies to prevent hepatitis and HIV infections

The strategies depend upon the countries in which the infection is present and related to the epidemiology of the infection. The treatment program in the developing countries will be successful, only after recognition of the country specific epidemiology; this varies and is mostly dependent upon the economic development, which the respective country has achieved.

Immunization

HBV Immunization is mandatory for the prevention of HBV infection in children and adults(25). Despite counseling and advice to parents more than 50 % of the children may not be immunized for HBV in various communities especially in those areas which are economically not well off(26). Hepatitis B virus infects many infants and children - more than 2 billion people have been infected with the virus at some point, and an estimated 350 million are lifelong carriers. However, most don't develop the clinical disease until several decades later when the virus can cause inflammation of the liver and lead to cirrhosis or liver cancer.

More than 30 million children are unimmunized either because vaccines are unavailable, because health services are poorly provided or inaccessible, or because families are uninformed or misinformed about when and why to bring their children for immunization. In such communities HBV and HCV infections continue to increase(26).

HCV is more difficult in terms of prevention of the disease as vaccine is not available, however treatment response in both adults and paediatric patients especially has shown a good response with genotype 2 and 3(27).

It is advisable that all family members are screened for HBV and HCV if a case of HBV or HCV is detected in the family(28). In some hospitals prior to surgery, regular screening of HBV and HCV is done to prevent the infection in the surgeons, in case of a prick with infected blood of patient.

The relative importance of various modes of transmission of HBV, HCV and HIV viruses differs in each country; hence, the choice of specific prevention and control strategies depends primarily on the epidemiology of infection in a particular country. Comprehensive hepatitis B prevention strategies should include (1) prevention of perinatal HBV transmission, (2) hepatitis B vaccination at critical ages to interrupt transmission and (3) prevention of nosocomial HBV transmission and (4) counseling of the parents.

The prevention of hepatitis C is problematic because a vaccine to prevent HCV infection is yet to be developed in the foreseeable future. From a global perspective, the greatest impact on the disease burden associated with HCV infection will be achieved by focusing efforts on primary prevention strategies to reduce or eliminate the risk for transmission from nosocomial exposures (e.g. blood transfusion, unsafe injection practices) and high-risk practices (e.g. injecting drug use). Studies have shown that the risk of infected blood causing hepatitis and HIV is still possible in countries where appropriately screened blood is not available. This is even more apparent in thalassaemic children requiring repeated blood transfusion. The infected blood causes increased morbidity and mortality in the children due to thalassaemia itself and as there is a high risk of the children being co-infected with HBV, HCV, HDV or HIV (29). A study of thalassaemic children from Karachi, Pakistan has shown that 43% of the patients were positive for HCV, 5 % for HBV and none for HIV. This indicates that

the hepatitis B vaccine is protecting the children against HBV and hence HDV. However, due to the absence of vaccine against HCV, there is a higher frequency of HCV in the general population and in thalassemics compared to HBV infection. Also, it is worthwhile to note that none of the patients in this study were positive for HIV. Hence, we have to be extremely vigilant in the prevention of these infections by creating awareness, education and counseling of the parents, children, health workers and policy makers. HIV has not reached the high proportions seen in other countries such as India and Indonesia(14,29) and we have to adopt all preventive strategies to contain HIV.

Lack of international and local organizations interaction and role of NGOs

NGO can play a great role in the prevention and treatment of hepatitis and HIV in the developing world and other parts of the world(30).

The role of organizations such as WHO, UNICEF and local organizations in various countries is important to prevent HBV, HCV and HIV in the paediatric population, due to the wide geographical area of coverage of these organizations, political will and available resources. It has also been observed in some of the developing countries that a decrease in HBV has occurred when compared to HCV, which has continued to rise due to non-availability of the vaccine against HCV. International forums provide treatment of HIV medications at a very low cost(10,11,23, 25).

Role of local paediatricians

Pediatricians taking care of a child should screen all children for HBV and HCV regardless of the status of the parents, especially when working in an endemic area. The child should be referred to a paediatric hepatologist for further investigation and treatment if found to be positive for HBV, HCV alone or co-infected. A Paediatric Infectious disease expert may be consulted in the management of co-infection with HIV. Local paediatricians should repeatedly counsel parents regarding child abuse especially sexual abuse and its relation with HIV or hepatitis to protect the vulnerable child. The local infectious disease experts, should include topics of HBV, HCV and HIV infection in children and their prevention in international conferences in developing countries so to create awareness among the Pediatricians.

Research

There is a need to collect data on the existing infected paediatric cases of HBV, HCV and HIV in the developing countries to determine the prevalence and incidence of these infectious diseases. By doing so strategies can be developed, which would then focus on the treatment of the existing population of children and in the prevention of the remaining paediatric population existing in the country. In a study conducted in Istanbul, Turkey,(31) very early onset of substance and polysubstance use indicated easy accessibility of legal and illicit substances by children and youth. These findings on Turkish children and youth who seek substances at an early age can be corrected

by means of early interventions at a stage when the child has just started substance abuse. The diseases such as HBV, HCV and HIV can be prevented in the child at early stage by appropriate early intervention and treatment facility(31).

Challenges in the developing countries

The main challenges that need to be met in developing countries include lack of qualitative ongoing training for health professionals. In some areas of the developing countries, training programs are non-existent, so that some health professionals though aware of the diseases, do not have sufficient knowledge for prevention, treatment or referral to tertiary care hospitals. Inter professional education (IPE)(32), involves close collaboration between health care professionals and can improve patient care. Training and educational programs including, continuing medical education (CME), can be done so that the health professional may work together to reach the objectives, which is primarily patient care. In these countries it is essential that regular seminars for health workers in a systematic fashion are held with ethical coverage by the newsmedia and appropriate discussions with the public and health workers and policy makers is done, so that prevention of HBV, HCV and HIV can be implemented. Children should be highlighted at all levels of the discussion, including that of an expecting mother (unborn baby), her delivery, role of the father and family, so that control of the prevention of HBV and HCV and HIV can be done by immunization and counseling.

Policy makers

The role of policy makers is crucial for the prevention of these infections. Unless the governments are serious about the prevention of these infections, the disease will spread and reach epidemic proportions. Hence, even if few cases are detected in any area, prompt action should be taken in terms of prevention of these infections.

A pertinent example is China where there is a high prevalence of these infections. HBV and HCV co-infection in HIV-infected children in China receiving ART has prompted policy makers to routinely screen for viral hepatitis co-infection, organize an intensive prevention strategy of childhood HBV and HCV transmission, and develop programs for the modification of the management of pediatric HIV infection(33).

Cost effective analysis

Analysts are required to make cost effective analysis of the resources(34) available to decision makers for the implementation of the strategies for the prevention of hepatitis and HIV especially in the poor countries. Existing interventions should be evaluated both in terms of outcome as well as resources, before a new intervention is introduced or approved. Research done in any one country or region or area should be such that it can be applied in another region with minimum cost. Also long-term effects need to be considered; as an example lack of immunization against hepatitis B can eventually lead to

HCC especially if the patient is exposed to the risk factors leading to HBV infection. In such a case the cost effective analysis of the intervention i.e. the immunization for HBV is definitely a good preventive strategy as HCC can be prevented. In the long run cost of immunization is negligible compared to the treatment for HCC and let alone the morbidity associated with HCC.

Hence, an economic analysis should always be done keeping in mind the objectives of the strategies, which will be used to prevent infective diseases such as HBV, HCV and HIV in the very vulnerable human population, our children in regions of the world, which are impoverished(34). In this regard it is essential to develop vaccines for HCV(35) and HIV, which can prevent these infections and will be cost effective in the long run.

Scenario

A young 19 year old woman of Afghani origin is married to a Pakistani man, as her family is very poor and need the money, which will be obtained from this marriage and as is the custom that money is given to the father of the bride.

This is the Pakistani man's second marriage. They are living in an area which is a slum area/camp, where there are migrating individuals from various parts of country Pakistan and people who have fled from Afghanistan due to the war.

Within a year a beautiful healthy baby boy, green eyes and golden hair, resembling his parents and grandparents is born. Living in an area of suburb of a major city of Pakistan, delivery takes place at home. Parents due to lack of awareness do not immunize the baby. Mother breastfeeds for 9 months exclusively. Weaning is inappropriate and the child gradually becomes malnourished and plots on the 3rd centile for both height and weight. Gradually he becomes stunted by the age of 5 years. Mother is unable to give him attention and food due to poverty, lack of awareness and education and little economic support from the husband or the family. The mother herself has lost weight and now looks like a middle-aged woman, even though she is only 26 years of age. She now has 2 more children ages 4 and 2, with the same nutrition history.

These children play in rubbish, (Figure 1) as their only means of recreation in the area. A nearby man has developed tuberculosis and is seen coughing out blood, by some of the neighbors. Another individual aged 23 years; living nearby due to severe depression has started taking drugs of all sorts. Later he is diagnosed to have HIV. Infected needles are thrown by this man and his community in the same rubbish where young children play(36).

Figure 1: Child playing in garbage with infected needles, in a poor community area, with no supervision, lack of awareness and lack of education



Despite the local government emphasizing immunization, very few children in the community are vaccinated, due to their own myths. This community is close knit and do not always welcome NGOs or local doctors. They do not allow their children to go to regular schools and the boys as soon as possible go out to work, which can be anywhere between 8 and 12 years of age.

The young boy aged 5 years now goes on a donkey cart all over the city with his older cousin, picking up old used stuff including used needles and supplying them to a local factory where they are recycled and used again in all major hospitals. He has by now become infected with HBV and HCV. He is also immune-compromised. Due to frequent visits to a distant relative with Tuberculosis; the child is now also exposed to TB.

The child is now 6 years of age, and looks like a wizened old person with no concept of childhood play and is brought to clinic finally as he is listless, severely malnourished with low grade fever every night. On further investigation he is found to be HBV, HCV and HIV positive. There is sharing of toothbrush, comb etc. by all the children due to non-affordability and lack of knowledge and awareness in the family. His sister who also develops HCV is given treatment by the NGO and in part by government funds from a local hospital. The girl becomes HCV negative, but the boy despite available treatment dies.

This scenario exists in many parts of both these neighboring countries and is increasing in frequency. This family like many others will be prone to the following causes of hepatitis and HIV co-infection. The prevention strategies for such children are described in the table on the following page.

Table 1: Strategies for the Prevention of HBV (hepatitis B), HCV (hepatitis C) and HIV in the Paediatric Population of Developing Countries

| Causes of Hepatitis and HIV co-infection in children | Prevention strategies (all have to be available free of cost or minimal cost to the population) |
|---|--|
| Vertical transmission | Screening and immunization of all women of child bearing age, with available vaccines |
| Lack of immunization | Immunization is available free of cost at all government hospitals. Encourage parents by local media, family physicians, and religious leaders and family elders. |
| Unsafe injections (contaminated needles and syringes) | Proper disposal by the government, local area in charge. Incinerators in all hospitals. A law has to be passed and implemented for appropriate disposal of all material from the hospitals, dispensaries and local clinics. Early screening of infected individuals. |
| Unsafe sex | Education of the parents, community and teenage children |
| Child abuse | Education of the parents and community to be vigilant and keep their children safe |
| Lack of awareness | Education and social programs in print and electronic media and community level one to one. |
| Susceptible group | Parents, community and government need to pass laws with strict implementation to protect children. Individuals with problems should be provided psychosocial help. |
| Economic situation of the country (poverty) | Can be only done if all countries together are sincere and humane to one another and NOT to themselves and their nations alone |
| Lack of Education | Basic education conducive to the environment the people are living in. |
| Myths | Education and awareness by family members and religious leaders |
| Risk factors | Awareness and education |
| Behavior | Awareness and education |
| Inappropriate care and treatment of infected persons | Improve government resources, remove corruption, so common man gets the required treatment with ease |
| Vaccines for hepatitis B, C and HIV | HBV is available at all government hospitals free of cost, HCV and HIV more research is needed |

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Critical Reading of an Article about Therapy

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Learning Objectives

The main objective of this paper is to understand the process of assessing the quality of a therapy article and how to apply its results to clinical practice. Specifically, the learners are expected to be able to: Assess the validity of a therapy paper; Determine the importance of the results of a valid therapy paper; and Determine how valid and important evidence from the therapy paper can be applied to patient care.

Introduction

This paper provides a step-by-step process on how to appraise a therapy article. The process includes assessing the validity of a therapeutic article, determining its importance, and applying it to an individual patient. We shall focus on randomized controlled trial (RCT) since it is considered the main source of high quality evidence. The essential components of RCT, e.g., randomization, concealment, intention to treat, number needed to treat, and so on, are discussed to help physicians decide on an article's strengths and weaknesses. One should keep in mind that the skills learned from appraising a therapy article will provide a basis for life-long learning and will help improve patient care.

Case Scenario

J. A., a 45 year old female patient visited a family medicine (FM) clinic to review her fasting blood sugar (FBS) results. The physician informed her that her FBS was 6.7 mmol/L. He prescribed Metformin, which she could not tolerate due to dyspepsia. Therefore, he offered her Voglibose 0.2 mg tablet three times daily. He assured her that it is a good medication, but J.A. was worried and asked for evidence.

Formulate an Answerable Question

Before looking for evidence, you should formulate an answerable question for the clinical situations you are faced with. A useful way of PICO can help as a global approach to the clinical question. The question should include the fundamental information about the patient, the intervention, the comparison, and the outcome. In the previous example given:

P: A patient with impaired glucose intolerance

I: Voglibose tab

C: Metformin /placebo

O: Diabetes/dyspepsia

So, we can ask in patients with impaired glucose tolerance: what is the effectiveness of voglibose compared to metformin in the prevention of diabetes and less dyspepsia?

Levels of Evidence for Therapy

RCT is considered as the most rigorous primary research and method of determining whether a cause-effect relationship exists between an intervention and outcome. Large RCT is one of the most reliable sources of evidence for assessment of intervention effects (see Figure 1).

Figure 1 shows the broad agreement on the relative strength of the principal types of research. RCTs rank above observational studies, while expert opinion and anecdotal experiences are ranked at the bottom.

A well designed and conducted RCT reduces the potential for bias and allows for comparison between intervention groups and control (no intervention) groups. It should provide two balanced groups.

Why Control Group

The inclusion of a control group is an integral part of the methodology of RCT. It adds protection against multiple well-defined biases:

1. Self-remitting: Some diseases are self-remitting where patients will be cured within a few days despite being given no medication (e.g., seasonal influenza). If one group of patients with such disease is followed up and given a new medication, investigators will claim that the effect is due to the new drug.

2. Placebo effect: A placebo is an inert substance that has no inherent pharmacological activity. A placebo need not always be pharmacological. It could be procedural, for example, surgical placebo is a procedure where the patient is anaesthetized and superficial procedures (e.g., skin incision, burr hole) are performed without the actual surgery. Patients feel better even if something inactive (placebo) is given. One may argue, is this improvement due to the new drug or the placebo effect. The control group, when present, will have the same placebo effect, then any extra effect will be considered due to the new drug. American anesthetist Henry K. Beecher (1955) coined the term "placebo effect." He reported that, on average, about a third of patients with a range of conditions improved when they were given placebos. This subsequently led to the development of placebo-controlled trials, whereby a new drug is said to have significant benefit only if it shows superiority over placebo.

3. Hawthorne effect: Individuals may change their behavior due to the attention they are receiving from researchers. The same concept as placebo effect but without any medication, just the feeling of being cared for

Figure 1: The evidence pyramid



has a positive effect and improvement. A subject's behaviour may change due to their awareness that they are being studied, or because they are receiving additional attention. This is especially a concern when subjects are not blinded or when they participate in observational studies. Practical studies in real-world settings may be particularly vulnerable to Hawthorne effects on intervention outcomes. For example, a practical intervention study design aimed to improve the clinical management of skin and soft tissue infections. Authors specifically examined the potential for a Hawthorne Effect from the extra attention some clinicians received when completing follow-up case reviews.(7)

Critical Appraisal of therapy paper

The quality of clinical trials may be defined as the confidence in the design, conduct, report, and analysis that restrict bias in the comparison of interventions. Critical appraisal of therapy paper is achieved by answering 3 questions:

1. Are the results of the trial valid?
2. How large and precise are the treatment effect?
3. Will the results help me in caring for my patient?

Assesment of Internal Validity

This is a crucial step before starting to use the results of a study. To assess the validity means to ask if the findings are true and accurate. It implies that the study is designed well and rigorously conducted to reduce potential bias . One should actively look at the study methodology to assess what was planned and the results ensure that it was actually done. It is common to find a study described as being randomized and upon careful assessment, is found to have poor randomization process. The following RCT components have to be critically evaluated to ensure validity:

1. Randomization
2. Concealed allocation
3. Balanced groups
4. Blinding
5. Equal treatment
6. Compliance
7. Complete follow up
8. Intention to treat analysis

1. Randomization

The patient distribution (allocation) has two steps: the first step is generation of randomization list, which is most often performed by computer programs; and, the second step is execution of allocation by concealment. Randomization is a process by which each subject has 50% chance to be distributed to the intervention or the control group. By randomization, the prognostic factors are distributed equally, which results in two balanced groups. The balance of distribution includes both the known (age, gender, co-morbidities) and the unknown prognostic factors (hereditary and genetic). Randomization protects against selection bias.

2. Concealed allocation

This means that neither the research team nor the patient should know to which group the next patient will be allocated to. If the next assignment is known, enrollment of certain patients may be prevented or delayed to ensure that they receive the treatment believed to be superior. Concealed allocation is based on the sequence generated randomization list. Adequate randomization requires that the allocation of the next patient be unpredictable. Therefore, randomization list must be kept and managed by somebody who is not part of the study (i.e., neither the research team nor the subject). This may be translated by one of two methods:

Remote telephone call can be made especially in multicenter trials. Enrolment of eligible subjects through a telephone call from the center that controls the randomization list will automatically get response and indicate the distribution arm (e.g., A or B).

A second method is by sequentially numbering sealed-opaque envelopes with the distribution (e.g., A or B) on a small piece of paper inside it. But previous evidence demonstrated that envelopes may be trans-illuminated. However, it is still debatable whether sealed envelopes truly provide adequate allocation concealment.

3. Balanced Groups

If the randomization process worked (that is, achieved comparable groups) the groups should be similar. The more similar the groups, the better it is. There may be some indication of whether differences between groups are statistically significant (i.e., p values). The Results should have a table of "Baseline Characteristics," which compares the randomized groups on a number of variables that could affect the outcome (i.e., age, risk factors, etc.).

4. Blinding (Masking)

In RCT, the term "blinding" refers to keeping participants, health-care providers, data collectors, outcome assessors, and/or data analysts unaware of the assigned intervention. The purpose of blinding is to prevent bias associated with patients' and investigators' expectations.¹⁸ Blinding usually reduces outcome assessment bias, improves compliance, and reduces drop-out and co-intervention. Blinding also protects against performance bias (i.e., systematic differences in the care provided to the participants in the comparison groups other than the intervention under investigation). Ideally, to minimize bias, both the participant and the investigator are kept blind to (ignorant of) the random assignment. The definition of single-, double-, and triple-blinding varies. Investigators should implement the greatest level of blinding that is feasible. If possible, the following level of blinding should be achieved:

- The patient: to avoid placebo effect and contamination;
- Clinicians: to prevent co-intervention;
- Nurses: to prevent co-intervention;
- Data collectors: to prevent bias in data collection;
- Outcome assessors: to prevent detection bias;

• Any other personnel who are dealing with patients and who are part of the research team (i.e., pharmacists, dietician, health educator, physiotherapist, etc).

If interventions are compared with no intervention, an identical placebo may be used. The compared interventions must be identical in taste, smell, appearance, and mode of administration.

5. Equal Treatment

Investigator should ensure that apart from the intervention the patients in the different groups should be treated the same in terms of additional treatments or tests. The results should include a section for the follow-up schedule and permit for additional treatments or contamination. Contamination occurs when either the intervention group or the control group receives part or all of the other group treatment. For example, in a trial of dietary change, people in the control group might learn about the experimental diet and adopt it themselves. Contamination may reduce the point estimate on the intervention. Two ways are used to reduce the effect of contamination: first, by increasing the sample size; and second, by cluster randomization where no interaction is allowed between intervention and control group (e.g., schools and PHCs randomization). Co-intervention implies additional Interventions other than the treatment or procedure defined per protocol under study that is applied differently to the treatment and control groups. Co-intervention is a serious problem when double blinding is absent or when the use of very effective non-study treatment is permitted. Example is the multiple sclerosis trial; the new drug may appear to be more effective at the end of the trial if patients allocated to the new drug received physiotherapy earlier and more intensively than patients allocated to placebo.

6. Compliance

Usually, treatment efficacy is based on the compliant subjects. Non-compliance with treatment regimen is a common protocol violation in RCT. It compromises the desired rigor of the trial. Non-compliance can seriously decrease study power resulting in widely varying estimates of the sample size required for a study. Thus, non-compliance is a significant issue to be considered when appraising trials involving long-term therapies.

7. Follow-up

Dropout in RCT is common and threatens the validity of results, as completers may differ from people who drop out. Lost to follow up includes all patients whose status is not known at the end of the study, such as:

- Complete non follow-up - left study
- Incomplete follow up - missed some visits
- Data was not collected or missing
- Data was corrupted or not analyzed

Rubin, and Donald (1976), classified dropout as:

a. Administrative: If patients withdraw from a study for a reason unrelated to their disease or treatment (for example, because they have moved overseas) their data are probably missing completely at random, because of

no systematic differences between them and the patients who remained in the study.

b. Clinical: If patients withdraw from the study for reasons related to their disease or treatment (e.g., progression or toxicity); their quality of life measures would have been worse than those of patients who remained in the study. Some authors considered loss to follow-up of 5% or lower, is usually of little concern; whereas, a loss of 20% or greater means that readers should be concerned about the possibility of bias. Losses between 5% and 20% may still be a source of bias.

c. If investigators stop following patients who do not adhere to the study protocol, they will be unaware if those patients suffered the target outcome. Investigators often include patients lost to follow-up in the denominators in calculating estimates of effect. This approach assumes that none of those lost to follow-up suffered the target outcome. Making this unlikely assumption opens the door to a misleading presentation of study results. Alternative strategies are available that impute outcomes to those lost to follow up. Some of these strategies include:

i. Attempt to follow up all randomized participants:

Following up participants who withdraw from randomized treatment can be difficult but is important because they may differ systematically from those who remain on treatment. A trial that does not attempt to follow participants after treatment withdrawal cannot claim to follow the intention to treat principle

ii. Perform plausible main analysis: The main analysis should be chosen to be valid under a plausible assumption about the missing data. For example, in a hypothetical trial, consider in 100 participants, 10 had dropped-out at 6 months and the rest (90 participants) are followed at least to 12 months. The outcomes at 6 months are similar in those dropped out and the completers. In case the reason of drop-out of the 10 participants is administrative (not treatment or disease related), it's logical to consider that the outcome rate remains similar in both groups at 12 months.

iii. Perform sensitivity analyses: For a bad outcome, apply the worst case scenario for lost to follow up at the intervention arm and best case scenario for lost-to-follow up at the control arm.

8. Intention to Treat Principle (ITT)

There is ongoing debate on which participants should be analyzed. Per protocol analysis (i.e., efficacy analysis, explanatory analysis, or analysis by treatment administered) describes the outcomes of the participants who adhered to the research protocol. Although investigators can use information from such an analysis to estimate the intervention's efficacy in those who actually received it in the intended intensity or dose for the intended interval; this estimate is likely to be seriously flawed. The problem arises because the reasons for non-adherence to the protocol may be related to prognosis. ITT analysis includes all randomized patients in the groups to which they were randomly assigned and their outcomes, regardless of their adherence with the entry criteria, regardless of the treatment they actually

received, and regardless of subsequent withdrawal from treatment or deviation from the protocol. In other words, ITT analysis includes every subject who is randomized according to randomized treatment assignment. It ignores non-compliance, protocol deviations, withdrawal, and anything that happens after randomization.

Excluding non-compliant or deviators may overestimate the efficacy of intervention by ignoring the harm that resulted in non-compliance and deviation. ITT analysis reflects the practical clinical scenario because it admits non-compliance and protocol deviations. ITT analysis maintains prognostic balance generated from the original random treatment allocation. It gives an unbiased estimate of treatment effect. If non-compliant subjects and dropouts are excluded from the final analysis, it might create important prognostic differences among treatment groups. Moreover, subjects may be non-compliant or may drop out from the study due to their response to treatment. ITT analysis preserves the sample size because if non-compliant subjects and dropouts are excluded from the final analysis, it might significantly reduce the sample size, leading to reduced statistical power. The drawback of ITT analysis is that, it is too cautious and more susceptible to type II error (cannot reject null hypothesis in the setting of effective treatment); and it is less likely to show a positive treatment effect.

A full application of the ITT analysis is only possible when complete outcome data are available for all randomized subjects. In other words, ITT analysis cannot minimize bias introduced by loss to follow-up, that is, patients whose outcome status is unknown.

Assesment of Internal Validity

Most often, results are presented as dichotomous outcomes (yes or no outcomes that happen or don't happen) and can include such outcomes as cancer recurrence, myocardial infarction, and death. Two types of measure effects are:

1. **How large was the treatment effect (magnitude)?**
 - Relative effects (Relative Risk [RR] and Relative Risk Reduction [RRR])
 - Absolute effects (Absolute Risk Reduction [ARR] and number needed to treat [NNT])
2. **How precise was the estimate of the treatment effects?**
 - 95% confidence interval (CI)

1. Relative Risk

The relative risk (RR) tells us how many times more likely it is that an event will occur in the treatment group relative to the control group. An RR of 1 means that there is no difference between the two groups thus, the treatment had no effect. An RR<1 means that the treatment decreases the risk of the outcome. An RR>1 means that the treatment increased the risk of the outcome. RR is a ratio of probabilities. It compares the incidence or risk of an event among those with a specific exposure with those who were not exposed (e.g., myocardial infarctions in those who smoke cigarettes compared with those who do not). RR is based upon the incidence of an event given that we already know the study participants' exposure status. It is only appropriate, therefore, to use RR for prospective cohort studies.

Consider this example of an RCT using Voglibose by Impaired Fasting Glucose patients to prevent progression to Type-2 diabetes mellitus. Subjects treated with voglibose had a significantly lower risk for progression to type-2 diabetes than those in placebo group (Table 1).

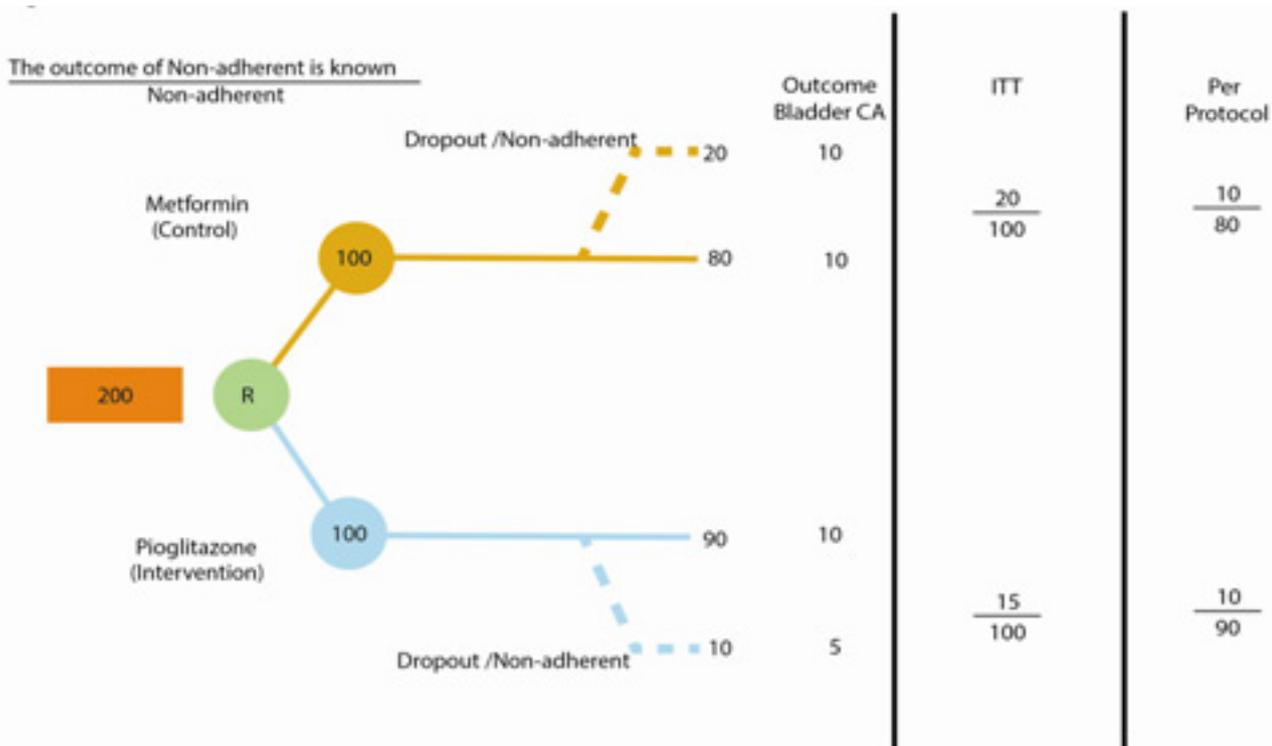


Table 1: Voglibose 50/897 vs Placebo 106/881

| | Diabetes | No Diabetes | |
|-----------|----------|-------------|------|
| Voglibose | 50 | 847 | 897 |
| Placebo | 106 | 775 | 881 |
| | 156 | 1622 | 1778 |

Table 1 shows the dataset of patients treated with either Voglibose or placebo. This example can be used to calculate the treatment effect (RR, RRR, ARR and NNT).

The risk (incidence) of diabetes among those treated with Voglibose may be calculated using the **experimental event rate (EER) or Risk in the treatment group (Rt)**:

$$\text{EER} = 50 \div 897 = 0.0557$$

The risk (incidence) of diabetes among Control group is equal to **control event rate (CER) or Risk in control group (Rc)**:

$$\text{CER} = 106 \div 881 = 0.1203$$

From these two risks, the **RR** is calculated as:

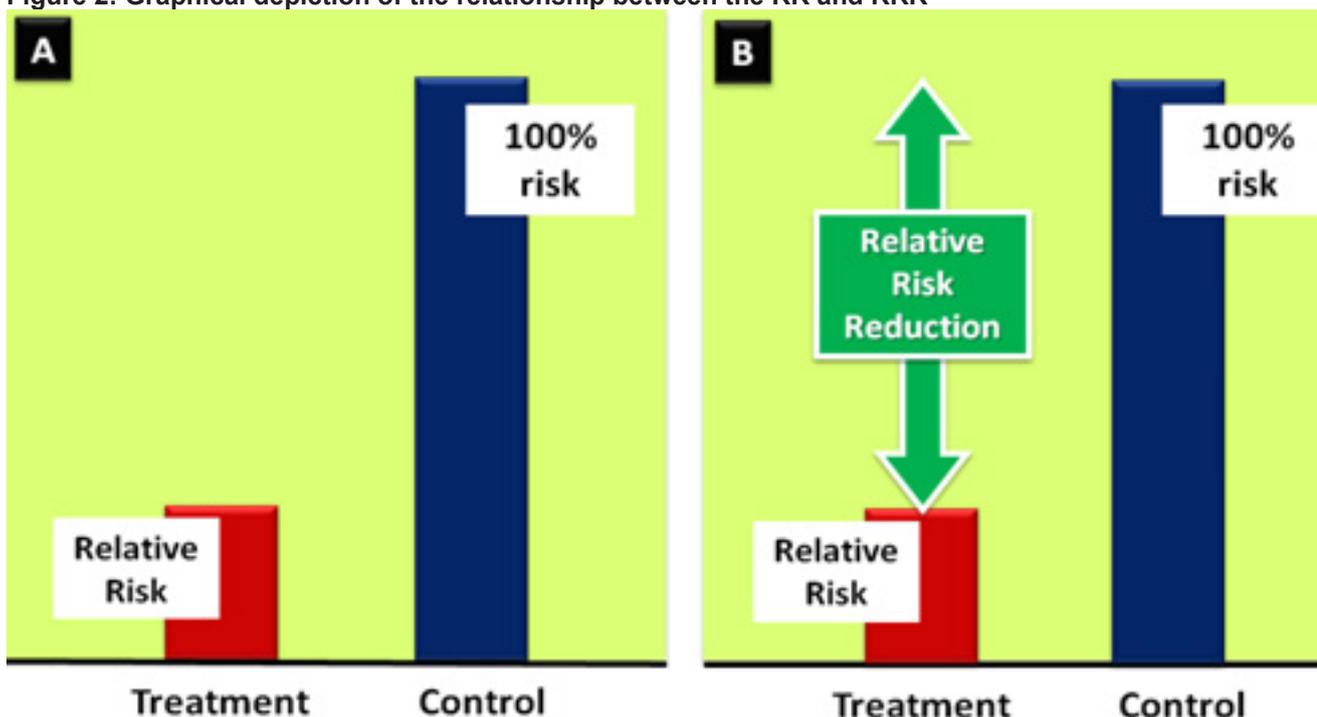
$$\text{RR} = \text{EER} \div \text{CER} = 0.0557 \div 0.1203 = 0.46$$

A RR of 0.46 means that the probability of voglibose users to develop type-2 diabetes is 0.46 times that of the controls. This is called also Risk Ratio and Risk Remaining. Risk Remaining indicates the risk occurrence in spite of using the intervention.

2. Relative Risk Reduction

The relative risk reduction (RRR) is a complement of RR and is probably the most commonly reported measure of treatment effects. It tells us the reduction in the rate of the outcome in the treatment group relative to that in the control group (Figure 2).

Figure 2: Graphical depiction of the relationship between the RR and RRR



$$\text{RRR} = 1 - \text{RR}$$

$$\text{RRR} = 1 - 0.46 = 0.54 = 54\%$$

The treatment reduced the risk of diabetes by 54% relative to that occurring in the control group.

3. Absolute Risk Reduction

The absolute risk reduction (ARR) tells the absolute difference in the rates of events between the two groups and gives an indication of the baseline risk and treatment effect. An ARR of 0 means that there is no difference between the two groups thus, the treatment had no effect. It is calculated as the difference in the risk of the outcome in the control group compared to the risk of the outcome in the treatment group. This is also known as the risk difference:

$$\text{ARR} = \text{CER} - \text{EER}$$

$$\text{ARR} = 12.03\% - 5.57\% = 6.46\%$$

4. Number Needed to Treat

The number needed to treat (NNT) is the number of patients you need to treat to prevent one additional bad outcome (e.g., death, stroke, etc.). For example, if a drug has an NNT of 10, it means you have to treat 10 people with the drug to prevent one additional bad outcome. The duration of the treatment has to be incorporated in the assessment of the NNT. To calculate the NNT, you need to know the ARR since the NNT is the inverse of the ARR:

$$\text{NNT} = 1 \div \text{ARR}$$

$$\text{NNT} = 1 \div 6.46 = 16$$

Therefore, in this example, 16 subjects have to be treated with voglibose for an average of 4 years to prevent one case of type-2 diabetes.

RRR does not take into account the individuals' risk of achieving the intended outcome without the intervention. Therefore, they do not give a true reflection of how much benefit the individual would derive from the intervention, as they cannot discriminate between small and large treatment effects. They usually tend to overemphasize the benefits of an intervention and, for this reason, drug companies and the popular media love RR measures! ARR measures overcome these drawbacks because they reflect the baseline risk and are better at discriminating between small and large treatment effects.

Using the data from Table 1, you will recall that we calculated the ARR as 6.46% and the relative risk reduction as 54%. Fifty four percent reductions in risk feels more impressive than 6.46%.

Consider an example of disease with rare event rate (e.g., 2 in 10,000). The proposed treatment reduced the event rate to 1 per 10,000:

$$\text{The CER is } 2/10,000 = 0.0002$$

$$\text{The EER is } 1/10,000 = 0.0001$$

$$\text{The relative risk is } 0.0001/0.0002 = 0.5$$

The RRR at 50% is obvious that the 50% reduction may not be as important as it looks. On further analyzing the ARR $0.0002 - 0.0001 = 0.0001$, has very tiny small benefit. How small the treatment effect is, it becomes even more obvious after calculating the NNT:

$$\text{NNT} = 1/\text{AAR} = 1/0.0001 = 10,000$$

Thus, 10,000 patients must be treated to prevent one event.

Precision of the estimates of treatment effect

The true risk of the outcome in the population is not known and the best we can do is estimate the true risk based on the sample of patients in the trial. This estimate is called the point estimate. We can gauge how close this estimate is to the true value by looking at the confidence intervals (CI) for each estimate. If the CI is fairly narrow then we can be confident that our point estimate is a precise reflection of the population value. The CI also provides us with information about the statistical significance of the result. If the value corresponding to no effect falls outside the 95% confidence interval, then the result is statistically significant at the 0.05 level. If the confidence interval includes the value corresponding to no effect, then the results are not statistically significant.

Application of study results to my patient

One should consider focusing on issues related to intervention, patient, potential harm, and patient preference [IPPP]. The first issue to address is how confident you are that you can apply the results to a particular patient or patients in your practice. If the patient would have been enrolled in the study had he/she been eligible? Patient is eligible if he/she meets all the inclusion criteria, and does not violate any of the exclusion criteria. In this case, there is doubt that the results are applicable. If this is not the case, judgment is required. A better approach than rigidly applying the study's inclusion and exclusion criteria is to ask whether there is some compelling reason why the results should be applied to the patient. A compelling reason usually would not be found, and most often you can generalize the results to your patient with confidence.

If the article's results are generalizable to your patient and its outcomes are important, the next question concerns whether the probable treatment benefits are worth the effort that you and your patient must put into the enterprise. For any RCT, safety issues have to be considered as secondary outcome. A fair balance must exist between the magnitude of benefit and potential harm. As discussed earlier, NNT can tell you the likelihood of benefit. Nevertheless, for each intervention we should also calculate the number needed to harm (NNH), i.e., the number of patients needed to treat before having serious harm. We might not hesitate to treat even as many as 400 patients to save one life if the treatment was cheap, easy to apply, compliant, and safe. In reality, however, treatments usually are expensive and they carry risks.

The patient is an integral part of the management. One of the most common sources of patient dissatisfaction is not feeling properly informed about (and involved in) their treatment. Shared decision-making, where patients are involved as active partners with the clinician in treatment decisions, can be recommended as an effective way to tackle this problem. Though unlikely, a patient may prefer to avoid taking treatment with clear benefit and small harm, merely due to cultural or religious reasons.

Conclusion

On concluding this chapter, we hope that you are developing a sense of how to use evidence-based medicine module to appraise therapy article. (40, 41) Once you find an article relevant to the therapeutic issue, be sure to assess the quality of the evidence. If the quality of the evidence is poor, any subsequent inference (and the clinical decision it generates) will be weakened. If the quality of the evidence is adequate, determine the range within which the true treatment effect likely falls.

Then, consider the extent to which the results are generalizable to the patient at hand, and whether the outcomes that have been measured are important. If the generalizability is in doubt or the importance of the outcomes questionable, support for a treatment recommendation will be weakened. Finally, by taking into account the patient's risk of adverse events, assess the feasibility of the intervention. This involves a balance sheet looking at the probability of benefit; and the associated costs and risks. Different aspects of the balance sheet help to guide your treatment decision.

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