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Comparison of POSSUM Atherosclerosis of Coronary

Highlights

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Surgeries and Cardiovascular System

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Contents of the Volume

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The Herbal Drug, Polysaccharide k, has an Immunological and Synergistic Anticancer Effect with Cetuximab for Gastrointestinal Cancer in Vivo

By Masayasu Hara, Takaya Nagasaki & Hiromitsu Takeyama

Nagoya City University, Japan

Abstract - Cetuximab, an anti-epidermal growth factor receptor (EGFR) antibody, has been widely used for therapy of several kinds of malignant diseases. However, the anticancer effect is incomplete. The purpose of this study was to examine the synergism between the herbal drug, Polysaccharide K, and Cetuximab against gastrointestinal cancer cell lines in vitro and in vivo. Two gastrointestinal cancer cell lines positive for EGFR expression were used for this study. In the in vivo study, mice were xenografted with cancer cell lines subcutaneously. Neither PSK nor Cetuximab suppressed cell proliferation. However, when both drugs were administered, cancer growth was suppressed significantly compared with treatment with Cetuximab alone. This study demonstrated that PSK has the potential to enhance Cetuximab's effect on gastrointestinal cancer.

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The Herbal Drug, Polysaccharide k, has an Immunological and Synergistic Anticancer Effect with Cetuximab for Gastrointestinal Cancer in Vivo

PSK with Cetuximab for Colon Cancer

Masayasu Hara [α] , Takaya Nagasaki [σ] & Hiromitsu Takeyama [ρ]

Abstract - Cetuximab, an anti-epidermal growth factor receptor (EGFR) antibody, has been widely used for therapy of several kinds of malignant diseases. However, the anticancer effect is incomplete. The purpose of this study was to examine the synergism between the herbal drug, Polysaccharide K, and Cetuximab against gastrointestinal cancer cell lines *in vitro* and *in vivo*. Two gastrointestinal cancer cell lines positive for EGFR expression were used for this study. In the *in vivo* study, mice were xenografted with cancer cell lines subcutaneously. Neither PSK nor Cetuximab suppressed cell proliferation. However, when both drugs were administered, cancer growth was suppressed significantly compared with treatment with Cetuximab alone. This study demonstrated that PSK has the potential to enhance Cetuximab's effect on gastrointestinal cancer.

I. Introduction

The use of monoclonal antibodies in the clinic has changed approaches to cancer chemotherapy. Specific, targeted antibodies can block signals from growth factor receptors by competing for receptor binding. Many kinds of monoclonal antibody chemotherapies have been established.

Cetuximab (Erbitax) is one of the available anti-epidermal growth factor receptor (EGFR) monoclonal antibodies that is used for treatment of tumors. Cetuximab is used commonly for treatment of colorectal cancer patients. There are two types of monoclonal antibodies for colorectal cancer therapy, anti-VEGF monoclonal antibody (Bevacizumab) and anti-EGFR antibody. Whereas Bevacizumab is usually used as a first or second line treatment combined with Oxaliplatin or Irinotekan, anti-EGFR antibodies are used as third line therapy. However, these anticancer treatments remain inadequate.

The primary anticancer mechanism of therapeutic antibody treatment is inhibition of growth factor signals. In addition, several monoclonal antibodies have immunological activities.

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These activities are due to NK cells (antibody-dependent cellular cytotoxicity (ADCC)) or complement (complement-dependent cytotoxicity (CDC)). These activities might not be the original therapeutic intent of monoclonal antibody treatment; however, it is desirable to enhance these activities if possible.

ADCC activity is dependent on specific antibody and NK cell activities. For example, Cetuximab promotes ADCC activity on cancer cells. The enhancement of NK cell activity can be difficult. We previously reported the use of daily interleukin-2 (IL-2) injections to enhance NK cell activity; however, it is very complicated clinically.

Recently, some herbal drugs were found to stimulate immunological activities. Polysaccharide K (PSK) is obtained from the mushroom *Trametes versicolor* and reportedly enhances ADCC activity[1], but the mechanism is still unclear. Some reported that it increased the number of NK cells, and others reported that it enhanced NK cell activity. Oral intake of PSK has been clinically used for colorectal cancer therapy when combined with 5-FU[2-4]. Here, we evaluated PSK's anticancer effect on gastrointestinal cancer cell lines *in vitro* and *in vivo* and discuss the therapeutic possibility of PSK combined with Cetuximab.

II. Materials And Methods

a) Cell Lines

DLD1, COLO320, COLM-5 and HT-29, human colon cancer cell lines, and GLM-1, MKN-28 and MKN-45, human gastric cancer cell lines, were used in this study. Among them, those cell lines positive for EGFR expression were emphasized. DLD1, COLO320, MKN-28 and HT-29 were purchased from RIKEN Cell Bank (Tsukuba, Japan), GLM-1 and COLM-5 was kindly provided by H. Nakanishi (Aichi Cancer Center Research Institute, Japan; Ito et al., 2010). These cells were maintained in DMEM (Nissui Pharmaceutical Company, Tokyo, Japan) supplemented with 10% FBS (Gibco, Grand Island, NY), 100 units/mL penicillin, and 100 μg/mL streptomycin in plastic dishes (BD Falcon;

BD Biosciences, Franklin Lakes, NJ) and incubated at 37˚C in 5% CO_2. After evaluation of cell surface EGFR expression by flow cytometric analysis, the cell lines with highest expression of EGFR were evaluated in the following proliferation assays and *in vivo* assays.

b) Agents

PSK was obtained from Kureha Corporation (Tokyo, Japan). Cetuximab (two mg/mL) was purchased from Merck (Darmstadt, Germany). These two drugs are clinically used at a dosage of three g/ person and 400 mg/m^2, respectively.

c) Flow Cytometry

Flow cytometric analysis was performed to evaluate the expression of EGFR on the cell surface of each cell line. Tumor cells were harvested with trypsin/EDTA and washed twice with buffer (five mM EDTA, five mg/mL bovine serum albumin in PBS) and reacted on ice with mouse anti-human EGFR monoclonal antibody (NeoMarkers) as the primary monoclonal antibody for 30 min. After washing twice with buffer, cells were incubated on ice for an additional 30 min with PE-conjugated polyclonal goat anti-mouse IgG, F(ab')$_2$ as the secondary antibody (Jackson ImmunoResearch, West Grove, PA). The labeled cells were then washed, and the intensity of fluorescence was evaluated with a FACSCalibur (BD Biosciences, San Diego, CA).

d) Cell Growth Assay

Cancer cells were harvested with trypsin/EDTA, plated at 5 x 10^4 cells/24-well plastic plate (BD Falcon) in DMEM supplemented with 10% FBS on day 0, then treated with a range of doses of PSK (5, 10, 50, 100 and 500 μg/mL) or Cetuximab (1, 5, 10, 50 and 100μg/mL) on days one and three. Both the total number of cancer cells and viable cells were measured in triplicate on day four with an Automated Cell Counter (Bio-Rad). Viable cells in controls, 500 μg/mL PSK, and 100 μg/ of Cetuximab were also counted with the Trypan blue exclusion procedure.

e) Animals

Five- to six-week-old male athymic nude mice of the KSN strain were purchased from Japan SLC (Hamamatsu, Japan) and maintained under specific pathogen-free conditions. The health of the mice was monitored by daily observation. Chlorinated water and food autoclaved for five min were provided ad libitum, and the animals were kept in a controlled light : dark cycle (12 hours : 12 hours). All experiments were carried out with the approval of the Institutional Ethical Committee for Animal Experiments of Nagoya City University and met the standard defined by the UK Co-coordinating Committee on Cancer Research guidelines.

f) Animal Experiments

To examine the anti-tumor activity of Cetuximab and PSK *in vivo*, growing tumor cells were harvested with trypsin-EDTA, washed with PBS, and 5 x 10^6 cells in 0.2 mL Hank's balanced salt solution (HBSS) were injected subcutaneously (sc) into the left abdominal flanks of male nude mice. When the subcutaneous tumors developed to approximately eight mm maximal diameter, treatment with intraperitoneal injection (ip) of Cetuximab (one mg/ mouse, twice a week) or PSK alone (2.5 mg/mouse, every two days) or a combination (same doses as above) or vehicle (ip, 400 μL/mouse, twice a week) was performed for four to five weeks (6 mice/group). The maximal tumor diameter (L) and the right angle diameter to that axis (W) were measured twice a week. Tumor volume was estimated by the following formula: L x W x W x 1/2. Mice were sacrificed after five weeks of treatment according to the ethical guideline of UKCCR as described above. Subcutaneous tumors were then removed and weighed.

III. Results

a) Flow Cytometric Analyses

The expression of EGFR on the cell surface was evaluated by flow cytometry. Expression was the highest on MKN-28 and HT-29 in gastric and colorectal cancer cell lines, respectively (Fig. 1). Thus, we used these two cell lines in the following assays.

b) Proliferation Assay

We evaluated MKN-28 and HT-29 cell growth using several concentrations of Cetuximab (one to 100 μg/mL), or PSK (five to 500 μg/mL) (Fig. 2). Neither Cetuximab nor PSK alone showed *in vitro* antitumor cell growth activity with MKN-28 or HT-29 even at the maximum concentrations. The numbers of viable cells in the control group and in the highest concentration of PSK (500 μg/mL) were almost the same. On the other hand, Cetuximab suppressed tumor cell growth in a dose-dependent manner. However, the suppression was incomplete.

c) Tumor Xenografts

Xenografted tumor sizes are shown in Fig. 3. Tumors were xenografted subcutaneously in the mouse inguinal region and were resected and evaluated after treatment. In both HT-29- and MKN-28-induced tumors, PSK alone failed to suppress tumor growth compared with the control group. Cetuximab alone did very little, and the difference was not significant statistically. However, when PSK was added to Cetuximab, the anticancer effect of combination therapy was enhanced remarkably ($p=0.01$, compared with Cetuximab group), as tumor volume was reduced 41% in HT-29 and 42% in MKN-28 compared with those control group. Similar results were seen in tumor weights. The resected tumor weights of control, PSK alone and Cetuximab alone

groups were not different significantly. However, the weights of tumors in the HT-29 and MKN-28 groups treated with a combination of drugs were 42% ($p=0.01$) and 51% less than the control groups, respectively.

IV. Discussion

Chemotherapy for colorectal cancer patients has changed dramatically over the past decade. Oxaliplatin and Irinotecan are used in two standard therapies as FOLFOX and FOLFIRI, respectively. Furthermore, two kinds of monoclonal antibodies, anti-VEGF antibody and anti-EGFR antibody, can make variation for these standard therapies[5-7]. Currently, the survival of patients with unresectable or recurrent colorectal cancer can be prolonged more than two years[8].

Many kinds of monoclonal antibodies have been established as therapeutic drugs. Some of them are used for neutralization of certain ligands, and others are used to block cell surface signals. There are many receptors on cancer cell surfaces that promote cell proliferation via receptor activation and the initiation of downstream signal cascades. Many monoclonal antibodies against these receptors function by attaching to the cancer cell surface and blocking these signals. On the other hand, some of these monoclonal antibodies possess an Fc region that can stimulate NK cells and enhance ADCC activity. Thus, Bevacizumab, which neutralizes VEGF cannot promote ADCC, and anti-EGFR antibody can.

Cetuximab and Panismumab are well-known anti-EGFR antibodies used for the treatment of colorectal cancer patients. The anticancer effect is caused by the inhibition of EGFR signaling. Cetuximab and Panismumab are structurally different. Whereas Cetuximab is a chimeric IgG_1 antibody, Panismumab is a complete human monoclonal IgG_2 antibody. Whereas Cetuximab might cause allergic or anaphylactoid reactions, the structure contributes to immunologic anticancer effects, such as CDC and ADCC[9,10]. However, there has not been a significant difference in outcome between Cetuximab and Panismumab when they were used under standard clinical conditions[11]. We previously reported that Cetuximab activity can be enhanced in gastric cancer when NK cell activity is stimulated by daily injections of IL-2[12]. However, daily use of IL-2 is clinically difficult.

An herbal drug, PSK, is obtained from a species of mushroom. This drug is administered by daily oral intake and has been used safely in Japan for cancer therapy. However, its antitumor activity has not been clarified. Recent studies have revealed that PSK can induce apoptosis in a pancreatic cancer cell line[13]. Polysaccharide K has also been known to stimulate a patient's immune system. Polysaccharide K has been used in Japan for treatment of gastrointestinal cancer. The drug is usually used with another chemotherapeutic drug such as 5-FU. Some investigators have reported that PSK stimulates NK cells and enhances ADCC activity. Our study showed that PSK or Cetuximab alone had no remarkable suppressive activity on HT-29 *in vitro*. Furthermore, PSK alone had no anticancer effect on either cell line following subcutaneous xenografting in mice. Cetuximab decreased tumor volume compared with controls, however the difference was very small. On the other hand, combination therapy of PSK and Cetuximab showed significant tumor growth suppression. One possible reason of this result is caused by ADCC.

Anti-EGFR monoclonal antibody is not recommended for use in colorectal cancer patients who have a mutation in KRAS[14]. This is because blocking EGF signaling by EGFR is not useful when EGF signaling is constantly activated by this mutation. Thus, these patients currently have no choice for third line therapy after earlier failures. However, ADCC is not influenced by KRAS mutations. Thus, this combination therapy might provide an option for patients carrying a KRAS mutation and who otherwise could not undergo anti-EGFR therapy as third line treatment.

V. Conclusions

As with monoclonal antibodies, PSK's synergic activity enhanced Cetuximab's anticancer effect on a gastrointestinal cancer cell line's growth *in vivo*. This might be an option for Cetuximab therapy for colorectal cancer patients.

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Legends

Figure 1 :

The expression of EGFR on the cell surface in various cell lines.

These cell lines had differing levels of expression of EGFR. Among colorectal cancer cell lines, HT-29 had the highest expression, and among gastric cancer cell lines, MKN-28 was highest.

Figure 2 :

The proliferation of HT-29 in several concentrations of PSK or Cetuximab.

HT-29 cells were cultured with several concentrations of PSK (5, 10, 50, 100 or 500 μg/mL) or Cetuximab (1, 5, 10, 50 or 100μg/mL). PSK had no suppressive activity on the proliferation of HT-29. Even at the highest concentration, viable cell numbers (VC/ total cell) of PSK 500 μg/mL (97%, grey bar) were almost the same as that of controls (95%, grey bar). On the other hand, Cetuximab suppressed both proliferation of HT-29 and the proportion of viable cells in 100μg/mL (52%, grey bar) compared with that of control (94%, grey bar). However, the number of total cells was not different significantly.

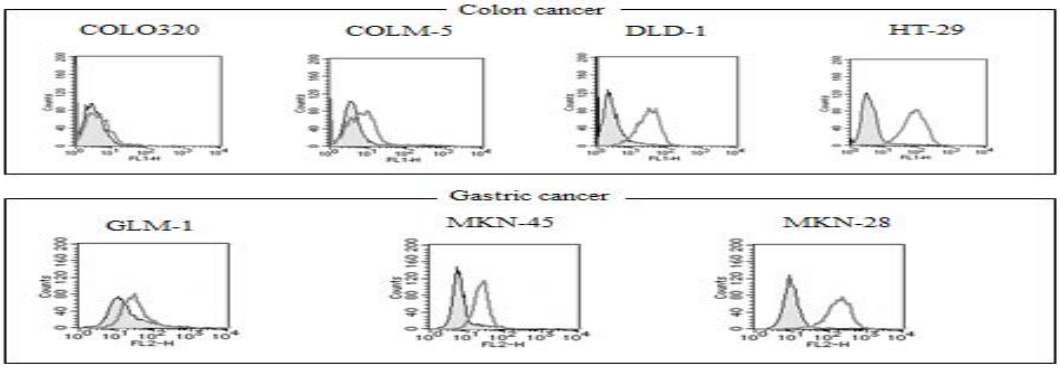
Figure 3 :

Xenografted tumor volumes and weights of HT-29- and MKN-28-induced tumors.

Tumor volumes were measured after a four- or five-week treatment (vehicle; PSK alone: 2.5 mg/ mouse every two days; Cetuximab alone: one mg/mouse twice/week; PSK and Cetuximab combined). Tumors in the control, PSK alone, and Cetuximab alone groups were not significantly different after xenografting either HT-29 or MKN-28 cells (A, B). However, growth was significantly suppressed when PSK was used with Cetuximab (p=0.01). Similar results were seen in tumor weight (C and D).

Cx: Cetuximab,

Figure 1 :



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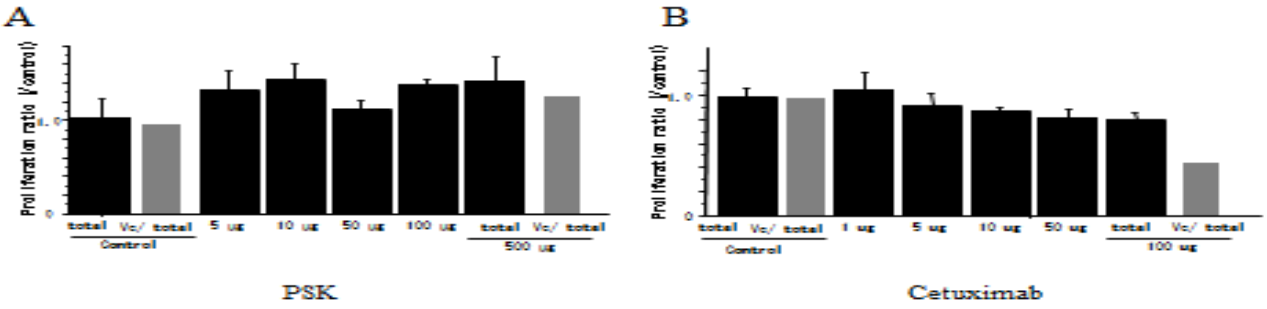

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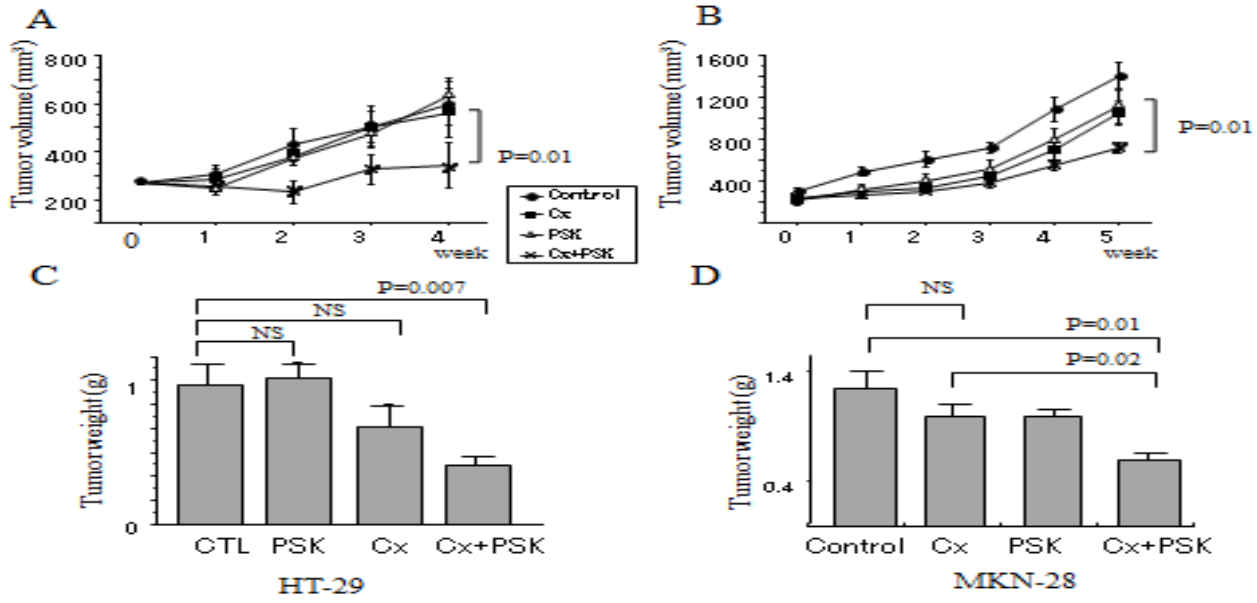

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Comparison of Possum and P-Possum as Audit Tools in Patients Undergoing Emergency Laparotomy for Secondary Bacterial Peritonitis

By Sunil Kumar
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Abstract - Background : Though POSSUM and P-POSSUM have been proposed as accurate tools of audit, our initial experience has not been encouraging. Therefore, a prospective study was conducted to find their accuracy for predicting outcome in peritonitis patients who underwent emergency laparotomy.

Methods : 172 patients treated in single surgical unit over two years were included. Expected morbidity and mortality, computed by POSSUM and P-POSSUM equations using linear as well as exponential methods of analysis, were compared with observed outcome by observed: expected (O:E) ratios. X2-test was done to draw statistical significance; $P<0.050$ was taken as significant.

Results : POSSUM significantly over-predicted mortality with linear as well as exponential methods with O:E ratios being 0.32 ($X2=57.35$, 1 d.f. $P<0.001$) and 0.25 ($X2=111.26$, 1 d.f. $P<0.001$), respectively. P-POSSUM also significantly over-predicted mortality by linear as well as exponential methods with O:E ratios being 0.55 ($X2=11.37$, 1 d.f. $P<0.001$) and 0.27 ($X2=92.30$, 1 d.f. $P<0.001$), respectively. POSSUM significantly over-predicted morbidity by linear and exponential analysis with O:E being 0.76 ($X2=47.94$, 1 d.f. $P<0.001$) and 0.81 ($X2=23.27$, 1 d.f. $P<0.001$), respectively.

Keywords : *peritonitis, risk scoring, possum, p-possum, mortality, morbidity.*

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Conclusions : Neither POSSUM nor P-POSSUM was found accurate for predicting the outcome by linear or exponential methods. Further studies are required to find their suitability for audit purposes in conditions prevailing in third world countries.

Keywords : peritonitis, risk scoring, possum, p-possum, mortality, morbidity.

I. Introduction

In most hospitals across the world, and especially in third world countries, surgical audit is done using crude morbidity and mortality figures. Such audits that are not based on risk-adjusted analysis have gross limitations and do not allow true assessment of quality of care. Clearly, such an exercise lacks educational punch by virtue of ignoring the problems of case-mix. The Physiological and Operative Severity Score for enUmeration of Mortality and morbidity (POSSUM) takes care of problems of case-mix and has been suggested as powerful tool of audit of general surgery patients.[1]

However, some studies suggested that conventional POSSUM may over-predict the mortality.[2-4]

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To counteract this problem the Portsmouth modification of POSSUM (P-POSSUM) was evolved,[4] and proved to be more accurate than POSSUM in predicting mortality.[3,4] One recent report from India found both of these to be reliable for predicting the outcome when correct methods of analysis were used.[5]

This prompted us to conduct a pilot study involving about 75 patients with perforation peritonitis wherein accuracy of both, POSSUM and P-POSSUM for predicting the postoperative outcome, was analysed. We found that neither POSSUM nor P-POSSUM were accurately predicting the outcome (unpublished data), even when the recommended statistical methods were used for analysis.[6]

Therefore, a larger study was undertaken to evaluate the value of POSSUM and P-POSSUM in predicting postoperative morbidity and mortality in patients with bowel perforation peritonitis in our set-up. Our working hypothesis was that neither equation, irrespective of the method of analysis, was accurate in predicting the postoperative outcome in our hands.

II. Patients And Methods

One hundred and seventy two consecutive adult patients, undergoing emergency laparotomy for non-traumatic bowel perforation peritonitis in one of the surgical units at Guru Teg Bahadur Hospital and University College of Medical Sciences were studied prospectively over two years. The physiological component of POSSUM data set was collected from parameters at admission before starting any kind of treatment intervention. The operative component was computed after laparotomy and revised if patient underwent re-laparotomy. Patients were treated as per their individual needs throughout their hospital stay. Previously given definitions[1] of postoperative complications were used while recording morbidity as yes or no. Mortality was also recorded as yes or no. Patients were *discharged* from the hospital only after satisfactory recovery. All discharged patients were followed up in surgical outpatient department for a minimum of three months for treating early postoperative complaints (mostly wound related) and recording death within this period if any. Expected mortality was calculated from POSSUM[1] and P-

POSSUM[4] equations using both linear as well as exponential methods as previously described.[6] Expected morbidity rates were calculated using POSSUM equation only as an equation of P-POSSUM for such purpose is still not available. The ratio of observed to predicted mortality and morbidity (O:E) were also calculated for each analysis separately. An O:E ratio above 1.0 indicates the risk is being under-estimated while an O:E ratio under 1.0 indicates the risk is being over-estimated.[6] Finally, X^2 test was used to find any difference between predicted and observed rates of morbidity and mortality. $P<0.050$ was accepted as significant.

III. Results

Indications for laparotomy are given in table 1. Mean (s.e.m.) age was 31.74 (2.42) and 138 (80%) were males. Mean (s.e.m.) length of hospital stay was 12.79 (0.98) days. One hundred and ninety four (194) episodes of postoperative complications were seen in 109 patients (table 2). Twenty-three patients died during the stay in the hospital. During follow-up in outpatient department there were no dropouts and deaths.

a) Mortality by POSSUM Equation

The results with linear and exponential methods of analysis are shown in table 3 and 4, respectively. Both methods significantly over-predicted the risk of death. The overall O:E ratio with linear analysis was 0.32 ($X^2=57.35$, 1 d.f, $P<0.001$). The overall O:E ratio with exponential analysis was 0.25 ($X^2=111.26$, 1 d.f, $P<0.001$).

b) Mortality by P-Possum Equation

The results of linear and exponential methods of analysis are shown in table 5 and 6, respectively. Both methods significantly over-predicted the risk of death. The overall O:E ration with linear analysis was 0.55 ($X^2=11.37$, 1 d.f, $P<0.001$). The overall O:E ratio with exponential analysis was 0.27 ($X^2=92.30$, 1 d.f, $P<0.001$).

c) Morbidity by linear and exponential analysis from POSSUM equation

These results are shown in table 7 and 8, respectively. Liner method significantly over-estimated the risk of morbidity, overall O:E being 0.76 ($X^2=47.94$, 1 d.f., $P<0.001$). Similarly, exponential analysis significantly over-predicted the risk of morbidity, with O:E being 0.81 ($X^2=23.27$, 1 d.f., $P<0.001$).

Table 9 gives the summary of above findings.

IV. Discussion

A number of risk-adjusted scoring systems have been developed to suit audit of specialty-based practices such as cardiovascular[7,8] and gastrointestinal[9-11] diseases and ICU-care.[12] One of the most widely used scoring system is APACHE II. Though ideal for intensive care patients, its application has been validated in general surgical patients also. However, some of its well known limitations namely, need for repeated measure of variables for 24 h, too many variables, failure to take into account operative aspects, need for weighing tables for individual disease states and failure to predict morbidity, do not make it a popular choice with surgeons. Therefore, to audit the quality of care across the general surgical spectrum a simple scoring system, POSSUM, was developed in 1991.[1] Following its development a number of trials proved its validity in general surgery set-up.[6,13-15] However, some authors subsequently reported that it over-predicted the outcome.[4,16] Therefore, P-POSSUM was evolved and a new equation was recommended.[4] This equation has also been modified since then for better prediction.[17]It was suggested that the over-estimation of the outcome by POSSUM is largely because of employment of linear method of analysis instead of exponential, much against the recommendations of Copeland et al.[6,18] This resulted in renewed interest in the use of POSSUM. A recent review heavily favors the use of POSSUM with proper analytical method but cautions against its use in patients with low-risk of mortality.[19]

Despite this general advocacy for use of POSSUM and P-POSSUM as the risk-scoring system for audit purpose sufficient evidence from tropical countries is lacking. This is desirable as the patients and treatment facilities in these countries tend to be quite different from those in developed countries. Patients here tend to present late, suffer from malnutrition and do not have access to world-class medical services. Our preliminary study involving 75 patients with perforation peritonitis suggested that neither POSSUM nor P-POSSUM were accurate in predicting the outcome (unpublished).

Subsequently, this larger study was undertaken. Predicted mortality rates were derived using equations of both scoring systems and linear as well as exponential methods of analysis. Since P-POSSUM equation has been not been proposed for deriving expected morbidity, it was used only for deriving expecting mortality.[4] Expected morbidity was derived using POSSUM equations with linear as well as exponential methods of analysis.

Our results show that POSSUM grossly over-predicted mortality by both linear as well as exponential method of analysis. P-POSSUM equitation also over-predicted mortality when analysed by either methods though linear analysis gave slightly better results than the other. POSSUM equation also over-predicted morbidity when analysed by either method though exponential analysis gave slightly better results than the linear method.

It is difficult to find the exact cause(s) of over-prediction in our study especially with availability of contrasting results of almost similar trial from another

government institution in Delhi.[5] Under-reporting of the in-hospital outcome and mortality beyond the period of the stay in hospital may be two important causes. However, we rule out under-reporting in our study as the consultant (SK) monitored the outcome on regular basis using strict suggested definitions. We also rule out any deaths beyond the period of stay in the hospital as we followed-up all discharged patients in outpatient department for three months postoperatively. This means that evidence is probably not sufficient to advocate the use of POSSUM or P-POSSUM in our kind of set-up. It is quite possible that a different regression equation is needed for predicting the outcome of the patients with life-threatening sepsis (such as secondary peritonitis) requiring emergency laparotomy. It is also possible that more variables are needed to generate a new 'usable' score as many a factors, known to have an impact on outcome,[4] have not been taken into account. Overall, the issue of suitability of either POSSUM or P-POSSUM in our kind of set-up requires further evidence by way of larger studies involving similar patients.

Thus, it can be summarized that both equations have not proved successful for accurate prediction of the outcome from perforation peritonitis in our hands. As suggested earlier, this may be because of many factors related to patients, treatment-practices or database. We feel that further studies are needed from third world countries addressing the suitability of either scoring system by standard analytical methods before employing the same freely for meaningful audit purposes.

Table 1 : Site of intestinal perforation (n=172)

Site of perforation	Number of patients (%)
Gastro duodenal	70 (40.6)
Jejunal	09 (5.2)
Ileal	79 (45.9)
Vermiform appendix	09 (5.2)
Colonic	05 (2.9)

Table 2 : Postoperative complications (seen in 109 patients; number of complications is larger than number of patients because some had multiple complications)

Complication	Number
Wound infection	80
Deep (intra-abdominal) infection	27
Anastomotic leak	23
Wound dehiscence	21
Chest infection	18
Septicemia	09
Others	16

Table 3 : Linear analysis of mortality predicted by POSSUM

Mortality group (%)	Patients (n)	Actual deaths (n)	Predicted deaths (n)	O:E ratio
<10	4	0	0	-
10-20	30	1	5	0.20
20-30	35	2	9	0.22
30-40	23	1	8	0.13
40-50	21	6	9	0.67
50-60	20	2	11	0.18
60-70	17	3	11	0.27
70-80	8	2	6	0.33
80-90	6	2	5	0.40
≥90	8	4	8	0.50
0-100	172	23	72	0.32

Table 4 : Exponential analysis of mortality predicted by POSSUM

Mortality group (%)	Patients (n)	Actual deaths (n)	Predicted deaths (n)	O:E ratio
0-10	4	0	0	0.00
0-100	172	23	86	0.27
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10-100	168	23	92	0.25
20-100	138	22	83	0.27
30-100	103	20	67	0.30
40-100	80	19	56	0.34
50-100	59	13	44	0.29
60-100	39	11	31	0.35
70-100	22	8	19	0.43
80-100	14	6	13	0.48
90-100	8	4	8	0.53
0-100	168+4=172	23+0=23	92+0=92	0.25

Table 5 : Linear analysis of mortality predicted by P-POSSUM

Mortality group (%)	Patients (n)	Actual deaths (n)	Predicted deaths (n)	O:E ratio
<10	60	2	3	0.67
10-20	35	4	5	0.80
20-30	29	5	7	0.71
30-40	14	1	5	0.20
40-50	11	2	5	0.40
50-60	6	3	3	1.00
60-70	3	0	2	0.00
70-80	4	1	3	0.33
80-90	7	3	6	0.50
≥90	3	2	3	0.67
0-100	172	23	42	0.55

Table 6 : Exponential analysis of mortality predicted by P-POSSUM

Mortality group (%)	Patients (n)	Actual deaths (n)	Predicted deaths (n)	O:E ratio
0-100	172	23	86	0.27
10-100	112	21	62	0.34
20-100	77	17	46	0.37
30-100	48	12	31	0.38
40-100	34	11	24	0.46
50-100	23	9	17	0.52
60-100	17	6	14	0.44
70-100	14	6	12	0.50
80-100	10	5	9	0.56
90-100	3	2	3	0.70
0-100	172	23	86	0.27

Table 7 : Linear analysis of morbidity predicted by POSSUM

Morbidity group (%)	Patients (n)	Actual morbidity (n)	Predicted morbidity (n)	O:E ratio
<10	0	0	0	-
10-20	0	0	0	-
20-30	1	0	0	0.00
30-40	2	0	1	0.00
40-50	2	1	1	1.00
50-60	5	1	3	0.33
60-70	16	8	10	0.80
70-80	33	17	25	0.68
80-90	37	21	31	0.68
≥90	76	61	72	0.85
0-100	172	109	143	0.76

Table 8 : Exponential analysis of morbidity predicted by POSSUM

Morbidity group (%)	Patients (n)	Actual morbidity (n)	Predicted morbidity (n)	O:E ratio
0-100	172	109	86	1.27
0-40	3	0	1	0.00
40-60	7	2	4	0.57
50-60	5	1	3	0.36
60-100	162	107	130	0.83
70-100	146	99	124	0.80
80-100	113	82	102	0.81
90-100	76	61	72	0.84
0-100	172	107+2=109	130+4+1=135	0.81

Table 9 : Summary findings of O:E ratios for mortality and morbidity

	POSSUM O:E ratio		P-POSSUM O:E ratio	
	Linear	Exponential	Linear	Exponential
Morbidity	0.76	0.81	-	-
Mortality	0.32	0.25	0.55	0.27

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Clinical Appraisal of TURP in Gezira Hospital for Renal Diseases and Surgery

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Abstract - Transurethral resection of the prostate(TURP) is the gold standard for the surgical treatment of benign prostatic hyperplasia(BPH)-related lower urinary tract symptoms (LUTS). Objective : The main goal is to evaluate patients selection the complications and the outcome following TURP in (Gezira hospital for renal diseases and surgery) GHRDS.

Methodology : This study was a prospective, hospital based, small scale study conducted in the period between January 2012 to June 2013 in Gezira Hospital for Renal Diseases and Surgery. Ninety four patients underwent TURP for (benign prostatic hyperplasia) BPH were included in this study. The management was done according to the European association of urological surgeons (EAU) guideline for the indication of surgery, procedure and postoperative treatment.The data was collected in a form of data sheet (patient's records, direct interviews and a pre-designed questionnaire). Data coded and fed in computer to handle statistical and mathematical procedure, using SPSS 17(statistical package for social sciences).

Keywords : *turp, ghrds, bph.*

GJMR-I Classification : *NLMC Code: WJ 378, WK 590*

Strictly as per the compliance and regulations of:

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Elssayed Osman Elssayed [α] , Mustafa O Mansour [σ] & Mohamed Elimam [ρ]

Abstract - Transurethral resection of the prostate(TURP) is the gold standard for the surgical treatment of benign prostatic hyperplasia(BPH)-related lower urinary tract symptoms (LUTS).

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Result : One hundred and thirty two patients were enrolled, twenty one patients were excluded due tunneling TURP for Ca prostate and 17 had incomplete follow up or record. Mean age of (69.02) years, mean hospital stay (1.5) days, mean follow-up of (7.19) month and mean operation time was (39.9) minute. Fortunately no mortality stated with significant improvement in international prostate symptoms score (IPSS) on the long term (87.2%) and minimal complication like perforation occur in 2 patients (2.1%), while 1 patient (1.1%) develop bleeding.

Conclusion : The outcome of TURP in GHRDS is good with minimum intraoperative and postoperative complications.

Keywords : *turp, ghrds, bph.*

I. Introduction

BPH is the most common benign tumor in men and its incidence is age related. The prevalence of histologic BPH in autopsy studies rises from approximately 20% in men aged 41 – 50 year to 50% in men aged 51 – 60 and to more than 90% in men older than 80 year. (1) TURP to treat BPH has been the gold standard for decades. It is still considered the standard as the "benchmark for surgical therapies" by the American Urological Association (2-3). Moreover, the European Urological Association considers TURP "the treatment of choice for prostates sized 30 to 80mL (4)

The most frequent indication (50–60%) for surgery is LUTS refractory to medical therapy. The following BPE/BPO complications are considered strong indications for surgery: (1) recurrent urinary retention (2) BPH- or BPE-related macro-hematuria refractory to medical therapy with 5a-reductase inhibitors (5-ARI) (3) renal insufficiency or upper urinary tract dilatation, (4) bladder stones and (5) recurrent urinary tract infection (UTI). About 20% of patients with mild or severe symptoms are treated using several types of surgical procedures. Among these, transurethral resection of the prostate (TURP) is considered to be the gold standard Conventional TURP uses monopolar technology (M-TURP) and is associated with several adverse effects, including morbidity related to blood loss and disturbances of serum fluid and mineral balance. In seeking to improve these negative aspects, TURP using bipolar technology (B-TURP) has been developed. The only contraindications for TURP are untreated UTI and bleeding disorders. (5)

II. Patients and Methods

This study was a prospective, hospital based, small scale study conducted in the period between January 2012 to June 2013 in Gezira Hospital for Renal Diseases and Surgery. Ninety four patients underwent TURP for (benign prostatic hyperplasia) BPH were included in this study. GHRS is a tertiary hospital; all male patients with lower urinary tract symptoms with or without acute urinary retention (AUR) suggestive of BPH were evaluated according to the European guidelines. Patients were subjected to full history taking, physical examination, digital rectal examination (DRE), IPSS, prostate-specific antigen (PSA) measurement, routine lab tests, renal function test and trans-rectal ultrasonography biopsy (TRUS) for the patients whose PSA values was 4 and above or who had any other risk factor (nodule on the DRE or hypo echoic lesion on ultrasounds) Patients who have pus cells in their urine analysis covered by antibiotic for 5 days. Urine for culture and sensitivity with antibiotic accordingly (uncountable pus cells or pus cells persist). Small dose of Alfa blocker and or finaesteride were initiated and the

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(uncountable pus cells or pus cells persist). Small dose of Alfa blocker and or finaesteride were initiated and the patient assessed 1 week later by IPSS. For those who were candidate for surgery TURP was advised according to the size of the prostate with a volume below 60 gram, volume above than 65gms were for open prostatectomy. All patients were operated under spinal or general anesthesia as well as 1 g of ceftriaxone administered intravenously. The procedure was performed by a senior urologist with fair experience in TURP procedures or general surgeon trainees under supervision of the urologist. All patients were treated similarly, apart from the intervention. Conventional M-TURP was performed with a 24F resectoscope (Olympus, Hamburg, Germany) and a loop electrode for TURP (5 mm diameter, Olympus), using an UES-30 generator (Olympus) set at 110 W (cutting mode) and 70 W (coagulation mode). Tap water used as irrigation fluid 60 cm height. Unipolar resection was performed with a 24F Resectoscope set at 160 W (cutting mode) and 80 W (coagulation mode). All the prostatic chips were removed from the bladder at the end of the procedure by Ellik. Subsequently, a 22-24F three-way Foley catheter was inserted into the bladder and initiated irrigate the bladder with normal saline solution in the operating room. The patient will continue on injectable antibiotics and catheter removed in 3rd day postoperative .all patients were subjected to a schedule of follow up during which IPSS was assessed and other symptoms were evaluated and dealt with.

III. Result

One hundred and thirty two patients were enrolled, twenty one patients were excluded due tunneling TURP for Ca prostate and 17 had incomplete follow up or record.

The mean age of (69.0±8).Most of the patients came from Gezira state (84%) but there were significant number from nearby States (Table 1)

Table 1 : Age and residence of patients underwent TURP in GHRDS January 2012- June 2013

		NO	%
Age	50 - 59	13	13.9
	60 - 69	30	31.9
	70-79	35	37.2
	80 – 89		
	90 -99	14	14.8
		02	2.2

Residency	Gezira state	79	84
	Gadarif state	6	6.4
	Sinar state	4	4.3
	Kassala state	3	3.2
	North Kurdfan state	2	2.1

The mean prostate volume was (46.64 ±11.58) grams
The mean PSA level was (6.64±6.54) ng\dl
The mean operative time (39.94± 7.87) minutes
The mean hospital stay was (1.53±1.07) days.

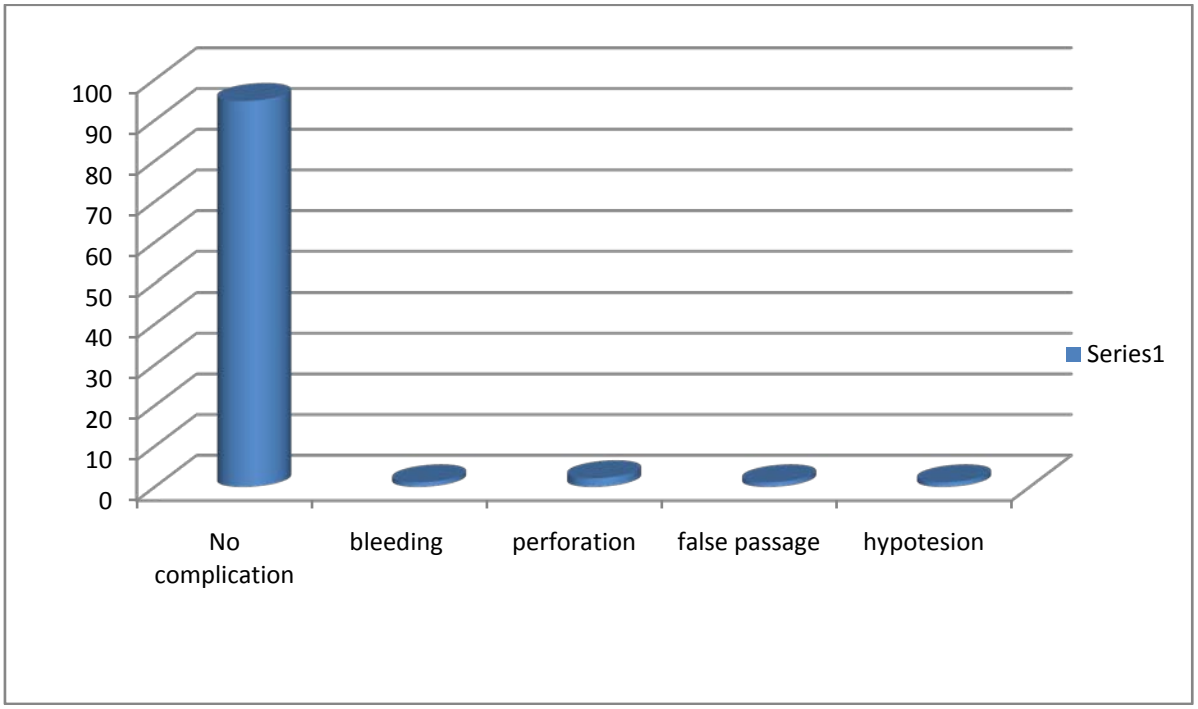
Concerning the indications for surgery,45 patients (47.9%)was due to refractory LUTS, while 18 patients(19.1%) was due to recurrent urine retention.11 patients (11.7%) had vesical stones. 8 patients (8.5%) had inguinal hernias .6 patients (6.4%) had recurrent UTI and similar number had obstructive uropathy. (table 2).

Table 2 : Indications for TURP in GHRDS January 2012-June 2013)

Indication	%
LUTs Refractory to medical therapy	47.9 %
Recurrent UTI	6.4 %
Obstructive uropathy	6.4 %
Recurrent AUR	19.1 %
Stones	11.7%
Hernia	8.5 %

Fortunately 89 patients (94.7%) had no intraoperative complications. Perforation occurred in 2 patients (2.1%), while 1 patient (1.1%) developed bleeding, another one developed hypotension and last one developed false passage. figure (1)

Figure 1 : Intraoperative complications for TURP in GHRDS January 2012-June 2013



Most of the postoperative complications that occurred was UTI in 16 patients (17%). 4 patients (4.3%) developed retrograde ejaculation, 3 patients (3.2%) developed urethral stricture, 2 patients (2.1%) developed incontinence and only one patients (1.1%) had urine retention. table (3).

Table 3 : show postoperative complications

Postoperative complication	Frequency	%
NO	68	72.3
UTI	16	17.0
Stricture	3	3.2
urine retention	1	1.1
Incontinenance	2	2.1
retrograde ejaculation	4	4.3
impotence	0	0
Total	94	100.0

IV. Discussion

A systematic review of the literature was undertaken two major databases (PubMed, MEDLINE) were searched, this is the first study addressed the complications and outcome of TURP in Sudan. One hundred and thirty two patients were operated upon, out of which 21 were excluded due tunneling TURP for Ca prostate, 17 had incomplete follow up or record.

Data were obtained from 94 patients who underwent TURP studied in GHRDS in the period from January 2012 to June 2013 with mean age of (69.02) years (range, 50 to 93 years), mean hospital stay (1.5) days (range 1 to 7 days) and mean follow-up of (7.19) month.

Fortunately no mortality was encountered. The study showed that most of the patients who underwent TURP age group were between 60 & 70 years and BPH was rare or even absent below the age of 50 years in Sudanese (1).The incidence of co-morbidity, DM, HTN or both increase with age inspite of that in the study, co-morbidity only (13.8%) no significant intraoperative or postoperative complication or age related complications, which goes with Wilson JR opinion and his group in study done in 2004, the population at present is older but this does not carry additional co-morbidity. (6)

The majority of the patients had severe preoperative IPSS 67 patients (71.3%), while 27 patients (28.3%) have moderate IPSS. In our follow-up we found that the IPSS was markedly improved on the long term, 82 patients (87.2%) had IPSS less than 7 points which comparable with the literature, in reviewing the literature, various clinical studies, they noted that the chance of improvement of patients' symptoms after a TURP was 70% to 96% confidence interval. The magnitude of reduction in symptom score was 85% (7). The postoperative IPSS was significantly lower than the preoperative and immediately postoperative values.

Concerning prostate volume the upper limit for the TURP is 60 gram in GHRD which is adopted according to their local facilities and experience, although the study showed that there were 3 patients with prostate volume more than 60 gram (70-75grams) and no intraoperative complication was recorded

specifically in those patients, however, in most of the international guideline American urology Association & European Urological Association consider prostates sized 30 to 80mL is optimum for TURP (4). Agarwal M, in study state that, the complication rate increased if the resected prostatic weight was 100 g or more (8). Strange enough Muzzonigro G and his group found that large prostate gland is a safe procedure without showing a different complication rate compared with TURP for recommended volumes (9). Panel's opinion who has assumed that upper limit of the prostate size depends on the surgeon's experience, resection speed, and resectoscope sizes (10). Increase the upper limit of the volume of the prostate from 60grm to 80gram may be justified by the above data concerning time of the operation and significant number of the successful operation in the study to increase the number of patients who benefit from TURP as gold standard and safe non-invasive procedure and there was enough data in the literature to support the decision of performing TURP for a large prostate in terms of safety and efficacy (8) (9).

45 patients (47.9%) the indication for surgery was LUTS refractory to medical therapy, which approximately goes with international figure 50 – 60% (5), while 18 patients (19.1%) was due to recurrent urine retention. Vesical stones 11 patients (11.7%). Hernia 8 patients (8.5%). Recurrent UTI and obstructive uropathy 6 patients for each (6.4%).

All the patients except one patient subjected to spinal anesthesia which is important for early record of TURP syndrome, fortunately enough no single case of TURP syndrome stated in the study.

Most of the patients 44 (46.8%) the operation had taken between 35 to 45 minute. Mean operation time was (39.9) minute, extremely lower than maximum time internationally which was less than 1 hour (11) up to 90 minutes in some centre(7). Agarwal M, directly correlate the complications if the time exceeded 75 minutes (8). Finding explains the absence of TURP syndrome in this study compared to 0% to 1.1% in one study (12). or (0.8% to 1.4%) in another one(13)(14). Hahn RG, stated that for TUR syndrome to develop, prolonged operation time, large prostates, and past or present nicotine abuse (15)

Recently, Tascı Ali Ihsan had collected data from the 3589 patients in Turkey highlighted that Intraoperative perforation of prostatic capsule or bladder neck was observed in 27 (0.75%) patients. Clot retention with secondary bleeding was observed in 81 patients (2.3%)(16). Perforation occur in 2 patients (2.1%), which goes with international figure ranging between 0.75% to 2% in two study respectively (16)(12). Bleeding developed in only one patient (1.1%), compared with literature bleeding which requires transfusions ranging between (2.0% to 2.9%)(13)(14) and 2.0% to 4.8% (12) in two study, it was far low, justified by the preoperative use of finaesteride which reduce intraoperative bleeding significantly (17)(18) or The advantages of using a larger, continuous flow, resection sheath were improved irrigation and vision with lower irrigation pressures. This contributes to better homeostasis hence the absence of blood transfusion and the absence of TUR syndrome observed in this study. One patient (1.1%) develop hypotension in the absence of bleeding or vomiting which could be considered as a complication of spinal anesthesia, and last one had false passage(1.1%).

Most of the postoperative complications were UTI in 16 patients (17%) which was higher in comparison to the literature (3.6% to 4.2%) (13) (14) the majority responded to the treatment with oral antibiotics. A great effort should be done in this aspect of the study to clarify the cause of the UTI, appropriate preoperative antibiotics regimes and drug resistance and the timing of catheter removal. 4 patients (4.3%) develop retrograde ejaculation, in the literature retrograde ejaculation is due to injury of preprostatic (internal) sphincter system. (1)The re-intervention rate for urethral strictures identified in this study were 3 patients (3.2%) Compared to the incidence of strictures quoted in the literature (2.2–9.8%) (19) (20) (21) was acceptable or even lower compared to F. Kallenberg and his group for long term follow urethral stricture was 14%(22) 2 patients (2.1%) develop incontinence and only one patients (1.1%) develop urine retention he was for re-doing of TURP for incomplete surgery due to intraoperative perforation (stop procedure).

Most of the postoperative complications occurred in 26 patient (73.1%) who underwent TURP due to LUTS refractory to medical therapy followed by those who had AUR (15.4%). In fact Chen JS and his colleague in Taiwan found that those with AUR who were treated by TURP were associated with a higher risk of complications (23). No case of impotence recorded.

Most of the patients 64 (68.1) stay for 1 day post-operatively with mean of (1.53) days and 1.07 standard deviations, which indicate that TURP is safe procedure did not need long hospital admission , and those who need longer hospital admission who develop complications or their bladder wash take more than 0ne day to clear. Mean follow up was (71.9) month, minimum 2 moth for those who were operated at the end of the study, maximum 14 month and (4.01) standard deviation.

V. Conclusion

The outcome of TURP in GHRDS is good with minimum intraoperative and postoperative complications comparable with which has been encountered in the literature with little increase postoperative UTI which needs evaluation by further study.

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Atherosclerosis of Coronary Arteries - An Autopsy Study

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Abstract - Atherosclerosis is a complex and common disease contributing to increased mortality and morbidity. The exact global incidence of atherosclerosis is beyond calculation. Autopsy studies can provide information about the impact and course of atherosclerosis. Present study is undertaken to study the spectrum and distribution of atherosclerotic lesions in the coronary arteries and the association of age, sex, diet, socio-economic status, smoking and alcohol consuming habits with atherosclerosis.

Methods : Heart specimens were obtained from medicolegal autopsies. Sections from representative areas were studied for gross and microscopic evidence of atherosclerosis.

Results : Among the 50 cases studied 35 were males and 15 were females. Coronary arteries of 24 males (72.72%) and 9 females (27.27%) showed atherosclerosis. Males were affected more than females. Age has a dominant influence on atherosclerosis, it increased with age. 33 (66%) cases showed coronary atherosclerosis. Upper class, obesity, alcohol consumption and cigarette smoking trends have dominant role in acceleration of atherosclerotic lesions. Religion and vegetarianism have lesser affect on atherosclerosis. Among coronaries, left anterior descending artery is most commonly involved.

Keywords : *autopsy, atherosclerosis, coronary arteries.*

GJMR-I Classification : *NLMC Code: WG 410*

Strictly as per the compliance and regulations of:

Atherosclerosis of Coronary Arteries - An Autopsy Study

Prabhu.M.H [α], Siraj Ahmed S [σ] & Aftab Begum [ρ]

Abstract - Atherosclerosis is a complex and common disease contributing to increased mortality and morbidity. The exact global incidence of atherosclerosis is beyond calculation. Autopsy studies can provide information about the impact and course of atherosclerosis. Present study is undertaken to study the spectrum and distribution of atherosclerotic lesions in the coronary arteries and the association of age, sex, diet, socio-economic status, smoking and alcohol consuming habits with atherosclerosis.

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Conclusion : Autopsy studies play a vital role in unraveling the spectrum and occurrence of atherosclerosis. Atherosclerosis is a complex and multifactorial disease. Smoking and alcoholism can accelerate the development of atherosclerosis. The incidence of atherosclerosis in developing countries (like India) is same as developed countries.

Keywords : *autopsy, atherosclerosis, coronary arteries.*

I. Introduction

The disease atherosclerosis has great relevance today. Atherosclerosis is a distinctive form of arterioscleorosis known from ancient times. The terms 'athere' (meaning-porridge) and sclerotic (hardening or fibrosis) derived from Greek terminology, do not represent the complete morphology of disease. Despite our familiarity with this disease, some of its fundamental characteristics remain poorly recognized and understood. The cause and pathogenesis of atherosclerosis remains subject of lively speculation and controversy.[1]

Atherosclerosis is a pathological entity and a multifactoid disease of large and medium sized arteries, characterized by plaque like intimal deposits which contain neutral fats, cholesterol, lipophages, blood elements, at times, other evidence of hemorrhage and calcium deposits. Complications of which are disastrous – ischaemic heart disease, cerebral stroke, peripheral gangrene and so on. It is a pandemic, percentage incidence of morbidity varies from country to country. It is a modern epidemic in U.S.A., Europe, Canada, New Zealand and Australia.[2]

Among the diseases in the western world, atherosclerosis is overwhelmingly the prime disorder leading to death and serious morbidity. Despite recent reduction in mortality of coronary heart diseases (CHD) about 50% of all deaths in US are still attributable to atherosclerosis related diseases.[1] The developing countries such as India, Singapore, Malaysia and Sri Lanka are catching up and registering a steady increase in the mortality rates due to atherosclerotic heart diseases.[3] In India coronary heart disease accounts for 10-15% of all cardiovascular diseases.[4]

The exact global incidence of atherosclerosis is impossible to calculate because it can exist without producing any symptoms or signs. These asymptomatic cases can be diagnosed only if an autopsy is done, in all cases of death due to any cause. However, the magnitude of the problem can be assessed by looking at the mortality rates in different countries due to atherosclerotic heart disease. In a survey conducted in males in the 45 to 54 years age group,[5] the mortality rates due to atherosclerotic heart disease in different countries are lowest in Japan (8%) and highest in Finland (41%). In U.K., U.S.A., and Canada the average mortality rate is 36%. The disease is increasing in countries undergoing industrialization.[6]

Unfortunately, in India there are no statistics giving the national incidence of this disorder.[3] However, Padmavathi and associates,[7] gave the average incidence of atherosclerotic heart disease in seven different states during 1958-59 as 0.51% per 1,000 population. In another study conducted at All India Institute of Medical sciences, New Delhi, with the help of autopsy studies and taking atherogenic index as an

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indicator, the incidence of coronary heart disease is given as 35.5% in males and in females as 14%.[5]

Although global incidence, a wide range of variation in the prevalence and severity of atherosclerosis has been shown to exist in different geographic population. Against this background the present study has been taken in order to determine the severity and distribution of coronary atherosclerosis in the selected autopsies of the deaths occurring in general population Karnataka state, which has good representation of all social classes.

II. Methodology

a) Materials And Methods

The material for the present study included 50 (fifty) heart specimens obtained from medico legal autopsies performed in the Department of Forensic Medicine, Basaveshwara Medical College and Hospital, Chitradurga and other heart specimens received at the Department of Pathology, Basaveshwara Medical College and Hospital, Chitradurga, sent for histopathological examination to define any suspected cardiovascular pathology. Hearts were obtained by standard procedures from all autopsies.

The age, sex and relevant information including age, sex, socio-economic status, dietary habits of the deceased were obtained from the informant accompanying the deceased.

The methods used for the analysis of the material was as per the procedure recommended by

1. White, Edward and Dry (1950).[8]
2. Gore and Tejada (1957).[9]
3. W.H.O. study group (Technical report series, 1958, 1962, 1964).[10,11,12]

All autopsies were carried out within four to twenty four hours after death.

All the specimens of right and left coronary arteries blocks were taken at a particular fixed distance at from 1.5 cm and 3 cm from the Ostia, also From the circumflex branch of the left coronary artery, bits were taken at the same distance form the point of branching of the left coronary artery into anterior descending and circumflex branches. Additional bits of tissue were taken from other regions of the vessels which showed stenosis. This stenosis is graded based on the luminal narrowing of the coronaries when examined by hand lens and is graded from grade 0 (no narrowing / normal) to grade IV (complete obliteration).

Grade – 0 : Normal
Grade – I : 1-25% stenosis
Grade – II : 26-50% stenosis
Grade – II : 51-75% stenosis
Grade – IV : 76-100% stenosis

The bits of the tissue were fixed in 10% formalin and embedded in paraffin. Sections for histological study were taken from the paraffin blocks and stained with haematoxylin and eosin. Special stains were also done whenever indicated, namely Verhoeff and Van-Gieson's for demonstration of elastic tissues, smooth muscle and collagen, and Alcain blue for the demonstration of mucopolysaccharide ground substance. All histological sections were studied for microscopic evidence of atherosclerotic lesions.

III. Results

The coronary arteries of fifty specimens of heart were examined in the department of Pathology, Basaveshwara Medical College and Hospital, Chitradurga, observations made from the study are as follows:

The youngest subject was 19 years and the oldest was a male of 80 year age, forming a age range of 19-80 years. The majority of the cases were from 3rd to 4th decades of life forming 58% of total number of cases studied. There were 35 males and 15 females in the ratio of 2.5:1. Among the fifty cases studied 33 cases showed evidence of coronary atherosclerosis.

Table 1: Smoking and Atherosclerosis

Habit of Smoking	No. of cases	Positive cases	
		No. of cases	Percentage
Smokers	24	19	79.16
Non-smokers	26	14	53.84
Total	50	33	-

The above table showed higher incidence in smokers (79.16%). When compared to non-smokers (53.84%).

Graph 1: Smoking and Atherosclerosis

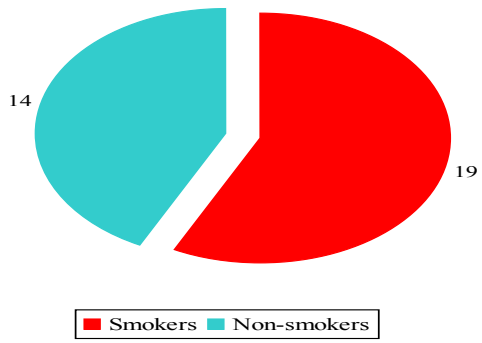


Table 2 : Alcoholism and Atherosclerosis

Alcoholism and habit	No. of cases	Positive cases	
		No. of cases	Percentage
Alcoholics	23	18	78.26
Non-alcoholics	27	15	55.55
Total	50	33	-

Incidence of atherosclerosis was greater in alcoholics (78.26%) than in non-alcoholics (55.55%).

Graph 2 : Alcoholism and atherosclerosis

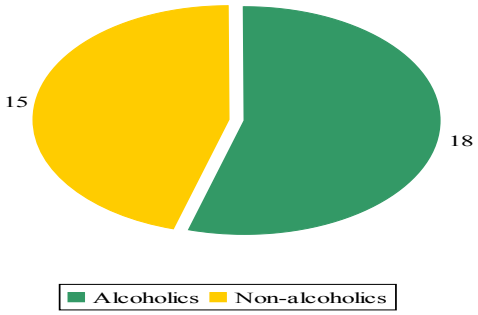
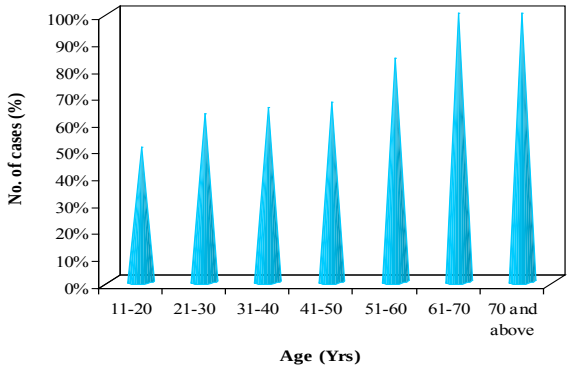


Table 3 : Coronary Atherosclerosis

Age group	Sex	Total No. of cases	No. of positive cases	Total positive	Percentage
11-20	Male	2	2	2/4	50
	Female	2	0		
21-30	Male	6	4	5/8	62.5
	Female	2	1		
31-40	Male	12	7	10/17	64.7
	Female	5	3		
41-50	Male	8	5	8/12	66.66
	Female	4	3		
51-60	Male	5	4	5/6	83.33
	Female	1	1		
61-70	Male	1	1	2/2	100
	Female	1	1		
70 and above	Male	1	1	1/1	100
	Female	0	0		
		50	33	33	66

Of the 50 cases studied 33 cases showed coronary atherosclerosis. This table shows that coronary atherosclerosis will increase with age and it also shows that males are more affected i.e., 24 cases (72.72%) and females are affected in 9 cases (27.27%). The coronary atherosclerosis was much common in males but after 5th decade it takes the same course in both male and female.

Graph 3 : Coronary Atherosclerosis



Of the 50 heart specimens studied 33 showed coronary atherosclerosis with various histological changes such as fibroblastic activity, mucopolysaccharide deposition, degeneration of internal elastic lamina, accumulation of lipid cholesterol crystals, hyalinization, calcification and hemorrhage.

Salient features of atherosclerotic lesions

i. Fatty streaks.
ii. Fibrous plaques.
iii. Atheroma.

Histological, examination of representative plaques in the second and third decades showed the presence of fat with little or no cellular reaction. In the 4th and 5th decades, there was generally a fibrous tissue reaction to the presence of fat. By the 5th decade, the fibrous reaction had become more pronounced and was associated with degenerative changes.

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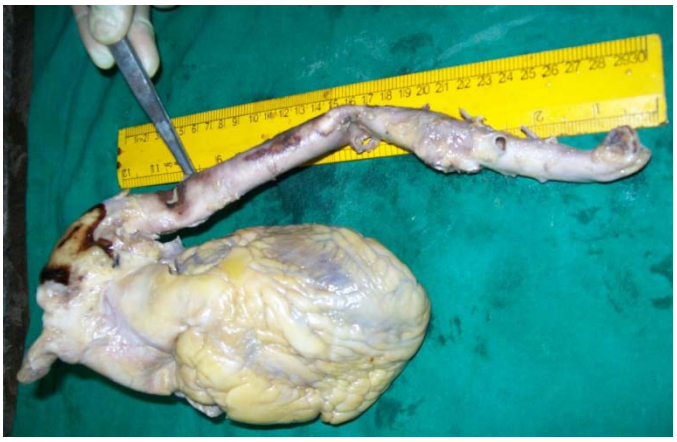

Fig. 1: Heart along with coronary arteries and aorta upto its bifurcation

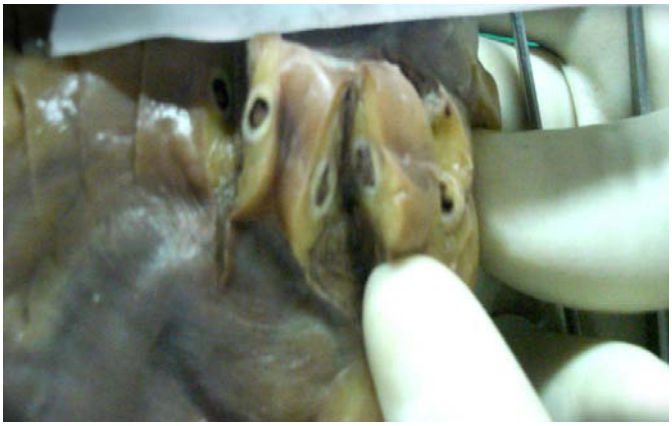

Fig. 2 : Coronary artery showing obliteration of the lumen by atheromatous plaque

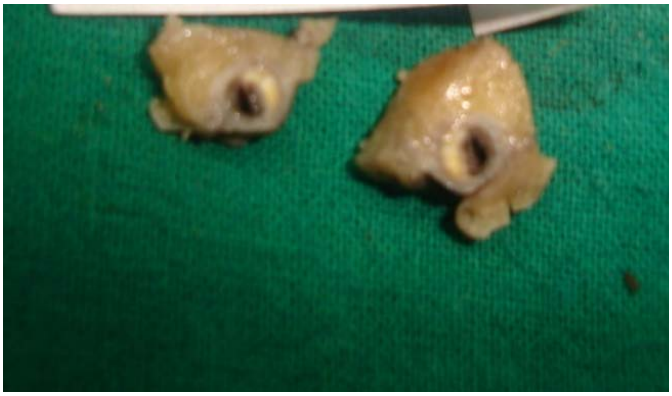

Fig. 3 : Cut section of coronary artery showing atheromas

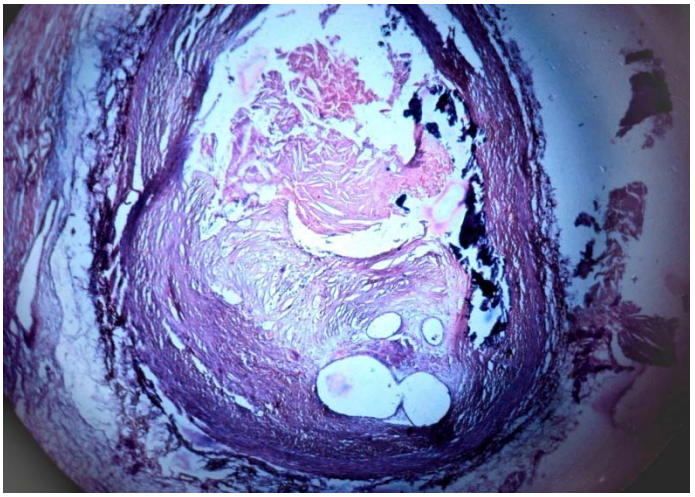

Fig. 4 : Athromatous plaque with complete obliteration of the lumen (Grade IV stenosis) with cholesterol clefts and calcification (H&E x 50)

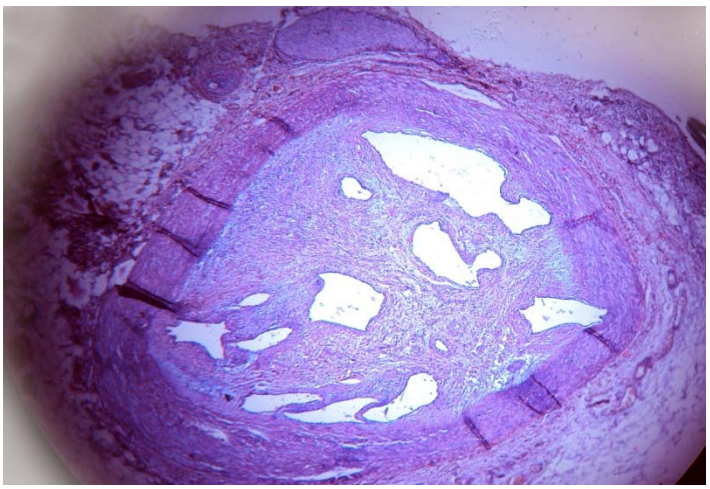

Fig. 5 : Atheromatous plaque which shows recanlisation in coronary artery (H&E x 50)

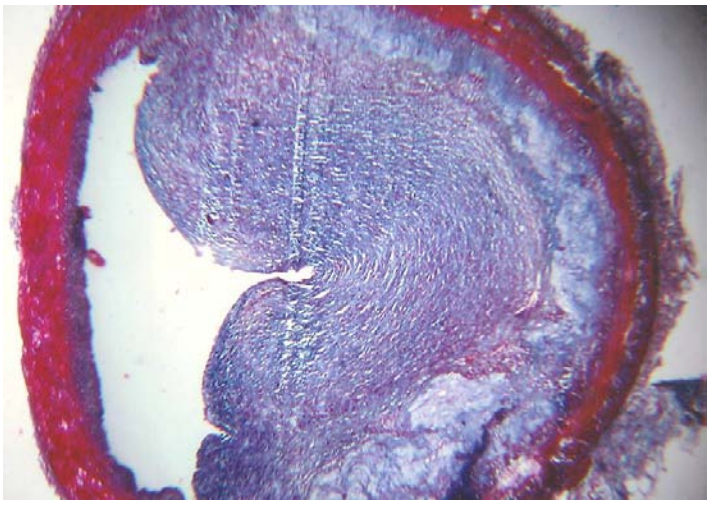

Fig. 6 : Atheromatous plaque with Grade IV stenosis collagen has stained blue and smooth muscle- red colour (Masson's Trichrome stain x 50)

IV. Discussion

The autopsy study provides a means of understanding the basic process which sets a stage for clinically significant atherosclerotic cardiovascular disease. There is no valid method of sampling of living population. It was, therefore, considered that deaths suspected due to cardiovascular pathology, probably provide the best sample of the living population for studying atherosclerosis. Many epidemiological studies have brought to light a number of factors that are of indisputable importance in the development of atherosclerosis.

Table 4 : Percentage incidence of atherosclerosis in various studies

	Study	Place	Percentage
1.	Wig and associates (1962)[13]	North India	64
2.	Enos et al., (1953)[14]	Korea	77.3
3.	Subramaniam R. et al., (1964)[15]	Madras	62
4.	Bhargava and Bhargavan (1975)[16]	North Karnataka	69.9
5.	Shirani J et al., (1995)[17]	USA	65
6.	Strong J.P. et al., (1999)[18]	USA	60-80
7.	McGill et al., (2000)[19]	USA	58
8.	Present Study	karnataka	66

The percentage incidence of atherosclerosis in various studies ranged from 58% in the study by Mc Gill et al., in United States to 77.3% by Enos et al., among soldiers killed in action in Korea. In present study, the incidence was 66% which was almost comparable to all studies and nearly equal to Wig and Associates, Shirani J et al., studies.

Table 5 : Shows age range in different studies in comparison with the present study

	Study	Age range
1.	Wig and Associates, (1962)[13]	0-80
2.	Enos et al., (1953)[14]	18-48
3.	Subramaniam R. et al., (1964)[15]	2.5-94
4.	Bhargavan and Bhargava, (1975)[16]	0-90
5.	Shirani J. et al., (1995)[17]	71-80
6.	Strong J.P. et al., (1999)[18]	15-36
7.	McGill et al., (2000)[19]	15-34
8.	Present study	19-80

The age group in above studies varied from neonates to 94 years, whereas in the present study, it was 19 to 80 years. The minimal age was almost equal to Enos et al., Strong J.P. et al., and McGill et al. The maximal age was similar to Wig and Associates and Shirani J. et al.

The prevalence and extent of atherosclerosis quite clearly increased with age. The datas of different studies are compared in Table -8.

Table 6 : Comparison of percentage of involvement by atherosclerosis in each decade of life in different studies

Decade	Wig and Associates (1962)[13]		Bhargava and Bhargava (1975)[16]		Present study	
	No. with lesions	%	No. with lesions	%	No. with lesions	%
< 1 year	-	-	0/13	0	0	0
1st Decade	2/18	11	2/20	10	-	-
2nd Decade	7/18	38	2/21	10	2/4	50
3rd Decade	24/38	63	12/30	40	5/8	62.5
4th Decade	23/24	95	21/25	84	10/17	64.7
5th Decade	23/25	92	17/21	80	8/12	66.66
6th Decade	19/19	100	10.12	83	5/6	83.33
7th Decade	8/9	88	3/3	100	2/2	100
8th Decade	-	-	1/1	100	1/1	100

In the present study the cases from the first decade were not included as the disease started in the 2nd decade, as stated by Gore et al (1960).[9] Wig [13] and associates observed that atherosclerosis started appearing in teen age itself.

In the 2nd decade, the incidence of atherosclerosis was 50% in the present study which was higher compared to Wig[13] and Associates Study (38%) and Bhargava's[16] Study (10%). This may be due to small sample survey.

Results of third decade were almost similar to the Wig and Associates, 40% incidence in the Bhargava's Study which was lesser when compared to present study (66%). The increase of incidence in our study may be due to change of life style of people in recent decades.

After fifth decade almost all the cases in the present study showed the evidence of atherosclerosis. The present study was almost comparable to the above studies in the remaining decades.

V. Conclusion

The present study concludes that coronary artery atherosclerosis is common in majority of cases. Atherosclerosis is a complex and multifactorial disease. Age has a dominant influence. Males are affected more than females. Smoking and alcoholism can accelerate the development of atherosclerotic lesions, though they are not atherogenic on their own.

All the observation in the present study showed that the incidence of atherosclerosis in the developing countries (like India) is same as developed countries. There is need of life style change in general public as well as cardiologists and treating physicians to think of early treatment, to avoid untoward complications.

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Incidence of Carcinoma of the Prostate in Patients with Normal Prostatic Specific Antigen Following Prostatectomy

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Abstract - Background/Aims: Prostate cancer is fourth most common male cancer, recent data showed an increased incidence among Sudanese males and it is becoming a major medical problems and gained increased attention from Sudanese urologists.

Objective: To detect patients with prostate cancer, in prostatectomy specimens, with normal preoperative PSA levels. To try to suggest a base line level of PSA above which prostatectomy should not be performed unless having a histological tissue diagnosis.

Materials and methods: This is descriptive, prospective cross sectional, hospital based study, conducted at Soba University Hospital, Omdurman Military Hospital, IbnSina specialized Hospital in the period from September 2012 to August 2013All patients above 40 years of age undergoing prostectomy with normal PSA levels in the above mentioned hospitals were enrolled in this study, their surgical specimens was sent for histology.

Results: The PSA level was below 4ng/ml in all cases, with a mean of 1.85ng/dl (total), and 0.36ng/dl free PSA. The histology of the prostatectomy specimens showed adenocarcinoma in 14 Pts (13.1%) and BPH in 93 pts (86.7%).

Conclusion: There was a detection rate of (13.1%) among patients with PSA below ng/ml, with high grade Gleason scores. Suspicious DRE in low PSA patients enhances the cancer detection rate.

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Elimam. A.M.Elaimam [α] & Abdel Raouf Sharfi [σ]

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I. Introduction

The fourth most common male malignant neoplasm worldwide is prostatic cancer, 18% of American men were affected with causing death in 3% in2005. (1)In Japan death from prostatic cancer was one- fifth to one-half the rate in United States and Europe in the 1990s. (2) It has gained increased attention from Sudanese urologists owing to its rapidly increasing incidence as recent reports have indicated.(3)

Prostatic cancers vary widely across the world, with the south and west Asia detecting less frequently than in Europe, and especially in United states. Prostatic cancer tend to develop in men over the age of fifty, and it's the second leading cause of cancer related death in men in the United States. (4) However many men with prostatic cancer never have symptoms, undergo no therapy, and eventually die of other unrelated causes .Many factors including genetic diets, have been implicated in the development of prostatic cancer .The presence of the prostatic cancer may be indicated by symptoms, physical examination, prostatic specific antigen(PSA) and biopsy. Prostatic-specific antigen increases the cancer detection but does not decrease mortality. (5) The American cancer Society position regarding early detection is research has not yet proven that the potential benefits of testing outweigh the harms of testing and treatment. The American cancer society believes that men should not be tested without learning about we know and don't know about the risks and possible benefit of testing and treatment Starting at age 50, if African American or brother or father suffered from condition before age of 65 he would know pros and cons of testing so you can decide if testing is the choice for you.(6) The only test that can fully confirm the diagnosis of prostatic cancer is biopsy, the removal of small pieces of the prostate for microscopic examination.There are also several other tests that can be used together for more information about prostate and urinary tract. Cystoscopy shows the urinary tracts from the inside the bladder, using a thin flexible camera tube inserted down the urethra. Transurethral ultrasanography creates a picture of the prostate using sound waves from the probe in the rectum. Prostatic specific antigen (PSA) testing, PSA is Kallikrein111seminin, semenorgelase, gama-seminoprotein and P-30 antigen is a 34KD glycoprotein. While PSA testing may help 1 in 1000 avoid death due to prostatic cancer, 4 to 5 in 1000 would die from prostatic cancer after 10 years even with screening.

PSA levels between 4 and 10 ng\ml are considered to be suspicious and consideration should be given to confirming the abnormal PSA with repeat test.If indicated prostatic biopsy is performed to obtain tissue sample for histopathology analysis. In the United Kingdom the National Health Service (2005) doesn't mandate, nor advice for PSA tests, but allows patients to decide based on their advice (7) PAS is normally present in the blood at very low levels. The reference rate of less than 4ng\ml for the first commercial PAS test, the Hybritech tandem-PSA test released in

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February 1986, was based on study that found 99% of 472 apparently healthy men had a total PSA level below 4ng\ml, the upper limit of normal is much less than 4ng\ml (6) Increase level of PSA may suggest the presence of prostatic cancer .However prostatic cancer can be present in the complete absence of an elevated PSA level, in which case the result would be false negative.(8)

Large series have shown that 21-43% cancers will occur in patients with PSA in the normal range (0-4 ng/ml)(9) in this study none of the cancer patients has abnormal PSA. The choice of a PSA threshold or cut point above which one would recommend further evaluation to rule out prostate cancer (prostate biopsy) is controversial (Carter, 2000; Catalona et al, 2000b, 2000c.(10) Although the PSA threshold of 4 ng/mL has been most commonly used, the PSA threshold that most efficiently balances the dual goal of reducing cancer mortality and reducing unnecessary testing (PSA measurements and biopsies) is not known. Many studies have made an effort to evaluate other thresholds to maximize the positive biopsy rate of PSA-based screening.

In the Sudan there was study titled Prostatic Specific Antigen versus Digital rectal examination as screening for prostatic cancer in Sudanese patients. A prospective study carried out in Elgezira Hospital for Renal Diseases and Surgery in the period June 2003-May 2005. An elevated PSA and DRE pointedto the diagnosis of prostate cancer in 100% and 88.9% respectively. The rate of prostate cancer detection showed to be 26% for combination of the positive DRE and PSA > 4 ng/ml, while it was only 4.1% in BPH patients. (11)

In a study carried out in the Urology Clinic of Soba University Hospital from August 2008 and January 2010 titled significance of serum total prostatic antigen and DRE in the diagnosis of prostatic cancer. The outcome was that combining DRE and tPSA test increase the sensitivity, specificity of prostatic cancer detection. (12)Prostate cancer is diagnosed in about 1% of men aged 50, rises abruptly in the sixth and seventh decade of life, the highest incidence being recorded in the seventh and eighth decade of life NAZ KR.(13)

II. Results

A total of 107 patients were included in the study, their ages ranged between 50-95 years, with a mean age of 67 years (table1).

The PSA level was below 4ng/ml in all cases, with a mean of 1.85ng/dl (total), and 0.36ng/dl free PSA. FPSA/tPSA ratio was is 1.4-50% with a mean of 18.4%, PSA density was o.02-2.2 with a mean of o.27 in 107 patients. From the 14 pts with prostate cancer 5 pts(35.7%) presented with acute urine retention,7 pts(50%) had haematuria and irritative symptoms of (frequency, urgency, dysuria, nocturia) in(12 pts(85%),13 pts(92%),11 pts(78.5%), 6 pts (42.8%) respectively. Obstructive symptoms as weak stream and dribbling were found in 7pts(50%),9(64.2%) respectively. 4pts (28.5%) complained of back pain, 2 pts (14.2%) were smokers,consuming more than 10 cigarette per day. Positive family history of prostatic cancer was found in 2pts (14.2%). The histology of the prostatectomy specimens showed adenocarcinoma in 14 Pts (13.1%) and BPH in 93 pts (86.7%) chart (2). The mean age of the patients with prostatic cancer was 72.7 years, ranging from (57-87) years table (2), with PSA ranging from (0.02 -3.4ng/ml) with a mean of 1.7ng/ml, the free PSA was between 0.00-0.8ng/ml with a mean of 0.33ng/ml. The Gleason score was ranged from 3-7 with a mean of 4.6, 3pts(21.4%) had a score of 7, in 4 pts(28.5%) a Gleason score of 5 was found and 5 pts(35.7%) had a Gleason score of 5 table (21). In this study when correlating tPSA to the Gleason score we found that pts who had cancer with tPSA level ranging from 0.02-1.02/ml had Gleason score of <4,tPSA ranging from 1.02-2.05ng/ml had Gleason score of 4-6 and Gleason score of more than 6 the tPSA was more than 2.05.ng/ml.

Table 1 : Age distribution in 107 pts

Age	40-50 yrs	51-60yrs	61-70ys	71-80yrs	>80	
	1	29	38	27	12	Total
	0.93%	17.1%	36.5%	25.2%	11.2%	107

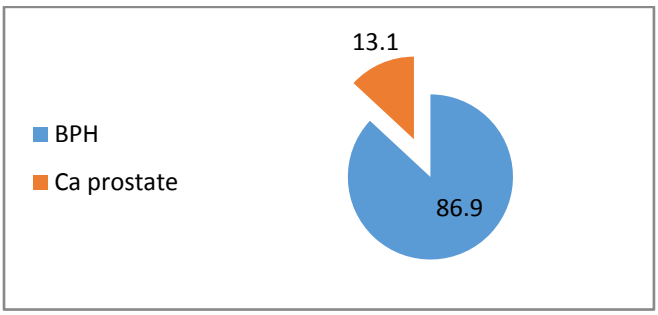
Table 2 : Age distribution in 14 patients

Age	Number	Percentage	Total
50-60 year	1	7.1%	14
61-70 year	5	35.7%	
71-80 year	6	42.4%	100%
81-90 year	2		

*Table (21).*The Gleason score in 14 pts and their tPSA ranges

Gleason score	>4	4-6	>6	Total 14
	5	5	4	100%
	35.7%	35.7%	42.8%	
tPSA ranges	0.02-1.02ng/ml	1.03-2.05ng/ml	>2.05ng/ml	

Chart no (2). The frequency of Ca prostate in 107 pts



III. Discussion

In this study group the patients ages were between 50 and 95 years of age, the commonest age for cancer was between 70-79 years, their tPSA range was between 0.3- 3.2, this is in contrast to a study conducted in Austria that showed that prostate cancer with a PSA value of 2 - 3.9 ng/ml occurs in younger patients.(13) It has been noticed that African males have in general higher tPSA values than European men.(14) In African men the cut off points for ages 50-59 years were (6.5 ng/ml), 60-69 years was (11.3ng/ml), 70-90 years was (12.5 ng/ml) .(15) A Sudanese study showed that age specific reference ranges in Sudanese men were even lower, cut off points for ages 50-59 years are (0 – 3.02 ng/ml), 60-69 years (0 – 3.8 ng/ml), 70-90 years (0 – 8.7 ng/ml). (16)

Literature reported that most of prostate cancer patients present with no symptoms initially because of the peripheral location of the tumour in the prostate gland. (17) The lower urinary tract symptoms present after invasion of the urethra and the prostate. (18) In this study the most common presenting symptoms were urgency, frequency and dysuria (80 - 92%) of patients; these symptoms are collectively known as LUTS. Most of our patients presented late after the establishment of their symptoms and were included in the study with symptoms and signs that warranted surgical intervention. In a study by Willam Hamilton, Deborah J Slap, they reported that most cases presented with urinary symptoms that uncovered their disease; these symptoms were urinary retention, frequency, hesitancy and nocturia which most probably represent enlargement of the prostate gland.(17)

Haematuria was present in 50% of patients in this study; a Belgian study (19) reported haematuria as the presenting symptom in 10.3% of all urologic cancer and recognized it as a risk for urologic cancer. Hamilton and Deborah reported haematuria as having a PPV of 1% in prostate cancer patients which accords with the figure in the Belgian study, as bladder and renal cancer will account for the majority of malignant causes of haematuria. (17)

Urine retention in this study was present in 35% of patients, in the same study by Hamilton, retention had the strongest association with prostate cancer.(20) They concluded that cancer should be clearly considered as a possibility when the PPV for retention is 3.1%. They argued that the risk for prostatic cancer is higher in symptomatic older men, and the results supported diagnostic testing in these circumstances, since some cases reported symptoms over 6 months before diagnosis. They concluded that diagnostic testing by such time period may not improve mortality but should at least allow for early remission of symptoms.(17)

In our study group regarding the risk factors for prostate cancer, positive family history was found in three patients (14.2%) of whom two had prostate cancer. The international reference studies show that positive family history of prostate cancer in 1st degree relatives (brothers) will double the risk of developing the disease. (21) Only nine patients were smokers consuming more than 10 cigarettes per day, the low exposure to risk factors in our study group may explain the relatively low incidence (13.1%) of prostate cancer among our patients compared to (15%) in international references.

Currently the suggested PSA cutoff to biopsy a male patient for screening differs between 2.6-4.0 ng/ml (22). In this study the results showed that half of the patients with prostate cancer had a PSA of (1.2 – 2.1 ng/ml), which is way below the cut-off point suggested. The group of patients in our study within the reference range of tPSA (<4 - >2.1) represented 14% of the study group. This suggests that the cut off point for screening should be lowered for our Sudanese patients. Most of

the studies are conducted in European patients with different environmental and genetic risk factors which might have an influence on the total PSA levels.

In this study DRE in patients with prostate cancer showed a soft gland in (57.1%), this shows the low rate of cancer detection on DRE in patients with low PSA. In a study by Fritz H.Schrode, ArotoBoeka et al, they concluded that use of DRE in detection of prostate cancer among patients with PSA 0-2.9 has a sensitivity of (4%-11%) while DRE detection rate was (83%) in patients with PSA 3 – 9ng/ml. (23)In a randomized study by Thomposon et al, DRE in patients with PSA less or equal to 3ng/ml with a normal DRE, after a 7 year follow up period the prostate cancer was found in 15% of pts. They concluded that men with low PSA level values less than 3ng/ml have a 15% prostate cancer detection rate with or without use of DRE.

In two Sudanese studies by El Imam et al.,Abdelkarim A. Abdrabo ,Adil I. Fadlallalmad M. Fadl-Elmula, the found that the combined use of DRE and PSA increases the cancer detection rate more than PSA or DRE alone. The rate of prostate cancer detection showed to be (25.7%) for PSA > 4ng/ml, (13.31%) for abnormal (positive) finding of DRE, and (27.8%) for combination of the positive DRE and PSA > 4 ng/ml. The rate of BPH detection showed to be (68.6%) for PSA > 4ng/ml, (28.6%) for positive finding of DRE, and (4.1%) for combination of the positive DRE and PSA >4 ng/ml.(25-25)

In studies conducted by Jewett in cancer screen, Jewett found that approximately 50% of palpable prostate nodules were diagnosed as prostate cancers on prostate biopsy.(26) However, DRE findings are only moderately reproducible, even amongst experienced urologists.(27) Further, DRE tended to diagnose prostatic cancer when they are pathologically advanced and therefore less likely to be curable by radical prostatectomy. (27) Cattolonaet al examined prostate cancer detection at low PSA levels by DRE; clinically aggressive tumours on omission of DRE at PSA levels less than 3ng/ml would have detected (14%) of Prostate cancer. (28) In contrast, Okotie OT, Roehl KA, Han they report that is that screening without DRE at low PSA levels (PSA<3.0 ng/ml) did not lead to the detection of significantly more (poorly differentiated) prostate cancer for 4 years follow up later compared to screening with the use of DRE in the ERSPC.(29)

The detection rate of cancer in the 107 postsurgical specimens was in 14 patients(13.1%) (chart 3), four of these patients (28.5 %) had a high Gleason scores of 7 and their tPSA ranged between 2.05-3.4 ng/ml, while Gleason score of < 4 and between 4 - 6 was(35.7 %) for each score.The tPSA for Gleason scores <4 ranged between 0.02 – 1.02 ng/ml, while Gleason scores between 4 – 6 their tPSAranged between 1.03 – 2.05 ng/ml (table 19). This is almost similar to the study from the Division of Urology, Department of Surgery, University of Texas Health Science Center at San Antonio about prevalence of prostate cancer among men with a low prostate-specific antigen, prostate cancer was diagnosed in 449 (15.2 %); 67 of these 449 cancer patients (14.9 %) had a Gleason score of 7 or higher. The prevalence of prostate cancer was (6.6%) among men with a PSA level of up to 0.5 ng/ml, (10.1%) among those with values of 0.6 to 1.0 ng/ml (17.0 %) among those with values of 1.1 to 2.0 n/ml, (23.9 %) among those with values of 2.1 to 3.0 ng/ml, and (26.9 %) among those with values of 3.1 to 4.0 ng/ml. (30)

In contrast to this study, and the American study, had low Gleason scores which may be due to early detection of cancers achieved by close follow up of asymptomatic patients in their study, which lead to early detection of low grade tumors' before the development of advanced high grade cancers.

IV. Conclusion

In this study we found that a significant number of patients with high grade Gleason score prostate cancer can be detected among patients with features of benign prostatic hyperplasia and a PSA less than 4 ng/ml. We suggest that the cut off point for tPSA used for screening Sudanese males for prostate cancer to be lowered to 0.2 – 2.1 ng/mland the f/t PSA of 11 – 20 %, instead of the current PSA age-specific reference range used.

AtPSA< 4 ng/ml and a negative DRE doesn't exclude the presence of prostate cancer; risk factors to be considered before excluding the possibility of malignant disease are in age groups between 70 – 79 years, significant lower urinary tract symptoms, haematuria, urine retention and positive family history. These patients should be considered for a prostatic biopsy; if negative a second biopsy preferably a TRUS biopsy should be taken to confirm absence of the disease and close follow up is recommended in this group of patients.

The combination of digital rectal examination and PSA increases the cancer detection rate more than PSA alone.

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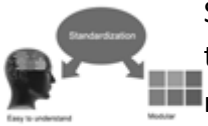

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"

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3. Submission of Manuscripts,

4. Manuscript's Category,

5. Structure and Format of Manuscript,

6. After Acceptance.

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14. Produce good diagrams of your own: Always try to include good charts or diagrams in your paper to improve quality. Using several and unnecessary diagrams will degrade the quality of your paper by creating "hotchpotch." So always, try to make and include those diagrams, which are made by your own to improve readability and understandability of your paper.

15. Use of direct quotes: When you do research relevant to literature, history or current affairs then use of quotes become essential but if study is relevant to science then use of quotes is not preferable.

16. Use proper verb tense: Use proper verb tenses in your paper. Use past tense, to present those events that happened. Use present tense to indicate events that are going on. Use future tense to indicate future happening events. Use of improper and wrong tenses will confuse the evaluator. Avoid the sentences that are incomplete.

17. Never use online paper: If you are getting any paper on Internet, then never use it as your research paper because it might be possible that evaluator has already seen it or maybe it is outdated version.

18. Pick a good study spot: To do your research studies always try to pick a spot, which is quiet. Every spot is not for studies. Spot that suits you choose it and proceed further.

19. Know what you know: Always try to know, what you know by making objectives. Else, you will be confused and cannot achieve your target.

20. Use good quality grammar: Always use a good quality grammar and use words that will throw positive impact on evaluator. Use of good quality grammar does not mean to use tough words, that for each word the evaluator has to go through dictionary. Do not start sentence with a conjunction. Do not fragment sentences. Eliminate one-word sentences. Ignore passive voice. Do not ever use a big word when a diminutive one would suffice. Verbs have to be in agreement with their subjects. Prepositions are not expressions to finish sentences with. It is incorrect to ever divide an infinitive. Avoid clichés like the disease. Also, always shun irritating alliteration. Use language that is simple and straight forward. put together a neat summary.

21. Arrangement of information: Each section of the main body should start with an opening sentence and there should be a changeover at the end of the section. Give only valid and powerful arguments to your topic. You may also maintain your arguments with records.

22. Never start in last minute: Always start at right time and give enough time to research work. Leaving everything to the last minute will degrade your paper and spoil your work.

23. Multitasking in research is not good: Doing several things at the same time proves bad habit in case of research activity. Research is an area, where everything has a particular time slot. Divide your research work in parts and do particular part in particular time slot.

24. Never copy others' work: Never copy others' work and give it your name because if evaluator has seen it anywhere you will be in trouble.

25. Take proper rest and food: No matter how many hours you spend for your research activity, if you are not taking care of your health then all your efforts will be in vain. For a quality research, study is must, and this can be done by taking proper rest and food.

26. Go for seminars: Attend seminars if the topic is relevant to your research area. Utilize all your resources.

27. Refresh your mind after intervals: Try to give rest to your mind by listening to soft music or by sleeping in intervals. This will also improve your memory.

28. Make colleagues: Always try to make colleagues. No matter how sharper or intelligent you are, if you make colleagues you can have several ideas, which will be helpful for your research.

29. Think technically: Always think technically. If anything happens, then search its reasons, its benefits, and demerits.

30. Think and then print: When you will go to print your paper, notice that tables are not be split, headings are not detached from their descriptions, and page sequence is maintained.

31. Adding unnecessary information: Do not add unnecessary information, like, I have used MS Excel to draw graph. Do not add irrelevant and inappropriate material. These all will create superfluous. Foreign terminology and phrases are not apropos. One should NEVER take a broad view. Analogy in script is like feathers on a snake. Not at all use a large word when a very small one would be sufficient. Use words properly, regardless of how others use them. Remove quotations. Puns are for kids, not grunt readers. Amplification is a billion times of inferior quality than sarcasm.

32. Never oversimplify everything: To add material in your research paper, never go for oversimplification. This will definitely irritate the evaluator. Be more or less specific. Also too, by no means, ever use rhythmic redundancies. Contractions aren't essential and shouldn't be there used. Comparisons are as terrible as clichés. Give up ampersands and abbreviations, and so on. Remove commas, that are, not necessary. Parenthetical words however should be together with this in commas. Understatement is all the time the complete best way to put onward earth-shaking thoughts. Give a detailed literary review.

33. Report concluded results: Use concluded results. From raw data, filter the results and then conclude your studies based on measurements and observations taken. Significant figures and appropriate number of decimal places should be used. Parenthetical remarks are prohibitive. Proofread carefully at final stage. In the end give outline to your arguments. Spot out perspectives of further study of this subject. Justify your conclusion by at the bottom of them with sufficient justifications and examples.

34. After conclusion: Once you have concluded your research, the next most important step is to present your findings. Presentation is extremely important as it is the definite medium though which your research is going to be in print to the rest of the crowd. Care should be taken to categorize your thoughts well and present them in a logical and neat manner. A good quality research paper format is essential because it serves to highlight your research paper and bring to light all necessary aspects in your research.

Informal Guidelines of Research Paper Writing

Key points to remember:

- Submit all work in its final form.
- Write your paper in the form, which is presented in the guidelines using the template.
- Please note the criterion for grading the final paper by peer-reviewers.

Final Points:

A purpose of organizing a research paper is to let people to interpret your effort selectively. The journal requires the following sections, submitted in the order listed, each section to start on a new page.

The introduction will be compiled from reference matter and will reflect the design processes or outline of basis that direct you to make study. As you will carry out the process of study, the method and process section will be constructed as like that. The result segment will show related statistics in nearly sequential order and will direct the reviewers next to the similar intellectual paths throughout the data that you took to carry out your study. The discussion section will provide understanding of the data and projections as to the implication of the results. The use of good quality references all through the paper will give the effort trustworthiness by representing an alertness of prior workings.

Writing a research paper is not an easy job no matter how trouble-free the actual research or concept. Practice, excellent preparation, and controlled record keeping are the only means to make straightforward the progression.

General style:

Specific editorial column necessities for compliance of a manuscript will always take over from directions in these general guidelines.

To make a paper clear

· Adhere to recommended page limits

Mistakes to evade

- Insertion a title at the foot of a page with the subsequent text on the next page
- Separating a table/chart or figure - impound each figure/table to a single page
- Submitting a manuscript with pages out of sequence

In every sections of your document

· Use standard writing style including articles ("a", "the," etc.)

· Keep on paying attention on the research topic of the paper

· Use paragraphs to split each significant point (excluding for the abstract)

· Align the primary line of each section

· Present your points in sound order

· Use present tense to report well accepted

· Use past tense to describe specific results

· Shun familiar wording, don't address the reviewer directly, and don't use slang, slang language, or superlatives

· Shun use of extra pictures - include only those figures essential to presenting results

Title Page:

Choose a revealing title. It should be short. It should not have non-standard acronyms or abbreviations. It should not exceed two printed lines. It should include the name(s) and address (es) of all authors.

Abstract:

The summary should be two hundred words or less. It should briefly and clearly explain the key findings reported in the manuscript--must have precise statistics. It should not have abnormal acronyms or abbreviations. It should be logical in itself. Shun citing references at this point.

An abstract is a brief distinct paragraph summary of finished work or work in development. In a minute or less a reviewer can be taught the foundation behind the study, common approach to the problem, relevant results, and significant conclusions or new questions.

Write your summary when your paper is completed because how can you write the summary of anything which is not yet written? Wealth of terminology is very essential in abstract. Yet, use comprehensive sentences and do not let go readability for briefness. You can maintain it succinct by phrasing sentences so that they provide more than lone rationale. The author can at this moment go straight to shortening the outcome. Sum up the study, with the subsequent elements in any summary. Try to maintain the initial two items to no more than one ruling each.

- Reason of the study - theory, overall issue, purpose
- Fundamental goal
- To the point depiction of the research
- Consequences, including definite statistics - if the consequences are quantitative in nature, account quantitative data; results of any numerical analysis should be reported
- Significant conclusions or questions that track from the research(es)

Approach:

- Single section, and succinct
- As a outline of job done, it is always written in past tense
- A conceptual should situate on its own, and not submit to any other part of the paper such as a form or table
- Center on shortening results - bound background information to a verdict or two, if completely necessary
- What you account in an conceptual must be regular with what you reported in the manuscript
- Exact spelling, clearness of sentences and phrases, and appropriate reporting of quantities (proper units, important statistics) are just as significant in an abstract as they are anywhere else

Introduction:

The **Introduction** should "introduce" the manuscript. The reviewer should be presented with sufficient background information to be capable to comprehend and calculate the purpose of your study without having to submit to other works. The basis for the study should be offered. Give most important references but shun difficult to make a comprehensive appraisal of the topic. In the introduction, describe the problem visibly. If the problem is not acknowledged in a logical, reasonable way, the reviewer will have no attention in your result. Speak in common terms about techniques used to explain the problem, if needed, but do not present any particulars about the protocols here. Following approach can create a valuable beginning:

- Explain the value (significance) of the study
- Shield the model - why did you employ this particular system or method? What is its compensation? You strength remark on its appropriateness from a abstract point of vision as well as point out sensible reasons for using it.
- Present a justification. Status your particular theory (es) or aim(s), and describe the logic that led you to choose them.
- Very for a short time explain the tentative propose and how it skilled the declared objectives.

Approach:

- Use past tense except for when referring to recognized facts. After all, the manuscript will be submitted after the entire job is done.
- Sort out your thoughts; manufacture one key point with every section. If you make the four points listed above, you will need a least of four paragraphs.

- Present surroundings information only as desirable in order hold up a situation. The reviewer does not desire to read the whole thing you know about a topic.
- Shape the theory/purpose specifically - do not take a broad view.
- As always, give awareness to spelling, simplicity and correctness of sentences and phrases.

Procedures (Methods and Materials):

This part is supposed to be the easiest to carve if you have good skills. A sound written Procedures segment allows a capable scientist to replacement your results. Present precise information about your supplies. The suppliers and clarity of reagents can be helpful bits of information. Present methods in sequential order but linked methodologies can be grouped as a segment. Be concise when relating the protocols. Attempt for the least amount of information that would permit another capable scientist to spare your outcome but be cautious that vital information is integrated. The use of subheadings is suggested and ought to be synchronized with the results section. When a technique is used that has been well described in another object, mention the specific item describing a way but draw the basic principle while stating the situation. The purpose is to text all particular resources and broad procedures, so that another person may use some or all of the methods in one more study or referee the scientific value of your work. It is not to be a step by step report of the whole thing you did, nor is a methods section a set of orders.

Materials:

- Explain materials individually only if the study is so complex that it saves liberty this way.
- Embrace particular materials, and any tools or provisions that are not frequently found in laboratories.
- Do not take in frequently found.
- If use of a definite type of tools.
- Materials may be reported in a part section or else they may be recognized along with your measures.

Methods:

- Report the method (not particulars of each process that engaged the same methodology)
- Describe the method entirely
- To be succinct, present methods under headings dedicated to specific dealings or groups of measures
- Simplify - details how procedures were completed not how they were exclusively performed on a particular day.
- If well known procedures were used, account the procedure by name, possibly with reference, and that's all.

Approach:

- It is embarrassed or not possible to use vigorous voice when documenting methods with no using first person, which would focus the reviewer's interest on the researcher rather than the job. As a result when script up the methods most authors use third person passive voice.
- Use standard style in this and in every other part of the paper - avoid familiar lists, and use full sentences.

What to keep away from

- Resources and methods are not a set of information.
- Skip all descriptive information and surroundings - save it for the argument.
- Leave out information that is immaterial to a third party.

Results:

The principle of a results segment is to present and demonstrate your conclusion. Create this part a entirely objective details of the outcome, and save all understanding for the discussion.

The page length of this segment is set by the sum and types of data to be reported. Carry on to be to the point, by means of statistics and tables, if suitable, to present consequences most efficiently.You must obviously differentiate material that would usually be incorporated in a study editorial from any unprocessed data or additional appendix matter that would not be available. In fact, such matter should not be submitted at all except requested by the instructor.

Content

- Sum up your conclusion in text and demonstrate them, if suitable, with figures and tables.
- In manuscript, explain each of your consequences, point the reader to remarks that are most appropriate.
- Present a background, such as by describing the question that was addressed by creation an exacting study.
- Explain results of control experiments and comprise remarks that are not accessible in a prescribed figure or table, if appropriate.
- Examine your data, then prepare the analyzed (transformed) data in the form of a figure (graph), table, or in manuscript form.

What to stay away from

- Do not discuss or infer your outcome, report surroundings information, or try to explain anything.
- Not at all, take in raw data or intermediate calculations in a research manuscript.
- Do not present the similar data more than once.
- Manuscript should complement any figures or tables, not duplicate the identical information.
- Never confuse figures with tables - there is a difference.

Approach

- As forever, use past tense when you submit to your results, and put the whole thing in a reasonable order.
- Put figures and tables, appropriately numbered, in order at the end of the report
- If you desire, you may place your figures and tables properly within the text of your results part.

Figures and tables

- If you put figures and tables at the end of the details, make certain that they are visibly distinguished from any attach appendix materials, such as raw facts
- Despite of position, each figure must be numbered one after the other and complete with subtitle
- In spite of position, each table must be titled, numbered one after the other and complete with heading
- All figure and table must be adequately complete that it could situate on its own, divide from text

Discussion:

The Discussion is expected the trickiest segment to write and describe. A lot of papers submitted for journal are discarded based on problems with the Discussion. There is no head of state for how long a argument should be. Position your understanding of the outcome visibly to lead the reviewer through your conclusions, and then finish the paper with a summing up of the implication of the study. The purpose here is to offer an understanding of your results and hold up for all of your conclusions, using facts from your research and generally accepted information, if suitable. The implication of result should be visibly described. Infer your data in the conversation in suitable depth. This means that when you clarify an observable fact you must explain mechanisms that may account for the observation. If your results vary from your prospect, make clear why that may have happened. If your results agree, then explain the theory that the proof supported. It is never suitable to just state that the data approved with prospect, and let it drop at that.

- Make a decision if each premise is supported, discarded, or if you cannot make a conclusion with assurance. Do not just dismiss a study or part of a study as "uncertain."
- Research papers are not acknowledged if the work is imperfect. Draw what conclusions you can based upon the results that you have, and take care of the study as a finished work
- You may propose future guidelines, such as how the experiment might be personalized to accomplish a new idea.
- Give details all of your remarks as much as possible, focus on mechanisms.
- Make a decision if the tentative design sufficiently addressed the theory, and whether or not it was correctly restricted.
- Try to present substitute explanations if sensible alternatives be present.
- One research will not counter an overall question, so maintain the large picture in mind, where do you go next? The best studies unlock new avenues of study. What questions remain?
- Recommendations for detailed papers will offer supplementary suggestions.

Approach:

- When you refer to information, differentiate data generated by your own studies from available information
- Submit to work done by specific persons (including you) in past tense.
- Submit to generally acknowledged facts and main beliefs in present tense.

Administration Rules Listed Before Submitting Your Research Paper to Global Journals Inc. (US)

Please carefully note down following rules and regulation before submitting your Research Paper to Global Journals Inc. (US):

Segment Draft and Final Research Paper: You have to strictly follow the template of research paper. If it is not done your paper may get rejected.

- The **major constraint** is that you must independently make all content, tables, graphs, and facts that are offered in the paper. You must write each part of the paper wholly on your own. The Peer-reviewers need to identify your own perceptive of the concepts in your own terms. NEVER extract straight from any foundation, and never rephrase someone else's analysis.

- Do not give permission to anyone else to "PROOFREAD" your manuscript.

- Methods to avoid Plagiarism is applied by us on every paper, if found guilty, you will be blacklisted by all of our collaborated research groups, your institution will be informed for this and strict legal actions will be taken immediately.)
- To guard yourself and others from possible illegal use please do not permit anyone right to use to your paper and files.

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Topics	Grades		
	A-B	**C-D**	**E-F**
Abstract	Clear and concise with appropriate content, Correct format. 200 words or below	Unclear summary and no specific data, Incorrect form Above 200 words	No specific data with ambiguous information Above 250 words
Introduction	Containing all background details with clear goal and appropriate details, flow specification, no grammar and spelling mistake, well organized sentence and paragraph, reference cited	Unclear and confusing data, appropriate format, grammar and spelling errors with unorganized matter	Out of place depth and content, hazy format
Methods and Procedures	Clear and to the point with well arranged paragraph, precision and accuracy of facts and figures, well organized subheads	Difficult to comprehend with embarrassed text, too much explanation but completed	Incorrect and unorganized structure with hazy meaning
Result	Well organized, Clear and specific, Correct units with precision, correct data, well structuring of paragraph, no grammar and spelling mistake	Complete and embarrassed text, difficult to comprehend	Irregular format with wrong facts and figures
Discussion	Well organized, meaningful specification, sound conclusion, logical and concise explanation, highly structured paragraph reference cited	Wordy, unclear conclusion, spurious	Conclusion is not cited, unorganized, difficult to comprehend
References	Complete and correct format, well organized	Beside the point, Incomplete	Wrong format and structuring

INDEX

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