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Editorial

Prof. Dr. K. Rajeshwar Reddy

Specimen Management in Diagnostic Microbiology

Unlike other areas of diagnostic laboratory, clinical microbiology is a science of interpretive judgment that is becoming more complex, not less. Even with the advancements in laboratory automation and integration of molecular (genetic) diagnosis in microbiology, interpretation of results still depends on the quality of specimens received. Specimen management in diagnostic microbiology is a new concept in the changing world of microbiology accreditation.

Clearly, all microorganisms grow, multiply, and die very quickly. If any of those events occur during specimen collection, transport, or storage, the results of microbiologic analysis will be compromised and could be misleading. Therefore, attention to preanalytical specimen management in microbiology is critical to accuracy.

Physicians need confidence that the results provided by the microbiology laboratory are accurate, significant, and clinically relevant. Anything less is below the community standard of care. In order to provide that level of quality, however, the laboratory requires that all microbiology specimens be properly selected, collected and transported to optimize analysis and interpretation.

Because result interpretation in microbiology depends entirely on the quality of the specimen submitted for analysis, specimen management cannot be left to chance, and those that collect specimens for microbiologic analysis must be aware of what the physician needs as well as what the laboratory needs, including ensuring that specimens arrive at the laboratory for analysis as quickly as possible after collection.

At an elementary level, the physician needs answers to 3 very basic questions from the laboratory: Is my patient's illness caused by a microorganism? If so what is it? What is the drug susceptibility profile of the organism so therapy can be targeted?

To meet these needs, the laboratory needs very different information. The microbiology laboratory needs a specimen that has been appropriately selected, collected and transported to the laboratory for analysis. Caught in the middle, between the physician and laboratory, are those who select and collect the specimen and who may not know or understand what work the physician or the laboratory needs to do. Enhancing the quality of the specimen is everyone's job, so communication between the physicians, nurses, and laboratory staff should be encouraged openly.

The critical role of the microbiology laboratory in infectious disease diagnosis calls for a close, positive working relationship between the physician and the microbiologists who provide enormous value to the health care team. The diagnosis of infectious disease is best achieved by applying in-depth knowledge of both medical and laboratory science along with principles of epidemiology and pharmacokinetics of antibiotics and by integrating a strategic view of host-parasite interactions. Clearly, the best outcomes for patients are the result of strong partnerships between the clinician and the laboratory specialist.

The impact of proper specimen management on patient care is enormous. It is the key to accurate laboratory diagnosis and confirmation, directly affects patient care and patient outcomes, influences therapeutic decisions, impacts hospital infection control, impacts patient's length of stay, hospital costs, and laboratory costs, and influences laboratory efficiency. Clinicians should consult the laboratory to ensure that the selection, collection, transport, and storage of patient specimens are performed properly.

There are some strategic tenets of specimen management and testing in microbiology that stand as community standards of care. Ten points of importance are:

1. Specimens of poor quality must be rejected. Microbiologists should act correctly and responsibly when they call physicians to clarify and resolve problems with specimen submissions.
2. Physicians should not demand that the laboratory report "everything that grows" thus providing irrelevant information that could result in inaccurate diagnosis and inappropriate therapy.
3. 'Background noise' must be avoided where possible. Many body sites have normal microbiota that can easily contaminate the specimen. Therefore, specimens from sites such as lower respiratory tract (sputum), nasal sinuses, superficial wounds, fistulae, and others require care in collection.
4. The laboratory requires a true clinical specimen, not a swab of a specimen. Actual tissue, aspirates, and fluids are always specimens of choice, especially from surgery. A swab is not the specimen of choice for many specimens because swabs pick up extraneous microorganisms, hold extremely small volumes of the specimen (0.05 mL), make it difficult to get bacteria or fungi away from the swab fibers and onto media and the inoculum from the swab is often not uniform across several different agar plates. Swabs are expected from nasopharyngeal and viral respiratory infections. Flocked swabs have become a valuable tool for specimen collection and have been shown to be more effective than dacron, rayon, and cotton swabs in many situations. The flocked nature of the swab allows for more efficient release of contents for evaluation.
5. The laboratory must follow its procedure manual. These manuals are usually supported by literature.
6. A specimen should be collected prior to administration of antibiotics. Once antibiotics have been started, the flora changes, leading to potentially misleading culture results.
7. Drug susceptibility testing should be performed on clinically significant isolates, not on all microorganisms recovered in culture.
8. Microbiology laboratory results that are reported should be accurate, significant, and clinically relevant.
9. The laboratory should be allowed to set technical policy. Good communication and mutual respect between clinicians and laboratory specialists will lead to collaborative policies.
10. Specimens must be labeled accurately and completely so that interpretation of results will be reliable. Labels such as "eye" and "wound specimens" are not helpful to the interpretation of results without more specific site and clinical information

The microbiology laboratory policy manual should be available at all times for all medical staff to review or consult and it would be particularly helpful to encourage the nursing staff to review the specimen collection and management portion of the manual. This can facilitate collaboration between the laboratories, with the microbiology expertise, and the specimen collection personnel, who may know very little about what the laboratory needs in order to establish or confirm a diagnosis.

Welcome and engage the microbiology laboratory as an integral part of the healthcare team and encourage the hospital or the laboratory facility to optimize infectious disease laboratory.

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The Relationship of the Primary Breast Tumor Size and Histological Grading with Axillary Lymph Node Metastases

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Key words:
Axillary lymph nodes,
Breast cancer,
Size of tumor,
Metastases.

ABSTRACT

Objectives: To determine whether or not the size and site of the primary tumor in the breast, age and menopausal status of the patient and histopathological grade of the tumor would be the better predictor of axillary nodal positivity.

Methods: Clinical and pathological data was analysed for 52 consecutive cases of invasive ductal carcinoma, who underwent modified radical mastectomy as part of their treatment. The data was analysed by the primary lesion's T-Category (TNM system), age and menopausal status, location of the tumor in the breast and histological grade of the tumor, from July 1996 through June 1998.

Results: Thirty six (69.23%) of 52 axillary nodule dissections contained metastases. The probability of lymph node involvement was significantly higher in larger tumors and the average tumor size was slightly but significantly larger in the node positive cases. The percentage of patients with favorable histological grade (I) was generally lower for node-positive cases than with higher grade (III). The probability of axillary node metastases increased in younger age and in pre-menopausal women. Upper outer quadrant and centrally located tumors had significantly more frequency of metastases than other quadrants. Tumors located in the upper-half metastasized more than lower half and lateral–half more than medial–half to the axillary nodes.

Conclusions: Axillary nodal positivity was significantly higher for larger tumors, for tumors located in the centre and upper-outer quadrant, for tumors of high grade of differentiation in younger age and pre-menopausal patients with breast cancer.

INTRODUCTION

Cancer of the breast is a major disease of women worldwide[2]. It is the commonest malignancy amongst females in Pakistan[1]. This disease deprives women of an average 10 years of life expectancy[2]. Axillary lymph node status continues to be the single important prognostic variable[3,4].

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Breast cancer is almost exclusively a disease of women. Although men are not exempt, women account for more than 99 percent of all cases[4,5]. The age specific incidence curve for the breast cancer rises with age but shows a notable inflexion in 45-55 years, the age of menopause. Then it continues to increase until the age reaches 75[6]. Breast cancer is similar to other human cancers in that all arise from a multifactorial process. A large number of external factors are implied in the etiology of cancers. Recent attention has focused on genetic predisposition to breast cancer. A family history of breast cancer increases the likelihood of breast cancer development. Breast cancer risk is 2-3 times higher for women with an affected first degree

relative[7]. The risk of breast cancer is associated directly with endogenous and exogenous exposure of women to estrogens. Bilateral oophorectomy before 35 years of age reduces the risk of cancer to one third. Early age at menarche (11 years) and late age at natural menopause (>55years) are associated with increased risk[7]. Nulliparity increases the risk and high parity decreases risk at least after age of 50[8,9,10]. The risk of breast cancer is relatively high among women currently using either estrogen alone or both estrogen and progesterone. The increased risk of breast cancer associated with more than 5 years of post menopausal hormone therapy is greater among older women (more than 60 years)[11,12]. The estrogen supplement appears to increase the risk of breast cancer by about 40 percent among women who are actively taking them with little increase with who are no longer taking them[13]. Combining progesterone with estrogen replacement does not appear to reduce the incidence of breast cancer and may add to it[14]. $BRCA_1$ is a susceptibility gene for breast cancer and is implicated in about 4-5 percent of cases in all age groups but in about 25 percent of those diagnosed before age 40. Women who carry $BRCA_1$ gene, have a 85 percent chance of developing breast cancer by the age of 80[15].

Various methods have been tried for early diagnosis of disease including self breast examination, ultrasound of breast and mammography. Because of awareness of the general public, different modalities of the investigations made easy for early detection of disease. This has made easy and early management of the disease with highly effective chemo and radiation therapy help to achieve quality of life and substitute radical surgery.

METHODS

This is a prospective study of consecutive series of 52 patients with invasive breast cancer. This study has been conducted at Department of General surgery and Department of Pathology, Shaikh Zayed Hospital, a Teaching and Tertiary Care Hospital, in Lahore, Pakistan.

Criteria for enrolment

All the female patients presenting consecutively to the surgical OPD from July 1996 through June 1998 with either a mass or mammographic abnormalities and diagnosed as operable primary breast cancer and proved by FNAC, incisional, tru-cut or excisional biopsy.

Exclusion criteria

Patients with in-situ carcinoma, infiltrating lobular carcinoma, tumors of pure histologic types.

Tumor examination

All the primary tumors and the axillary specimens were examined by a consultant pathologist at the Department of Pathology, Shaikh Zayed Hospital, Lahore.

Statistical Analysis

The data for all patients as well as for node–positive and node-negative was analysed. The inter-relationship between the lymph node status and other variables like age, menopausal status, grade and size of the tumors was determined by 2 X 2 contingency table analysis. The statistical significance of different proportions was analysed by chi-squared test, Fisher's exact test and by student 't' test. The P-values so derived from one-tailed tests if found greater than 0.05 was reported as non-significant.

RESULTS

Among 52 female patients, 50 patients were Muslim housewives, only two were non-Muslims (Christians) and two were working women (school teachers). The majority of patients were postmenopausal (27 cases, 51.93%), the rest (25 cases, 48.07%) were pre-menopausal.

Out of 52 patients, 5 were unmarried and 47 married. Among married women 7 (14.58%) were nulliparous and others had an average of 5.02 children with a range from one to ten. The range of age at first pregnancy was from 15 years to 38 years, with a mean of 21.27 years, and a median of 18 years. All the women had breast fed their babies.

Two patients had one of their first degree relatives, three patients had one of their first degree relatives and three patients had second degree relatives with history of breast cancer.

All the 52 cases had undergone modified radical mastectomy.

Size of tumor

The largest tumor identified histopathologically was 17 cm and the smallest was 1.5 cm diameter. The mean tumor size among 52 cases was 5.11 cm.

Table 1: The distribution of axillary lymph node metastases

Axillary lymph nodes	Metastases		
	Present	Absent	Total
	No. %	No. %	No.%
Palpable	26 (78.79%)	7 (21.21%)	33 (100%)
Non-Palpable	10 (52.63%)	9 (47.37%)	19 (100%)
Total	36 (69.23%)	16 (30.77%)	51 (100%)

In these 52 cases with modified radical mastectomy and level I and II axillary clearance, the average number of lymph node retrieved was 11.60 with a minimum of 5 to a maximum of 21. Although axillary lymph nodes were palpable clinically in 33 (63.46%), metastases was found in 26 (78.79%) cases in the palpable group. In clinically non-palpable group of patients (19 cases) also axillary nodes were harvested surgically and found positive for malignancy on histopathological examination in 10 (52.63%) cases. So, 36 cases (69.23%) among 52 had axillary nodal metastases.

Table 2: The distribution of nodal metastases in different degrees of differentiation

Grade	Node Positive	Node negative	Total	Node positive %	P value
Well differentiated	4	4	8	50%	0.294
Moderately differentiated	15	12	24	57.24%	
Poorly differentiated	17				
Total	36	16	52		

Altogether, we had 8 cases of well differentiated, 27 cases of moderately differentiated and 17 cases of poorly differentiated tumors. Among 8 cases of well differentiated tumors, 4 cases (50%) had axillary nodal metastases. The observation was almost similar in moderately differentiated tumors as 15 out of 27 cases (55.56%) had axillary lymph nodal involvement. But all the 17 cases (100%) of poorly differentiated tumors had axillary lymph node metastases at the time of presentation. The difference in the rate of metastases at the time of presentation was not significant in well and moderately differentiated tumors (P = 0.299) but were highly significant in poorly differentiated tumors (P <0.001) and also in well and poorly differentiated tumors (p = 0.005).

Table 3: The distribution of nodal metastases in different sizes of primary tumors

Tumor Size	No of patients	Node +	%	P value
<2 cm	8	4	50	0.258
>2-5cm	29	18	62.1	0.115
>5-10 cm	9	8	88.9	0.6
>10 cm	6	6	100.00	
Total	52	36		

Table 4: The distribution of axillary nodal metastases and location of tumors

Quadrant	No. of cases	Node positive cases	%
Upper-Outer	21	15	71.4
Upper-Inner	9	5	55.6
Lower-Outer	5	3	60
Lower-Inner	3	2	66.7
Central	2	2	100
Central+UIQ/LOQ+UIQ	4	4	100
UOQ+UIQ	5	4	80
UOQ+LOQ	2	1	50
UIQ+LIQ	1	-	0
Total	52	36	69.2

All the tumors in >10 cms category and almost all cases (except 1 tumor involving the whole quadrants) in >5-10 cms category had axillary nodal involvement. So, comparison of similar size tumors located at different sites in the breast is possible only in less than 5 cms category of tumors. In <2 cms category, 100% of the tumors from central area and also lower outer quadrant and 50% of the tumors from upper-outer quadrant had axillary nodal metastases. In >25cms category, 100% of the tumor and in central area of the breast, 67% of the tumors in the upper-outer quadrant, 50% in the upper-inner and lower-outer quadrants and 100% of (2 cases) tumors involving both upper quadrants had axillary nodal metastases. 23% of the tumor had involvement of more than one quadrant of the breast and 75% of them were found to have axillary nodal metastases.

DISCUSSION

Breast cancer is the number one killer malignant disease among women all over the world[2]. The main risk of lymphatic metastases from breast carcinoma is through the axilla. So, the axillary nodes being the first to be involved in the regional lymphatic filter. Successful treatment of breast cancer begins with local regional control of the breast[16]. The speculated determinants of tumor spread from the breast, such as histological type, grade and size of the primary tumor should also be considered in the management of the disease[17]. Carcinoma of the breast is almost exclusively a disease of women. Men account for less than 1% of all cases of breast cancer[5]. We did not have any case of breast cancer in males in this study. The left breast was more frequently involved (1.21:1) than the right. The reason behind needs more research but the increased frequency in the left side is also observed by other researchers[18,19,20]. Bilateral cancer was found in 1.96% of cases of ductal carcinoma in this study which in other studies ranged from 0.1 to 2%[21]. The mean age of breast cancer patients in this study (45.66 years) is almost 10 years less than in the USA (55 years)[22].

In the present study, 27 (51.92%) patients had moderately differentiated tumors whereas, in other series, the majority were a poorly differentiated type[22]. The well differentiated tumors were the least common type in all the series.

In this study, 50% of well differentiated tumors were axillary node positive, whereas 56% of moderately differentiated and 100% poorly differentiated tumors were axillary node positive. Thus, as the tumor differentiation becomes less, the rate of axillary node positivity is increased.

In the <5 cm size tumors, the distribution of axillary node metastases gradually increase as the tumor becomes less differentiated.

CONCLUSIONS

The patients with smaller size tumors had less number of metastases in the axilla in comparison to the larger ones. The tumors in the upper-medial and central metastases are more as compared to lower and lateral. The poorly differentiated tumors metastases 100% to the axillary lymph node.

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Maternal Blood Loss in Cesarean Section under General and Spinal Anaesthesia

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Key words:
Anaesthesia (General and Spinal),
Blood Loss,
Cesarean Section,
Postpartum hemorrhage.

ABSTRACT

Objectives: To study the effect of anaesthesia (either general or spinal) on maternal blood loss during cesarean section.

Methods: A hospital based prospective, comparative study was conducted at Paropakar maternal and womens hospital in the year 2004 (from 20th May to 23rd September), in 200 consecutive cases of cesarean section. Women with singleton pregnancy with gestation age of 28 weeks and onwards with or without prior cesarean section were enrolled in the study. Blood loss during cesarean section was estimated and correlated with pre-operative Hb and PCV to post-operative fall in Hb and PCV value in general and spinal anaesthesia.

Results: During the study period, the rate of cesarean sections was around twelve percent (11.98%). Estimation of blood loss of more than 500 ml in general anaesthesia (G/A) group was 18% and only 6 % in spinal anaesthesia (S/A) group with statistical significance difference (P <0.009). Mean post-operative hemoglobin was 10.52 gm/dl in G/A group and 11.13 gm/dl in S/A group, with statistically significant difference (P<0.001). In this study, induction and augmentation of labor with oxytocin, repeat cesarean section, non progress of labor >=6 cm, and weight of baby did not increase the risk for excessive blood loss during cesarean section.

Conclusions: From this study, women who received general anaesthesia for cesarean section showed 3.43 times higher risk of having blood loss more than 500 ml than that of spinal anaesthesia with Odds ratio 3.43 (95% CI, 1.25-10.22).

INTRODUCTION

Cesarean section (C/S) is defined as delivery of the fetus through the incision in the abdominal wall (laparotomy) and the uterine wall (hysterotomy)[1]. In modern obstetrics, incidence of this operation is increasing all over the world. Women are now opting for higher education, professional career, late marriage and smaller family size. Hence, every pregnancy today is more precious than ever before. So, women are visiting the hospitals for antenatal check-ups and safer delivery. The ideal mode of delivery should combine safety to both mother and fetus. In modern medicine, cesarean delivery is considered a relatively safe operative procedure because of availability of safer anaesthesia, blood transfusion facilities and broad spectrum antibiotics. The cesarean delivery rate has increased throughout the world but it is still substantially lower than that of the USA. In 1985, the cesarean delivery in the USA was 20-27%, in comparison to 19% in Canada, 13% in Denmark, 10% in UK and 7% in Japan[2].

Spinal anaesthesia (S/A) seems to be safer compared to general anaesthesia (G/A) since it does not involve uterine relaxation as in general anaesthesia[3]. In addition, spinal anaesthesia allows the mother to be awake at the time of birth of her child thereby minimizing the risks of maternal aspiration pneumonitis and problems of difficult intubation. Compared to general anaesthesia, regional anaesthesia is associated with reduced maternal mortality, decreased blood loss, and the ability to use fewer drugs along with providing excellent post operative

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analgesia. Anaesthetic practice for cesarean section has changed during the last decade; the trend worldwide is in favor of regional anaesthesia[4].

Although general anaesthesia has some advantages like faster induction, less hypotension, better cardiovascular stability, and better control of airways and ventilation, regional anaesthesia is the first choice for cesarean section because of its high effectiveness, low incidence of side effects and high degree of patient's satisfaction[5].

Post partum hemorrhage is one of the leading cause of maternal mortality and morbidity and morbidity worldwide, and the leading cause of direct obstetric death. The condition is further accentuated in developing countries like Nepal, where many women are already in poor health status during pregnancy due to poor nutritional status and anemia. Blood loss is expected to be higher in operative delivery as compared to vaginal delivery and more so in general anaesthesia than in spinal anaesthesia[6].

METHODS

Study design and setting

This was a hospital based prospective, comparative study, conducted at Paropakar Shree PanchIndraRajyalaxmi Devi PrasutiGriha Hospital, located at Thapathali, Kathmandu. Study period was from 20th May to 23rd September, 2004. In spinal anaesthesia, first 100 cases meeting the inclusion criteria undergoing for cesarean section were enrolled in the study. Similarly among in general anaesthesia group, initial 100 cases meeting the inclusion criteria were enrolled in the study.

Inclusion criteria

Singleton pregnancy of 28 weeks and onward with or without prior cesarian section.

Exclusion criteria

1. Multiple pregnancies
2. Antepartum hemorrhage (Placenta previa and abruption placenta)
3. Ruptured uterus
4. Known case of bleeding disorders

Data collection

After taking the verbal consent from the patient, her socio-demographic data were collected. Details of the clinical history, labor pain, spontaneous or artificial rupture of membrane, use of oxytocin and antibiotics were also noted in post-operative ward afterwards. Indication for cesarean section were recorded. Use of oxytocin for induction of labor was also noted.

Anaesthesia

The decision of the type of anaesthesia and its dose was left to the concerned anaesthetist to decide and any complications there of were recorded.

General anaesthesia

Nitrous oxide and oxygen (50%) and halothane (0.5-1.0%) were given.

Spinal anaesthesia

Spinal anaesthesia with 2ml of 0.5% heavy bupivacaine.

Surgery

Incision on the skin was either pfannenstiel or lower paramedian. Incision on uterus was transverse in lower segment of uterus.

Data management

All data was tabulated and presented in different frequency tables. The chi-square test and Z-test were applied at appropriate places with significance taken as 95% confidence interval with a P value less than 0.05.

RESULTS

The most common indication of LSCS was fetal distress (thick meconeum stained liquor in early stage of labor) in both the types of anaesthesia, accounting for 34.6% in general anaesthesia and 53.16% in spinal anaesthesia.

Table 1: Pre-operative Hb and PCV in relation to general and spinal anaesthesia

Pre operative	Type of anaesthesia	Total Cases	Mean	P (Z-test)
Hb%	G/A	100	12.2160	0.123
	S/A	100	12.4640	
PCV	G/A	100	37	0.840
	S/A	100	37.8	

Pre operative hematological values were comparable in two groups of women undergoing C/S under general anaesthesia. P=0.12 and P= 0.84 respectively.

Table 2: Post-operative Hb and PCV in relation to different types of anaesthesia

Post operative	Type of anaesthesia	Total cases	Mean	P Value (Z test)
Hb%	G/A	100	10.52	0.001
	S/A	100	11.138	
PCV	G/A	100	32.150	0.0004
	S/A	100	34.160	

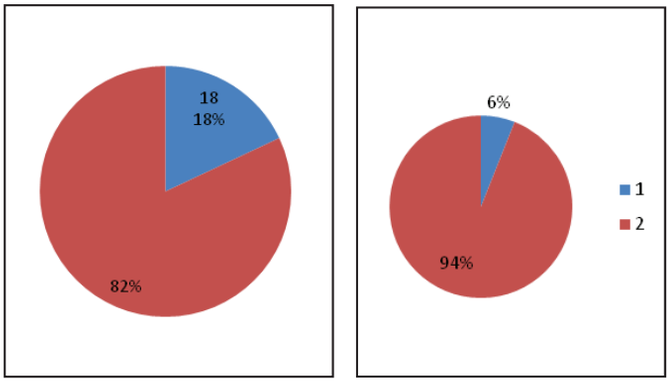
Post operative hematological values were decreased in women under spinal and general anaesthesia. Decrease in hematological values (Hb and PCV) were significantly higher in general anaesthesia group than decrease in hematological values (Hb and PCV) in spinal anaesthesia group, P value 0.001 and 0.004 respectively.

Table 3: Relation of estimated blood loss with the type of anaesthesia

Blood Loss	Type of anaesthesia		P-Value X^2- test
	General anaesthesia (n=100)	Spinal anaesthesia (n=100)	
>500	18 (18%)	6 (6%)	0.009
<500	82 (82%)	94 (94%)	
Total	100	100	

Odds ratio 3.43 (95% CI, 1.25-10.22)

Fig 1: General anaesthesia and spinal anaesthesia



There were 18% of women in general anaesthesia group in whom blood loss during cesarean section was more than 500 ml as compared to only 6% in spinal anaesthesia group. This shows that blood loss of >500 ml during cesarean section was significantly higher in general than in spinal anaesthesia group (X^2P=0.009). Women who received general anaesthesia for spinal anaesthesia showed 3.43 times higher risk of having blood loss more than 500 ml than that of spinal anaesthesia. Odds ratio 3.43 (95% CI, 1.25-10.22).

Table 4: Relation of average amount of blood loss with the type of anaesthesia

Type of anaesthesia	No. of Women	Average blood loss	P-Value (Z- test)
General anaesthesia	100	402.20ml	0.00001
Spinal anaesthesia	100	271.25 ml	

Table 5: Relation of post operative Hb with blood loss in general and spinal anaesthesia category

Post operative Hb%	Blood loss <500ml			Blood loss >/= 500ml		
	G/A	S/A	P	G/A	S/A	P
11 and more (Normal)	41	62	0.009	6	2	0.03
10-10.9 (Mild anemia)	19	23		3	4	
7-10 (Moderate anemia)	22	9		9		
Total	82	94		18	6	

Blood loss of more than 500 ml was more in general anaesthesia group than spinal anaesthesia group, the difference was statistically significant (P=0.009). Blood loss of more than 500 ml was also significantly more in general anaesthesia group as compared to spinal anaesthesia group. It also reached to the level of statistical significance (P<0.03).

DISCUSSION

Cesarean delivery is a method of choice for those women who can not give birth per vagina either due to risk to the baby and/or the mother. Effects of type of anaesthesia in cesarean section have been reviewed in many studies. This study was carried out to find out the feasibility of type of anaesthesia in cesarean section in our context where resources are limited. It has been found in several studies that the incidence of cesarean section has increased over recent years. The global increase in cesarean section rate, increasing use of electronic fetal heart monitoring and fear of litigation[7]. The cesarean section rate in study was 11.98% which was due to the fact that the cesarean section rate in our hospital is also increasing in near past as global trend is increasing.

It is noted that the cesarean section rate in developed countries are higher than in developing countries. Cesarean section rate in this was even lower than other developing countries like India. In a prospective study done by Kumar A *et al*[8] (September 1993 – May 1994) showed the incidence of cesarean section rate as 14.8 % out of 1418 deliveries, including 15.8% of elective and 82.2% of emergency cesarean section. Another study done in India by Jayaram VK found that cesarean section rate of 16% out of 16782 deliveries. 62.75% were primary cesarean section, because of associated risk factors and late referrals. Among the primary cesarean sections, 91.4% were emergencies and 8.6% were elective[9].

The mean age in this study was 25.24 years among general anaesthesia group and 24.86 years among spinal anaesthesia group which is similar to those reported by Sirjusingh A *et al* as 25 years. The mean age in this study is slightly less than reported by Duthie SJ *et al* as 29 years[10] and Ahmad N and Mehboob R as 20-30 years[11]. Most of the women who underwent cesarean section rate in this study were in the age group of 20 – 25 years.

In this study, the most common indication of cesarean delivery was fetal distress in both the groups. In primary cesarean section, it accounted for 53.16% among spinal anaesthesia group and 34.6% among general anaesthesia group.

In this study, when cesarean section rate was performed under general anaesthesia, it resulted in significant blood loss, lower post operative hemoglobin and hematocrit (PCV) as compared to spinal anaesthesia. 18% of women had blood loss among general anaesthesia group where as it was only 6% among spinal anaesthesia group. The difference in blood loss among anaesthesia group and spinal anaesthesia was statistically significant (P= 0.009) (Chi-square test).

The average amount of blood loss was also higher in general anaesthesia (402.20 ml) than in spinal anaesthesia (271.25 ml). This value also had statistical significance (P < 0.0001) (Z-test). Hemorrhage is the commonest complication in developed as well as in developing countries. One patient (1%) in spinal anaesthesia group and 4 patients (4%) in general anaesthesia group receive blood transfusion but not more than

2 units. Similar finding was noted by Sirjusingh A *et al*. In their study, 606 women (22.3%) among 2725 cesarean section had blood loss of more than 500ml, and 93 (3.5%) women received blood transfusion. In another study conducted by Chama CM *et al* found that hemorrhage was the most frequently occurring complication. They had also recorded hemorrhage in 89 cases (43.2%) out of 205 cesarean section (emergency + elective) which seems to be higher when compared to this study[12].

The study conducted to measure intra-operative blood loss under general anaesthesia by Duthie SJ *et al* found that the mean estimated blood loss was 425 ml which was slightly higher than the present study (402.20 ml) in general anaesthesia group[11].

In this study, preoperative mean Hb under general anaesthesia group was 12.21 gm/dl and mean Hb for spinal anaesthesia was 12.46 gm/dl. Preoperative Hb in two types of anaesthesia was comparable ($P < 0.123$). Similarly, preoperative hematocrit (PCV) was also comparable in the two types of anaesthesia ($P=0.840$) (Z-test).

Postoperative mean Hb was 10.50 gm/dl in general anaesthesia group of patients and 11.13 gm/dl in spinal anaesthesia group. This showed definitive statistical significance in favor of spinal anaesthesia ($p=0.001$)(Z-test).

Similar findings were observed by Adeghe AJH *et al*. They had noted that fall in hemoglobin after cesarean section under general anaesthesia was greater than in spinal anaesthesia, but their result did not reach to statistical significance. This may be due to the fact that the study was conducted for a very short period of time and with small sample size (Total no. of cases= 53, G/A = 32, S/A = 21)[13].

In this study, mean pre-operative PCV was 36.704 vol% among general anaesthesia group and 37.445 vol% among spinal anaesthesia groups. The postoperative PCV among general anaesthesia group and spinal anaesthesia group of patients were 32.150 vol% and 34.160 vol% respectively. This difference was highly significant ($P <0.0004$) Z-test. Similarly, Maberry and colleagues (1992) observed a postoperative decreased in hematocrit level of 5 vol% in 25% of women in general anaesthesia group compared to 7% in spinal anaesthesia group[14]. A study conducted by Gilstrap LC 3rd *et al* and Lertakyamanee *et al* found similar finding showing post operative hematocrit less than 30% in most of the cases which was higher than in this study. They also showed a difference of 8 vol% in hematocrit level when compared to pre to post operative states. This lower side value is even lower than what we observed in this study[15,16].

Post operative hemoglobin in general anaesthesia group of patients was definitely on the lower side in this study which showed that relationship between blood loss and post operative hemoglobin has low degree of negative correlation, but it did not reach to statistical significance. Similarly post operative Hb and PCV, both were on lower side among spinal anaesthesia group also. The difference was statistically significant, with P value 0.052 and 0.02 respectively.

Factors likely to be responsible for excessive blood loss as started by different literature were injury during surgery or extension of incision, non progress of labor at or more than 6 cm, oxytocin induction or augumentation of labor, repeat cesarean section and also weight of baby[8,17,18]. But in the present study, these factors did not have significant role for excessive blood loss in both groups of patients.

In this study, there were 3 cases of extension of incision among spinal anaesthesia group and one among general anaesthesia group but none of them had PPH.

Similarly, cesarean section performed in this study for non progress of labor in 6 cm was 5 (5%) in general anaesthesia and 4 (4%) in spinal anaesthesia, but none of them had blood loss of more than 500 ml. Another parameter i.e., oxytocin infusion for induction of labor was 9 (9%) in spinal anaesthesia and 6 (6%) in general anaesthesia either of the group did not develop postpartum hemorrhage.

CONCLUSIONS

Since general anaesthesia resulted in more blood loss, low post-operative hemoglobin and hematocrit, it is recommended that spinal anaesthesia is the choice of anaesthesia in hemodynamically stable patients. But still there is role of general anesthesia in hemodynamically unstable patients.

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A Comparative Study to Assess the Maintenance of Intravascular Volume Without Blood Transfusion

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Key words:
Hypervolemic hemodilution, Major elective surgery, Colloid.

ABSTRACT

Objectives: The study was done to find out the role of the colloid solutions as a substitute of blood to prevent the hazards of blood transfusion during surgery and to compare the clinical (BP, Pulse) and laboratory values (Hb, hematocrit, platelet count, prothrombin time) pre-and post-operatively with or without acute hypervolemic hemodilution.

Methods: This was a prospective and experimental study of two years duration, from January 1997 to December 1998, conducted at Department of Anesthesiology and ICU in Services Hospital, Lahore, Pakistan. A total of 100 patients of either sex, with the age ranging from 16 to 45 years and body weight of 40-80 Kgs undergoing major orthopedic surgery were included into the study. The patients were divided into two groups of 50 patients each. Patients in group A underwent hypervolemic hemodilution in the immediate pre-operative period whereas patients in group B did not. The clinical and laboratory values were taken preoperatively and repeated at the end of the surgery, and on 1st and 7th postoperative day.

Results: Though there were some changes in clinical and laboratory values pre- and post-operatively between the two groups, the changes were however not statistically significant.

Conclusions: Study showed that, there was neither the need of any blood transfusion nor any complications in patients who had undergone hypervolemic hemodilution. Colloid solution can be used safely as substitute of blood to prevent hazards of blood transfusion during operation.

INTRODUCTION

The risk of alloimmunisation and transfusion of viral infection such as Human Immunodeficiency Virus (HIV), hepatitis B virus or hepatitis C virus from homologous blood is well known[1]. In addition it is suggested that transfusion may promote tumor growth[2]. Leaving aside minor transfusion reaction, one of the most lethal effects of transfusion reactions is renal shut down, which can lead to death[3].

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In acute blood loss, red cells and plasma are lost together, such that in the first few hours, hemoglobin (Hb) and hematocrit measurements change little but in continued acute bleeding the hemoglobin and hematocrit move in parallel[4]. Since most planned surgical procedures are not associated with a blood loss sufficient to require transfusion, the collection of autologous blood is not appropriate for all patients. Homologous blood transfusion poses substantial risks to the patients[5].

Latta, in 1832 was the first to demonstrate the use of intravenous saline solution to treat hypovolemic shock. The maintenance of an adequate circulatory volume and central venous pressure with an intravenous infusion of warm saline resulted in reduced mortality rate in experimental hemorrhagic shock[6].

A variety of techniques can aid the anesthetist in reducing perioperative requirements for blood products. These include careful preoperative assessment of the patient and employing techniques during surgery, which reduce the blood pressure and help preserve the normal hemostatic mechanism. If the level to which hematocrit will be permitted to decrease is decided, then physiological crystalloid or colloid solutions may be used to maintain circulatory volume. There is no evidence that any fluid is better than any other in terms of the incidence of perioperative morbidity[7].

Hemodilution, itself is not free from problems. There are risks involved when patients are older or those with significant cardiovascular, cerebrovascular and pulmonary disease are hemodiluted below Hb content of 10gm/dl[8].

Normal circulatory blood volume with adequate content of Hb is the aim of intraoperative fluid therapy[9]. Perioperative fluid therapy includes replacement of routine losses (maintenance requirement), preexisting fluid deficits, and surgical wound losses including blood loss. Several colloid solutions are generally available. All are derived from either plasma proteins or synthetic glucose polymers and are supplied in isotonic electrolyte solutions. Colloid solutions are administered most frequently for intravascular volume expansion during the perioperative period. Infusion exceeding 20 ml/Kg can interfere with blood typing, may prolong bleeding time and have been associated with renal failure. Coagulation studies and bleeding time are generally not significantly affected following infusion up to 1 - 2 litre[10].

Intra-operative fluid therapy should include basal or maintenance basic fluid requirements and replacing residual preoperative deficit as well as intra-operative losses (blood, fluid redistribution and evaporation). Selection of the type of intravenous solution depends upon the surgical procedure and the expected blood loss. Ideally, blood loss should be replaced with crystalloid and colloid solutions to maintain intravascular volume until the danger of anemia out-weighs the risks of transfusion. Patients with a normal hematocrit should generally be transfused only after losses greater than 10 - 20% of their blood volume[10].

Pre-operative acute hemodilution can be achieved in two ways. First, by withdrawing the blood along with the simultaneous infusion of plasma substitutes (normovolemic hemodilution) and second by rapid infusion of fluid without withdrawing of blood (Hypervolemic hemodilution)[2].

A recent controlled study[11] concluded that moderate hemodilution is a cost-effective alternative to autologous blood pre-deposit in patient undergoing prostatectomy. The procurement of autologous blood is a standard practice for elective surgery. However, the cost and potential complications as well as the benefits of autologous blood procurement strategies need to be re-considered[12].

Hussain[13] in his study stated that clinical applications of hemodilution and intra-operative blood salvage have been shown to be beneficial in cardiac, vascular, orthopedics and trauma surgery. Intra-operative blood pressure should be analyzed in relation to the patient's preoperative blood pressure. Prolonged changes of more than 20 mm Hg or 20% in relation to preoperative levels were significantly related to complications[14].

METHODS

This was a prospective and experimental study of two years duration, from January 1997 to December 1998, conducted at the Department of Anesthesiology and ICU in Services Hospital, Lahore, Pakistan. The aims of the study were to find out the role of the colloid solutions as a substitute of blood to prevent the hazards of blood transfusion during surgery and to compare the clinical (BP, pulse) and laboratory values (Hb, hematocrit, platelet count, prothrombin time) pre- and post-operatively with or without acute hypervolemic hemodilution.

After institutional approval, a total of 100 patients of either sex (ASA I and II), of the age range 16-45 years and bodyweight 40-80 Kgs undergoing major orthopedic surgery like hip surgery and open reduction and internal fixation of long bones in elective major surgery were included into the study. The patients were divided into two groups of 50 patients each. Patients in group A underwent hypervolemic hemodilution in the immediate pre-operative period whereas patients in group B did not. Written consent was taken from each patient before study.

Exclusion criteria: Patients below 16 years and above 45 years of age, patients with anemia (Hb <9 gm%), patients with clinically evident limitations of cardiac and pulmonary functions, patients with untreated hypertension, patients with coagulation disorders, patients who needed blood transfusion (in group A) and patients with renal and liver disease.

Anaesthesia: Induction of anaesthesia was done as per the protocol.

Technique of hemodilution: Immediately after induction of anaesthesia, hemodilution was performed in group A patients (acute hypervolemic hemodilution). 15 ml/Kg of the colloid solution, haemaceel (Hoechst, Hoechst Marion Roussel) was infused at the rate of 100 ml/minute. Per operatively, Ringer's lactate was infused in a volume equal to the urine output plus 8 ml/Kg/hour (to compensate for fluid loss from the wound) for maintenance. Blood loss was replaced by an equal volume of colloid solution. Immediately before surgery, the forced infusion was stopped.

In group B, all above-mentioned methods were performed except the administration of colloid solution.

Evaluation: Measurements were taken preoperatively and repeated at the end of the surgery, and on 1st and 7th postoperative day.

Data collected was analyzed by the application of different suitable statistical tools like one way of analysis of variance (ANOVA), students Z-test etc.

RESULTS

During the study period, total of 100 patients were allocated into two groups. Patients in group A underwent hypervolemic hemodilution, whereas patients in group B did not.

Table 1: showing age, weight, duration of surgery

	Mean	Minimum	Maximum	p-value
Age (years)				
Group A	29.64 ±0.99	16	43	0.2683
Group B	29.20 ±1.20	17	44	
Weight (kg)				
Group A	67.38 ± 0.85	53	82	0.6667
Group B	66.44 ± 1.09	56	81	
Duration of surgery (minutes)				
Group A	104 ±8.06	89	125	0.1342
Group B	112 ±7.19	105	135	

Patients included in both the groups were similar in respect to age (p=0.26863) and weight (p=0.6667). Similarly, there was no statistically significant difference in regards to the duration of the surgical procedures (p=0.1342).

Blood was transfused in group B patients only. In total, 96 units of blood was transfused in 43 patients during intra-operative and trans-operative period. Blood was transfused at an average of 2.23 units per patients.

Table 2: Systolic blood pressure (mm/Hg)

	Group A	Group B	p-value
Preoperative	110 ±5.6	113.33 ±12.02	0.0265
Postoperative	120 ±10.57	113.33 ±80.82	0.1346
Day 1	110 ±29.94	123.33 ±8.82	0.0953
Day 7	115 ±12.64	120 ±9.37	0.1321

In both the groups, systolic blood pressure was stable during post-operative period. Statistically, overall there was no significant difference in the systolic blood pressure between the hemodiluted patients in comparison to non-hemodiluted patients.

Table 3: Diastolic blood pressure (mm/Hg)

	Group A	Group B	p-value
Preoperative	70 ±5	83.33 ±3.33	0.9685
Postoperative	80 ±12	73.33 ±8.82	2.5600
Day 1	70 ±10	80 ±5.57	0.9962
Day 7	80 ±10	80 ±5.21	0.9696

In the study, diastolic blood pressure increased in the hypervolemic hemodilution group in postoperative period and decreased in nonhemodilution group. But there was no significant difference in diastolic blood pressure between two groups.

Table 4: Pulse rate (beat/minute)

	Group A	Group B	p-value
Preoperative	87 ±0.82	89.6 ±3.54	0.6352
Postoperative	85 ±0.82	88.4 ±3.06	0.5325
Day 1	87 ±0.82	87.6 ±2.32	0.8653
Day 7	86 ±0.74	88.6 ±2.96	0.8845

When the pulse rates were compared between the groups there was no statistically significant difference.

Table 5: Hemoblogin

	Group A	Group B	p-value
Preoperative	11.2 ±0.98	12.06 ±1.01	0.9635
Postoperative	9.15 ±0.49	11.17 ±1.61	0.6868
Day 1	9.3 ±0.30	11.5 ±0.92	0.2365
Day 7	10.6 ±0.48	10.4 ±0.32	0.6856

The hemoglobin level in group A was decreased in postoperative and day 1 but was increased at 7th postoperative day, where as in group B hemoglobin level was decreasing till day 7. But statistical analysis showed no difference in these observations.

Table 6: Hematocrit

	Group A	Group B	p-value
Preoperative	31.55 ±1.55	36.13 ±1.74	1.99
Postoperative	25.95 ±1.25	33.23 ±2.89	1.93
Day 1	27.35 ±0.25	34.23 ±2.02	1.76
Day 7	30.46 ±1.76	35.33 ±1.92	1.63

Comparison of hematocrit values between group A and group B in our study revealed that there was no significant difference between two groups. The overall hematocrit values were decreased in postoperative period that gradually increased in later days in both the groups.

Differences in hematocrit values during different study time in each individual group were found to be significant (p- value of 0.0000).

Table 7: Platelet count (in thousands)

	Group A	Group B	p-value
Preoperative	220 ±29	154 ±18.21	1.69
Postoperative	204 ±6	140 ±22.18	1.29
Day 1	225 ±18	158 ±12.34	1.43
Day 7	249 ±21	162 ±14.38	1.44

Platelet count was increased in both the group at 7th postoperative day in compared to preoperative period. Statistically the data was not significant between the two groups. However, differences in platelet count during different study time in each individual group were found to be significant (p-value of

0.0000).

Table 8: Prothrombin time

	Group A	Group B	p-value
Preoperative	12 ±1	11.67 ±0.67	0.9632
Postoperative	11.56 ±1.23	11.26 ±0.63	0.8327
Day 1	11.23 ±1.56	10.64 ±0.32	0.9632
Day 7	11.96 ±0.86	11.39 ±0.57	0.9632

There was no significant difference in prothrombin time between the two groups. However, differences in prothrombin time during different study time in each individual group were found to be significant (p- value of 0.0000).

DISCUSSION

Avoiding homologous blood transfusion is a high priority in the perioperative case of surgical patients since many potentially serious complications are associated with transfusion of homologous blood and blood products. These serious side effects (transmission of infectious diseases and immunosuppressant) need to be considered prior to transfusion of any homologous blood or blood products.

The risk associated with transfusion of homologous blood has provided the impetus for the development of techniques to minimize transfusions. Preoperative autologous blood donation, intra and postoperative salvage of the patient's blood and its retransfusion and acceptance of lower hemoglobin levels have all been used to avoid homologous blood donation. A more time and cost effective blood conservation strategy is preoperative acute normovolemic hemodilution in which the patient's blood is withdrawn prior to operation simultaneously with infusion of crystalloid or colloid solutions. However this technique requires a certain amount of extra time and equipment.

Hemodilution with colloid solution is possible alternative to avoid homologous blood transfusions. Experimental studies on normovolemic and hypervolemic hemodilution decreased the incidence of blood transfusion. Acute normovolemic hemodilution has been used for many years as a means of reducing requirement for homologous blood transfusion during surgery[15,16,17]. Acute normovolemic hemodilution remains underutilized due to extra amount of time and money[18,19].

Hypervolemic hemodilution is easier, less time consuming and less expensive than acute normovolemic hemodilution. Hypervolemic hemodilution can cause greater degree of hemodynamic stability during anaesthesia by augmenting preload and obviating the usual decrease in arterial blood pressure as in this study[20].

Using hypervolemic hemodilution, dilution of blood is solely achieved by preoperative infusion of the plasma expander without removal of autologous blood. Hypervolemic hemodilution is not accompanied by an increased risk of excessive intravascular volume and can be applied for patients by following the same rules used for acute normovolemic hemodilution. A study on hypervolemic hemodilution and acute normovolemic hemodilution by Mielke *et al*[20] concluded that hypervolemic hemodilution seems to be a good alternative to acute normovolemic hemodilution, because of less time and effort.

Hypervolemic hemodilution allowed major surgery without transfusion and was tolerated safely by all patients[2]. Hypervolemic hemodilution improves cerebral circulation[21] and may be useful treatment for hemorrhagic disorders.

In our study, there were no significant differences in age (p=0.2683), weight (p=0.6667) and duration of surgery (p=0.1342. Group A received 15 ml/Kg of haemaceel (colloid) for preoperative hypervolemic hemodilution. Amount of colloid used in other study is similar with our study as 14.5 ml/Kg[15], 15 ml/Kg[20] 1000 ml of colloid[22].

In our study, record of blood pressure and pulse rate in predetermined study time was used to evaluate the clinical values of the patients in hemodiluted and non-hemodiluted groups. Systolic blood pressure was stable in both the hemodiluted and non-hemodiluted patients but statistically there was no significant difference.

In our study, systolic blood pressure was found to be increased in postoperative period in hemodilution group. In halothane anaesthesia, blood pressure reduces due to myocardial depression as halothane result in 50% decrease of blood pressure and cardiac output. Halothane causes coronary artery vasodilatation and decreased coronary blood flow owing to the drop in blood pressure[10]. Colloid solution in hemodilution causes increased blood pressure by maintaining blood volume, which is not seen in non-hemodilution patients.

Our study is similar with the study by Mielke *et al*[20], Cohendy *et al*[23], Trouwborst *et al*[2,24] where systolic blood pressure was significantly increased. It is possible to administer an appropriate volume of colloid solution to induce hypervolemic hemodilution without any adverse hemodynamic effects by using halothane as a vasodilator. In fact hypervolemic hemodilution can cause greater degree of hemodynamic stability during halothane/isoflurane anaesthesia by augmenting preload and obviating the usual decrease in arterial blood pressure[20] as we demonstrated in our study.

Diastolic blood pressure was also comparable between two groups. In the study diastolic blood pressure increased in the hypervolemic hemodilution group in postoperative period and decreased in non-hemodilution group which was not comparable statistically.

Mielke *et al*[20] stated in his study between acute normovolemic hemodilution and hypervolemic hemodilution that in acute normovolemic hemodilution group mean arterial blood pressure was decreased after hemodilution while in hypervolemic hemodilution group mean arterial blood pressure did not changed significantly. Comparing diastolic blood pressure values in hypervolemic hemodilution group were significantly higher than in the acure normovolemic hemodilution group.

In our study, change in pulse rate had no statistical significant difference, the finding that was similar to the study by Mielke *et al*[20], Trouwborst *et al*[2,24] and Cohendy *et al*[23].

Hemoglobin percent level was assessed by cell dyne machine in predetermined time. We found that hemoglobin percent level between two groups were not significantly different. This result is in agreement with previous study done by Mielke *et al*[20], Trouwborst *et al*[2] and Rainaldi *et al*[25]. Hemoglobin level was decreased in postoperative period and 1st postoperative day in hypervolemic hemodilution group, but slightly increased in 7th postoperative day with no significant difference. In normal patients even in 7th postoperative day hemoglobin percent level was lower than the preoperative value. Again there was no statistical difference between two groups in any study time. Although one might expect higher hemoglobin values in group B (Without hemodilution) after blood transfusion, we observed no difference between the groups in any hemoglobin percent value variable at the end of the study. These results were consistent with similar study by Mielke *et al*[20] and Lorentz *et al*[26].

Comparison of hematocrit values between group A and group B in our study revealed that there was no significant difference. The overall hematocrit values were decreased in postoperative period and gradually increased in later days in both the groups.

In the study by Trouwborst *et al*[2], hematocrit values were also similar to our study which was decreased in postoperative period. Decreased hematocrit level is just due to the dilution of blood with crystalloid solution, maintenance colloid and hemodilution. Hemodilution's effect of lowering early postoperative hematocrit did not affect the postoperative course or length of hospital stay[15].

A study of hypervolemic hemodilution in a Jehovah's witness by Trouwborst *et al*[2] reported that hematocrit level was decreased from 0.27 to 0.20 till the hemodilution but the hematocrit value increased to 0.26 after forced infusion was stopped after 4 hours of the operation. Four weeks after the operation hematocrit value was 0.33. This report is also similar with our report.

Using hypervolemic hemodilution, dilution (lowering hematocrit level) of blood is solely achieved by postoperative infusion of plasma expander without removal of autologous blood. hypervolemic hemodilution is not accompanied by an increased risk of excessive intravascular volume[20].

In our study, there was no significant difference in platelet count in between two groups. In a different study, platelet count decreased and increased in same pattern. In postoperative period platelet count was decreased and on 1st and 7th postoperative day platelet count gradually increased, which were higher than postoperative platelet count. This report is similar with the study done by Mielke *et al*[20] and Ruttmenn[22] where platelet count first decreased in postoperative period and gradually increased in postoperative days.

Platelet count predictably decreased when colloid solution was used for hemodilution because of less immediate extravascular redistribution of fluid[22]. The absence of significant increase in platelet aggregation with the colloid is because of antiplatelet effect of colloid[27]. Platelet aggregation appears to be enhanced by saline, but not by colloid[22].

Hemodilution by itself can result in an impairment of primary hemostasis and platelet function[20]. In addition, an increase in capillary flow and higher cardiac output could theoretically result in higher intra-operative blood loss, especially during operations where surgical hemostasis is difficult. In our study, there was no significant difference between the groups. This result is similar with Mielke *et al* [20] and Lorentz *et al*[26].

There is no significant difference in prothrombin time among the two groups. The postoperative changes in prothrombin time usually after liver resection were increased in the study of Sejourne *et al*[15]. The slight prolongation of prothrombin time after hemodilution probably reflects dilution of coagulation factors in plasma[22]. Ruttmann[22] concluded that in their study hemodilution per se induced a procoagulant state by an unknown mechanism and that this may be clinically significant.

In the study between acute normovolemic hemodilution and hypervolemic hemodilution by Mielke *et al*[20], it has been reported that coagulation variables showed the dilution effect. Values showed no significant difference between groups after hemodilution with prothrombin time, but after operation and on 3rd postoperative day in the acute normovolemic hemodilution group prothrombin time value was lower than in hypervolemic hemodilution group. It may be due to decrease of fibrinogen during surgery.

There is no direct effect on the activity of the coagulation factor (prothrombin time) after hypervolemic hemodilution with colloid solution approximately at the rate of 12 ml/Kg[23]. Hypervolemic hemodilution would increase bleeding tendencies through dilution of coagulation factors, in reality the reserve capacity of the coagulation system under normal condition is probably so great that dilution is of no relevance unless large volumes are used.

CONCLUSIONS

Our study showed that, there was neither the need of any blood transfusion nor any complications in patients who had undergone hypervolemic hemodilution. Therefore, colloid solution can be used safely as substitute of blood to prevent hazards of blood transfusion during operation.

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Functional Outcome Between Intra Articular Steroid with Oral Glucosamine Vs Oral Glucosamine Alone in OA Knee Patients: A Comparative Study

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Key words:
FIQ scores,
Glucosamine,
Osteoarthritis,
Steriod,
VAS scores.

ABSTRACT

Objectives: To compare the functional outcome between intra articular steroid with oral glucosamine Vs oral glucosamine alone in knee osteoarthritis patients.

Methods: Fifty elderly patients (18 males, 32 females) of osteoarthritis (OA) knee are divided into two groups. Group A got intra articular steroid injection with oral glucosamines and group B received oral glucosamines only. All patients are above 50 years of age. Functional outcomes are assessed by means of Visual Analog Scale (VAS) and Functional Index Questionnaire (FIQ). VAS and FIQ were recorded on day 1, after 1 week, after 1 month and after 3 months to every patient.

Results: There were no differences in VAS scores in between intra articular group and oral glucosamine group at first day of study (8.72 / 8.32). After 1 week, VAS scores of intra articular group were significantly decreased to 1.96 (oral group - 5.0). There was significant difference in FIQ scores after 1 week in between two groups. But there was no significant difference in both VAS and FIQ scores after 3 months.

Conclusions: There is sharp decrease of pain after intra articular steroid injection in OA knee patients acutely but there are no differences on functional outcomes after 3 months between injection group and oral glucosamine group.

INTRODUCTION

Knee osteoarthritis (OA) is one of the most common knee joint diseases in the elderly, and is characterized by progressive cartilage degradation and concomitant bony hypertrophy. In clinical practice, diagnosis and assessment of knee OA are conventionally based on clinical history and radiological findings[1,2]. Patients' chief complaints are pain and stiffness of their knees, and radiological findings of knee OA include joint space narrowing, osteophyte formation, subchondral sclerosis and cysts[3]. However, radiological findings do not always reflect patients' knee symptoms.

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Osteoarthritis may be broadly categorized as primary (idiopathic) or secondary. According to the American Academy of Orthopedic Surgeons, primary OA of the knee can be defined as a process in which articular degeneration occurs in the absence of an obvious underlying abnormality[4]. Secondary OA of the knee is often the result of injury (trauma) or repetitive motion such as found in certain occupations. It can also result from congenital conditions and underlying diseases, including systemic metabolic diseases, endocrine diseases, bone dysplasia, and calcium crystal deposition diseases. Secondary OA is more likely to manifest itself at an earlier age than primary OA, and may be an initial clue to the presence of a potentially dangerous and treatable systemic disease.

The diagnosis of osteoarthritis is established using a combination of clinical information derived from history, physical examination, radiologic, and laboratory evaluation. An algorithm of diagnostic criteria for osteoarthritis of the knee has been proposed by the American College of Rheumatology (ACR)[5]. A diagnosis of OA of the knee is defined as presenting with pain, and meeting at least five of the following criteria:

- Patient older than 50 years of age
- Less than 30 minutes of morning stiffness
- Crepitus (noisy, grating sound) on active motion
- Bony tenderness
- Bony enlargement
- No palpable warmth of synovium

The presence of clinical symptoms of OA does not always correlate well with the degree of abnormality seen on radiographs.

Treatment for OA of the knee aims to alleviate pain and improve function in order to mitigate reduction in activity[6]. However, most treatments do not modify the natural history or progression of OA, and thus are not considered curative. Nonsurgical modalities include education, exercise, weight loss, and various supportive devices; acetaminophen or nonsteroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen; nutritional supplements (glucosamine and chondroitin), and intra-articular steroid and visco supplements.

If symptom relief is inadequate with conservative measures, invasive treatments may be considered. Operative treatments for symptomatic OA of the knee include arthroscopic lavage and cartilage debridement, osteotomy, and ultimately total joint arthroplasty[7]. Surgical procedures intended to repair or restore articular cartilage in the knee, including abrasion arthroplasty, microfracture techniques, autologous chondrocyte implantation, and others are appropriate only for younger patients with focal cartilage defects secondary to injury[8].

Glucosamine and Chondroitin

Glucosamine is an aminomonosaccharide which is the principal component of *O*-linked and *N*-linked glycosaminoglycans, which comprise the matrix of all connective tissues, including cartilage[9]. This compound historically has been derived by extraction of chitin, a component of crustacean shells, though it is produced through fermentation of a vegetarian source. Chondroitin sulfate is a glycosaminoglycan with a polymerized disaccharide base linked to a sulfate moiety, and is a component of proteoglycans of articular cartilage. It is usually derived from bovine trachea, although other sources such as ovine or porcine trachea and shark cartilage are used. The mechanisms of action of these compounds are unknown, but it is speculated they may promote maintenance and repair of cartilage.

METHODS

The study was conducted for one year, at Gandaki Medical College, and Fishtail Hospital, Pokhara, between January 2012 and December 2012 (1st Magh 2068 to 30th Poush 2069). Ninety patients were included in the study but 35 patients absconded during this period. Out of 55 patients, only 50 patients (18 males and 32 females) are involved in this current study to make it equality in group A and group B. The involved knees are Right 15, Left 25 and both knees 10. The populations of interest are patients with primary or secondary OA of the knee, as defined by the American Academy of Orthopedic Surgeons[4]**.** All patients were above 50 years of age. 25 patients (50%) are treated with intra articular steroid at the first day of visit with oral glucosamine and remaining 25 patients (50%) are treated with oral glucosamine only. NSAIDs are given for 7 days to all patients. Glucosamine is given orally at 1,000 mg daily, usually in two divided doses. At minimum, treatment duration is 3 months, and may be continued indefinitely if the patient experiences improvement.

The primary outcomes are assessed by pain severity or intensity, self-reported physical function, patient global assessment and quality of life. Pain and function should be measured by instruments with established validity and reliability. Among established instruments, pain severity is assessed by a visual analog scale (VAS) and functional assessment is measured by Functional Index Questionnaire (FIQ), adapted from Stratford[10] (Fig 2).

For VAS, patients were asked to indicate their greatest level of knee discomfort during the past week by placing a dash at the appropriate level on the 10 cm horizontal line. For Functional Index Questionnaire (FIQ), eight items related to knee function were scored as (1) unable to do-0, (2) can do with a problem-1, or (3) can do with no difficulty-2, resulting in a score ranging from a possible minimum of 0 to a maximum of 16.

Fig 1: Visual Analog Scale used to assess pain severity

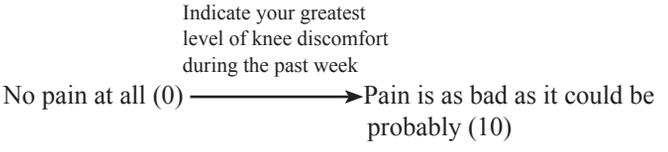

Table 1: Functional Index Questionnaire (FIQ)
(Patient completes items 1-8 in the appropriate column)

		Unable to do (0)	Can do with problem (1)	With no problem (2)
1	Walking as far as 1 km			
2	Climbing up 2 stairs (16 steps)			
3	Squatting			
4	Kneeling			
5	Sitting for prolonged periods with your knees bent in one position			
6	Climbing up 4 stairs (32 steps)			
7	Running a short distance of 100 meters			
8	Walking a short distance (about a city block)			

VAS and FIQ were recorded on day 1, after 1 week, after 1 month and after 3 months to every patient.

RESULTS

This was a randomized controlled trials. So the patient samples included in this study were heterogeneous with respect to age, sex, knee involvement, knee radiographic grade, and baseline pain, reflecting varied patient selection among the study. All 50 patients completed the VAS and FIQ tests for reliability evaluation at 1st day, 1st week, 1 month and 3 months follow up.

Table 2: VAS scores

	Intra articular injection group	Oral Glucosamine group
V0	8.72	8.32
V1	1.96	5.0
V2	2.12	4.72
V3	2.2	3.56

Table 3: FIQ scores

	Intra articular injection group	Oral Glucosamine group
F0	1.76	2.2
F1	8.72	6.0
F2	9.96	8.16
F3	11.64	11.64

There were no differences in VAS scores in between intra articular group and oral glucosamine group at first day of study (8.72 / 8.32). After 1 week, VAS score of intra articular group was significantly decreased to 1.96 (oral group- 5.0). After 1 month, VAS scores between two groups were significantly different too (2.12 / 4.72). But after 3 months, VAS scores between two groups were not so different (2.2 / 3.56). It shows that VAS scores significantly decrease in 1st week after giving intra articular injection in group A patients but there is no much difference in VAS scores in between injection and oral groups after 3 months.

Functional outcome measures were pooled separately as FIQ scores for four time periods: day 1, after 1 week, after 1 month and 3 months. There was significant difference in FIQ scores after 1 week in between two groups. Those patients who got intra articular injection in first day had a high FIQ scores after 1 week than who had only oral glucosamines. There were no differences in FIQ score after 3 months in two groups. However, significant differences were demonstrated between 1st week and 1 month.

DISCUSSION

Osteoarthritis (OA) of the knee is a common condition in elderly age group. There are many modes of treatment but mainly 3 interventions are widely used in the treatment of OA of the knee. We are using glucosamine/chondroitin with or without intra articular injection for the treatment of OA of the knee. Yet, there are no trial evidences to proof the superior method of treatment. The Glucosamine/chondroitin Arthritis Intervention Trial (GAIT) (n=1,583) found that neither glucosamine hydrochloride, chondroitin sulfate, nor the combination was superior to placebo. The double-blind, randomized, controlled trial by Moseley JB *et al* (n=180) found that arthroscopic lavage with or without debridement was not superior to the arthroscopy[11].

Clinically meaningful results require outcome measures, establishing that patients experience improvement that is important to them (meaningful clinically important improvement). The range of magnitude of improvement clinically important to patients has been estimated for VAS scores. Few RCTs reported results in terms of response: the proportion achieving a meaningful clinical improvement in pain and function. The vast majority of trials compared only mean change between groups. Follow up duration and intervals for measurement, appropriate to each intervention, should be established by expert consensus.

As OA knee is characterized largely by subjective reports of pain and functional disability, functional tests would seem to be particularly appropriate. The VAS and the FIQ are two such tests which are simple to use and have been shown to be reliable for documenting knee pain[10]. In this study, however, both measures exhibited poor day-to-day reliability. This may be explained by the variability in the day-to-day complaints of this patient population. In this respect, injection group did exhibit large score changes between measurement at time 0 and time 1 on both the VAS and the FIQ. This contributes to the variability and would be expected to reduce the power of the statistical test in such a small sample size. However, despite the small number of subjects, a significant difference between time O, time 1, time 2 and time 3 scores did indicate that the VAS and FIQ are valid measures for the detection of clinical change.

The intensity of the activities that are evaluated with the VAS is considerably higher than the intensity of activity with FIQ testing in this study. This may explain the apparent discrepancy in the ability of these two measures to detect significant clinical change. More sensitive outcome measures for this group of patients might include endurance tests which measure the time to onset of symptoms during activities such as a standard step test, sitting with the knees flexed to 90°[12] or on downhill walking[13]. These are also simple tests to apply in the clinical environment compared to the specialized instrumentation requirements in GAIT assessment.

There were several limitations in this study. One was that it was performed in a limited region, which may not be representative of Nepal as a whole. Because this study was to investigate the response of treatment in OA patients in Nepal, there were only two modes of treatment. This may have caused the lack of correlation between different types of treatment like arthroscopy, visco supplementation, TKR etc among OA knee patients.

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Vaginal Birth After One Previous Cesarean Section

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Key words:
Cesarian section,
Lower segment,
Labor,
VBAC.

ABSTRACT

Objectives: To determine the maternal and fetal outcome of trial of labor in patients with previous one lower segment cesarean section at term.

Methods: It was a descriptive study, conducted in the Department of Obstetrics and Gynecology of Gandaki Medical College Teaching Hospital during the period of two years starting from16th January 2010 to 15th January 2012 (2nd Magh 2066 to 1st Magh 2068). During this period, total of 60 patients were given trial of labor. Detailed history, examinations and investigations were carried out. In inclusion criteria, patients with term pregnancy (37 weeks or beyond completed weeks of gestation) with previous one lower segment cesarean section having single alive fetus with cephalic presentation were enrolled.

Results: During the study period, 128 patients were admitted with the history of one previous cesarean section, 60 (69%) patients were selected for trial of labor. Out of 60 patients, 12 (20%) patients were delivered vaginally and 48 (80%) patients failed in trial of labor and were delivered by cesarean section.

Conclusions: It is concluded that well monitored trial of labor leads to increased percentage of vaginal deliveries, which is a contribution towards bringing down the rising rate of cesarean section.

INTRODUCTION

In the first half of the 20th century, the cesarean section became a viable obstetric option and the elective repeat cesarean section became an established practice. There is a dramatic rise in the cesarean section over the past 30 years[1].

The cesarean section rate has increased, both in the developed and developing countries alike. It is partly due to availability of safe anesthesia, excellent blood transfusion services, and advances in operative technology and development of broad spectrum antibiotics. The relative safety of the operative procedure has led to relaxation of indications, resorting to the procedure for relative indications and even 'cesarean on demand' by some women. This tendency needs to be controlled as it puts a great drain on health care resources. It is costly and associated with serious risks to the mother and the baby. This rising cesarean section rate has created an expanding high risk obstetric sub-population "Women with scarred uterus"[2].

Chile and Brazil have the highest cesarean section rate in the world respectively (40% and 37%)[3]. In USA and Canada, high cesarean section rate of 25% and 20% respectively is considered a major health problem and they are trying to reduce it[4]. Current medical evidence indicates that 60-80% of women with previous one cesarean section can be successfully delivered vaginally. Careful case selection for trial of scar and close observation during labor will achieve successful maternal and perinatal outcome[5] and a shorter hospital stay[6].

Cesarean section is not always a safe option, especially in a developing country where there are less than adequate medical facilities in many places. Ignorance and lack of education, poor understanding of the operation and its subsequent management, both on the part of the patient and her family leads to poor acceptance of both first and repeat cesarean section. Failure

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to seek antenatal care in subsequent pregnancy, attempts of delivery at home or report late in advanced labor, after unskilled vaginal examination and injudicious use of oxytocin at home leads to high maternal and perinatal morbidity/ mortality. The risk of repeat cesarean section increases in such cases with its own morbidity and mortality.

Women admitted in spontaneous labor with good bishop score at the time of admission and no outside interference have a successful vaginal delivery as was noticed in other studies[7].

METHODS

It was a descriptive study conducted in the department of Obstetrics and Gynecology of Gandaki Medical College & Teaching Hospital, during the period of two years starting from 16th January 2010 to 15th January 2012 (2nd Magh 2066 to 1st Magh 2068).

During this period, a total of 128 patients were admitted with the history of one previous cesarean section for any cause with 37 completed weeks of gestation and above. Out of those 60 patients were selected for trial of labor.

Inclusion criteria involved one lower segment cesarean section from non-recurrent cause or imprecisely labeled cephalopelvic disproportion (CPD) not proven clinically or singleton pregnancy with cephalic presentation and no absolute contraindication to normal delivery in present pregnancy. Patients having gestation less than 37 weeks, more than one cesarean section and uterine scar due to other causes were excluded from the study.

The study included all patients fulfilling the inclusion criteria. Detailed history, examinations, baseline investigations and ultrasonography were carried out.

During labor, continuous maternal and fetal monitoring in the form of maternal blood pressure, pulse-record, fetal heart sounds record (every 30 minutes in early first stage of labor and every 15 minutes in late first stage of labor and before and after every contraction in second stage) was done.

During the trial of labor, the senior physician responsible for the labor room was informed about the case. Intravenous line was established and maintained with infusion of R/L. At least 1 unit of blood was typed and cross-matched for each woman. During the trial of labor fetal cardiac activity, vital signs and uterine contractions were assessed every 30 min in the first stage and 15 min in the second stage. The uterine scar was assessed every 30 min by noting maternal tachycardia, scar tenderness, fetal tachycardia, hematuria, vaginal bleeding and loss of the presenting part on vaginal examination. The progress of labor was assessed by abdominal and/or vaginal examination 4 hourly in the first stage and more frequently in the second stage or when membranes were ruptured or bleeding ensued. This monitoring was continued throughout the trial of labor.

The trial of labor was terminated after six hours of active labor, if delivery was not imminent.

During post-natal period patient was kept under observation due to the risk of post-partum hemorrhage and neonatal well being was also observed. The outcome measures were mode of delivery, needs of assistance in case of vaginal delivery and associated maternal and fetal complications with either mode of delivery.

RESULTS

The number of patients with history of one previous cesarean section was 128. Out of those, 60 patients were given trial of labor and 68 patients were excluded from this study.

Out of 60 patients, 12 (20%) patients had successful vaginal delivery and 48 (80%) patients failed in trial of labor and were delivered by cesarean section. Out of 12 patients, 7 had uncomplicated vaginal delivery, 5 patients had instrumental delivery. Maternal complications were noticed in the form of post-partum hemorrhage, wound infection, febrile complications, third degree perineal tear, retained placenta, angle tear during cesarean section and scar dehiscence.

Table 1: Mode of delivery after previous one cesarean section

Mode of delivery	No.	Percentage
Spontaneous vaginal delivery	7	11.66
Instrumental vaginal delivery	5	8.33
cesarean section	48	80

Table 2: Progress of labor on admission and mode of delivery

Labor status	Vaginal delivery (n=12)		cesarean section (n=48)	
	No.	%	No.	%
Latent phase	2	16.66	18	37.49
Active phase	4	33.33	26	54.16
Second stage	6	50	4	8.33
total	12	100	48	100

Table 3: Indication of repeat cesarean section in the index pregnancy (n=48)

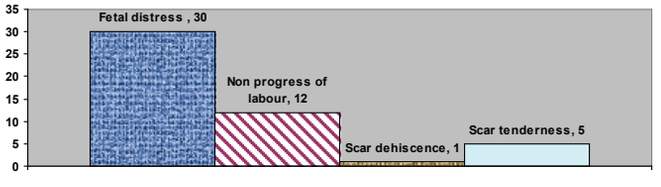

Table 4: Analysis of indication of instrumental delivery

Indication of instrumental delivery	Instrumental delivery (n=5)	
	No	%
Fetal distress	2	40
Prophylactic	3	60
Total	5	100

Table 5: Analysis of maternal complication

Complication	Vaginal delivery (n=12)		Cesarean section (n=48)	
	No.	%	No.	%
PPH	2	16.66	6	12.5
3rd degree perineal tear	0	0	0	0
Retained placenta	2	16.66	1	2.08
Purperal pyrexia	1	8.33	1	2.08
Wound infection	0	0	0	0
Tear during CS	0	0	4	8.33

Table 6: Fetal outcome among total delivery after previous one cesarean section

Fetal outcome	Vaginal delivery (n=12)		Cesarean section (n=48)	
	No.	%	No.	%
Live birth	11	91.66	48	100
Still birth	1	8.33	0	0
Neonatal death	0	0	0	0

Table 7: Fetal birth weight among total delivery

Birth wt. in kg	Vaginal delivery (n=12)		Cesarean section (n=48)	
	No.	%	No.	%
2 – 2.49	4	33.33	2	4.1
2.5 – 2.99	7	58.33	30	62.5
3 – 3.49	1	8.33	15	31.25
> 4	0	0	1	2.08
total	12	100	48	100

DISCUSSION

The majority of women had been referred directly from a local primary health unit in rural areas, often unbooked, or they had been mismanaged by untrained birth attendants and were given high doses of oxytocin at home. In these situations, they are often managed in hospital by primary cesarean section. In subsequent pregnancies, these women may seek early booking and special management both antenatally and in labor and delivery. These women are often very young and poorly educated. When they come again to the hospital with one previous lower segment cesarean section, a trial of VBAC is offered, depending on the selection criteria, after proper counselling and assessment.

Attempting vaginal birth after cesarean section is important because it reduces high rate of cesarean section. Most of our population is not educated. They live in villages and small towns where efficient pre-natal care is not available. Various unhealthy customs regarding confinement, contraception and preference of women to deliver at home even when hospital facilities are available further aggravate the situation. Due to fear of repeat cesarean section, many women have an unsupervised trial of scar at home by untrained traditional birth attendants. Proper counseling and education of women who have had cesarean section enable us to give a trial of scar of women with previous one cesarean section for non-recurrent cause.

Moreover, with the help of partogram and drawing alert and action lines and labor curves, one can identify the abnormal labor patterns earlier and timely and accurate action can result in safety of both mother and fetus[8].

Nevertheless, the dictum “once a cesarean, always a cesarean” began changing approximately 30 years ago as improvements in obstetric care made a trial of labor after a previous cesarean delivery safer for both the mother and the infant[9].

In my study of 60 patients, who presented with spontaneous labor; 12 (20%) patients delivered vaginally and 48 (80%) patients underwent emergency cesarean section. So the cesarean section rate is higher in the trial group.

Our findings reinforce similar previous studies suggesting that vaginal delivery after one cesarean section is safe as regards neonatal outcomes[10].

Scar tenderness was previously meant for idea of scar integrity but studies have now revealed that it has no positive co-relation with the scar's condition. Similar is the observation in this study. Scar tenderness was the indication of emergency cesarean section in 5 patients but intraoperative findings revealed an intact scar.

CONCLUSIONS

The policy of VBAC is a contribution towards bringing down cesarean section rate. There is no doubt that trial of scar is a relatively safe procedure but it is not risk free and should not be undertaken in a casual fashion. Each delivery method has its own advantages and disadvantages. It is ultimately the responsibility of Obstetrician to ensure that delivery plan is appropriate for the individual patient.

RECOMMENDATIONS

It is recommended that nationwide measures should be taken to improve antenatal care at primary and secondary level hospitals. Traditional birth attendants and other paramedical staffs involved in taking care of these patients during labor and delivery should be properly trained and issued certificates allowing them obstetric clinical practice so that they are able to make timely referrals in appropriate cases.

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Profile of Diabetes Retinopathy in a Tertiary Centre in Western Nepal

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Key words:
Diabetes Mellitus,
Diabetic Retinopathy,
Blindness,
Refraction.

ABSTRACT

Objectives: The study was conducted to find out the prevalence of diabetic retinopathy among diabetics on treatment.

Methods: A descriptive study of 504 diabetic patients on treatment presenting to eye OPD in Gandaki Medical College was done from January 2011 to December 2013. Visual acuity was taken by Snellen chart, refraction was done when needed. Slit lamp examination and funduscopy was done. The stages of diabetic retinopathy were classified according to the early treatment of diabetic retinopathy classification and were classified as nonproliferative diabetic retinopathy and diabetic retinopathy with and without macular edema. All the data were entered and analyzed by spss software version 11.6.

Results: A total of 509 patients were included in the study of which 274 (54.4%) were males and 230 (45.6 %) were females. 95.2% of the patients had type II diabetes and 4.8% of the patients had type I diabetes. Diabetes retinopathy was seen in 18.5% (98) patients. NPDR was seen in 14.3 %, PDR in 2.8%, maculopathy in 1.4%. Majority (88.7%) of patients had diabetes for less than or equal to ten years and only 2% patients had diabetes for more than or equal to 20 years.

Conclusions: The prevalence of diabetic retinopathy is quite significant in the people with diabetes. Regular eye examination with evaluation of retina is necessary to avoid blindness due to the diabetic retinopathy.

INTRODUCTION

Diabetes is the fourth leading cause of death in industrialized countries. Diabetes is a disease of considerable concern because of its severe long-term complications. These include cardiovascular disturbances, retinopathy, neuropathy and nephropathy. Diabetic retinopathy is the most important cause of blindness, and is a growing concern in the developing world[1]. It is the major cause for new cases of blindness in people aged 25-74 years[2].

Diabetes retinopathy (DR) is a common complication of diabetes and despite availability of effective treatment; it remains one of the leading causes of visual loss[3-5].

Diabetic retinopathy is due to microangiopathy affecting the retinal precapillary arterioles, capillaries and venules. Damage is caused by both microvascular leakage and microvascular occlusions. Vision threatening retinopathy is usually due to maculopathy and neovascularization and its complications.

The most common cause of visual impairment in diabetics is due to the retinopathy and associated macular edema.

After 15 years of diabetes, approximately 2% of people become blind, and about 10% develop severe visual impairment[6]. According to the World Health Organization, approximately 5 million individuals have diabetic retinopathy, accounting for 5 percent of world blindness. By 2025, an estimated 300 million people will have diabetes, with half expected to develop some level of retinopathy. In developed countries, DR is recognized

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as the leading cause of blindness in the working-age population (20–74 years old) and is responsible for 12% of new cases of blindness each year[8]. In Nepal, the prevalence diabetes was 436000 in the year 2000 and the projected figure for year 2030 is 1328000[9].

Almost all Type I diabetics and 60% of Type II diabetics develop some level of diabetic retinopathy after 20 years of disease process. Macular edema which is the main cause of visual impairment can occur during any phase of the disease.

According to Peter J Watkins, diabetes is the commonest cause of blindness in people aged 30-69 years. Twenty years after the onset of diabetes, almost all patients with type I diabetes and over 60% of the patients with type II diabetes will have some degree of retinopathy. Even at the time of diagnosis of type II, about a quarter of patients have established background retinopathy. Treatment can now prevent blindness in the majority of cases, so it is essential to identify patients with retinopathy before their vision is affected[10].

Diabetic retinopathy is classified into non-proliferative or proliferative stages according to the presence of defined clinical findings. The non-proliferative diabetic retinopathy is characterized by the presence and extent of intraretinal hemorrhages, microaneurysms, venous beading, and intra retinal microvascular anomalies (IRMA). In the mild to moderate non-proliferative category also known as background retinopathy, there are a few small intraretinal hemorrhages and microaneurysms, minimal venous changes, and IRMA. The severe nonproliferative stage represents increasing ischemia. Proliferative Diabetic Retinopathy (PDR) is characterised by the neovascularisation as well as the absence or the presence of preretinal/vitreous hemorrhages.

There are various treatment modalities available for the treatment of diabetic retinopathy. Studies have shown that appropriate treatment can decrease the loss of vision caused by proliferative DR by up to 90%[11].

In general, laser photocoagulation is the treatment of choice for patients with macular edema and high risk proliferative disease.

METHODS

A hospital based descriptive study was done. A total of 509 patients diagnosed as diabetes mellitus attending the ophthalmology out patients department of Gandaki Medical College from January 2011 to December 2013 were included in the study. Ocular evaluation was conducted by a team of Ophthalmologist and ophthalmic assistant. Visual acuity was taken by Snellen chart, refraction was done when needed. The anterior segment was evaluated using slit lamp. Retina was evaluated after pupil dilatation with tropicamide eye drop instilled three times at interval of ten minutes. The 90D and 20D aspheric lens with slit lamp was used to evaluate the retina. The stages of diabetic retinopathy were classified according to the early treatment of diabetic retinopathy classification. The stages were classified as nonproliferative diabetic retinopathy and diabetic retinopathy with and without macular edema. All the data were entered and analyzed by spss software version 11.6.

RESULTS

A total of 509 patients were included in the study of which 274 (54.4%) were males and 230 (45.6 %) were females. 19.4% of the patients were in age group of 40 to 49 (Table 1). Majority of the patients 33.7 % (170) were Brahmins followed by Chhetris 22.4 % (113), Gurungs 16.5 % (83) (Table 2).

In our study, 95.2% of the patients (n=480) had type II diabetes and 4.8% of the patients (n=24) had type I diabetes. Majority of patients 88.7% (n=447) had diabetes for less than or equal to ten years and only 2% (n=10) patients had diabetes for more than or equal to 20 years (Table 3). Majority 64.9 % (n= 327) of the patients had uncontrolled diabetes.

Hypertension was seen in 19% (n=96) of patients. Diabetes retinopathy was seen in 18.5% (98) patients. NPDR was seen in 14.3% (72), PDR in 2.8% (14), maculopathy in 1.4% (7) (Table 4).

Table1: Age distribution of patients

Age	Frequency	Percentage (%)
‹ 40 yrs	61	12.1
40-49 yrs	98	19.4
50-59 yrs	166	33
60-69 yrs	101	20
› 70 yrs	78	15.5
Total	78	100

Table 2: Ethnic distribution of patients

	Number	Percentage
Brahmin	170	33.7%
Chhetri	113	22.4%
Newar	51	10.1%
Gurung	83	16.5%
Magar	32	6.3%
Others	55	10.9%
Total	504	100%

Table 3: Duration of diabetes

Duration of diabetes	No of patients	Percentage
≤ 10yrs	447	88.7%
11-20 yrs	47	9.3%
21-30 yrs	10	2%
Total	504	100%

Table 4: Distribution of diabetes retinopathy

Condition	No of patients	Percentage
No diabetes retinopathy	411	81.5%
NPDR	72	14.3%
PDR	14	2.8%
Maculopathy	7	1.4%
Total	504	100%

DISCUSSION

In our study, majority of the patients were in the age group of 50 to 59 years. Similarly majority of patients in the age group of 50-69 were seen in a study by Tilganga[12]. Likewise a study by Karki DB showed majority of patients in the age group of 50-59 years[13]. 54.4% of the patients were males and 45.6% were females. Similarly more males than females were seen in other studies too[12,13]. However a study by Shrestha MK showed more females[14].

Brahmins and Chhetris were the main ethnic groups in our study. The high representation of Brahmins may be due to the higher proportion of literate, educated people in this ethnic group, leading to more awareness. Likewise majority of Brahmins were seen in a study by Tilganga[12]. But a study from Kathmandu showed predominance of Newars[14].

Diabetes retinopathy was seen in 18.5% of patients. Studies reported varied prevalence of diabetic retinopathy in the diabetic population. Similar findings showing 20.31% diabetes retinopathy was seen in a study done by Shrestha RK[15]. While other hospital based studies have reported higher prevalence of retinopathy of 44.7%[14] and 47.3%[16].

Varied prevalence of diabetic retinopathy has been reported from different parts of the world. 18% prevalence of diabetes retinopathy was seen in a study from India[17]. Likewise a study done in United Arab Emirates (UAE) showed 19% prevalence of diabetes retinopathy[18]. While fourteen WHO study centers throughout the world had shown a prevalence of 35.8%[19]. Two large clinic-based studies in Southern India had found its prevalence as 34.1% and 37% respectively[20,21].

In our study, nonproliferative retinopathy was seen in 14.3% of patients, proliferative retinopathy in 2.8% of patients and maculopathy in 1.4% of patients. Variance of prevalence is seen from different studies in Nepal. A study by Shrestha RK[15] showed NPDR in 13.28% cases and PDR in 7.03%. While a study by Karki DB[13] showed NPDR in 31%, PDR in 29%, maculapathy in 24% of cases.

In a study from Yemen, the prevalence of NPDR was 33% and proliferative diabetic retinopathy (PDR) was 17%[22]. The difference in the prevalence of diabetic retinopathy and different stages of retinopathy in different studies from Nepal and from different parts of the world could have resulted due to the variation in diabetic patients attending these institutes. The prevalence of retinopathy and specifically proliferative diabetic retinopathy could have been higher in the studies which included participants from the area with little health access or those institutes which receives referral from other primary and secondary institutes such as in our study.

In our study, majority of the patients (88.7%) had diabetes for less than or equal to 10 years and only 2% had diabetes for more than 20 years. Similarly a study by Shrestha RK[15] showed that 67.97% patients had diabetes for less than 10 years, 26.56% had diabetes for 10-20 years and only 5.47% had diabetes for more than 20 years. Similarly a study by Maskey R *et al*[23] showed 50% of patients with diabetes retinopathy had diabetes for more than 10 years.

CONCLUSIONS

The prevalence of diabetic retinopathy is quite significant in the people with diabetes. Majority of patients were in the age group of 50-59 years. Diabetes retinopathy was seen in 18.5% of patients, nonproliferative retinopathy was seen in 14.3% of patients, proliferative retinopathy in 2.8% of patients and maculopathy in 1.4% of patients. Majority of the patients (88.7%) had diabetes for less than or equal to 10 years and only 2% had diabetes for more than 20 years. Regular eye examination with evaluation of retina is necessary to avoid blindness due to the diabetic retinopathy.

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CD4 T Cell Count in HIV Infected People Visiting for Assessment of Eligibility to Highly Active Anti-Retroviral Therapy at Nepal Public Health Laboratory, Kathmandu

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Key words:
CD4 T Cell Count,
HIV infection,
Highly Active Anti-Retroviral Therapy.

ABSTRACT

Background: CD4 T cell count is an useful tool for indication of the stage of the disease and the initiation and the follow-up of the anti-retroviral therapy response in Human Immunodeficiency Virus (HIV) infected individuals.

Objectives: The objective of the study is to evaluate the CD4 T cell counts of all HIV infected individuals visiting for assessment of eligibility to highly active anti-retroviral therapy at Nepal Public Health Laboratory, Kathmandu**.**

Methods: A cross-sectional study was conducted in all HIV infected people visiting Nepal Public Health Laboratory from March, 2005 to December, 2008 for assessment of eligibility to highly active anti-retroviral therapy.

Results: Of the 1809 HIV infected subjects, 66% were males and 34% were females. The mean CD4 T cell count of total subjects was 303.5 ± 230.2 cells/µL, of males was 287.9 ± 219.2 cells/µL and of females was 333.9 ± 247.5 cells/µL. The majority, 64.8% had CD4 T cell count <350 cells/µL, consisting of 68% males and 32% females. Males are 1.36 (CI, 1.10-1.67) fold more likely to have CD4 T cell count <350 cell/µL as compared to females. Married people are 4.15 (CI, 2.95-5.88) times more likely to have CD4 T cell count <350 cell/µL as compared to unmarried. CD4 T cell count found to be decreased with increased age of the participants ($p<0.001$). Longer duration since the diagnosis of HIV was associated with the CD4 T cell count <350 µL/ cell count ($p<0.001$).

Conclusions: About 65% had CD4 T cell count < 350 cells/µL indicates they were already in the stage requiring commencement of highly active anti-retroviral therapy. Priority must be given to monitor the stage of HIV infected individuals and starting treatment earlier in the course of their illness.

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INTRODUCTION

CD4 T lymphocyte cell count is a major indicator of the stage of the disease in HIV infected individuals[1]. Depletion of CD4 T cells is one of the hallmarks of progression of HIV infections[2]. The absolute CD4 cell count is used routinely in the evaluation and monitoring of HIV-infected persons[3]. CD4

T cell count is a standard test to stage HIV disease and to make therapeutic decisions for the initiation of anti-retroviral therapy and follow-up of the anti-retroviral therapy response[4,5]. The main biological event in HIV infection is the immune system collapse, especially gradual destruction of CD4 T cells that lead to a severe immune depression and consequently a high risk of opportunistic infections and cancers[5]. The increased risk for opportunistic diseases and increased mortality are associated with low CD4 T cell counts[6].

The results of studies suggest that 350 cells/μL should be the minimum threshold for initiation of anti-retroviral therapy, and should help to guide physicians and patients in deciding when to start treatment[7,8]. In Nepal also, new National Anti-Retroviral Therapy Guidelines recommends baseline CD4 cell count of less than 350 cells/μL to offer highly active anti-retroviral therapy (HAART) to patients with WHO stage 1 or 2 disease which was less than 200 cells/μL in the previous guidelines till 2009[9,10].

METHODS

A cross-sectional study was conducted in people infected with HIV, not yet on HAART attending at National Public Health Laboratory (NPHL) for CD4 T cell count in Kathmandu, Nepal primarily for the purpose of assessing their eligibility for HAART. NPHL is the largest referral center in country equipped with automated CD4 T cell count facility. Although the facility was located in the capital city, the participants came from various parts of the country as CD4 T cell count service was not available in other parts of the country until the middle of 2008.

A total of 1809 participants were included in the study from March, 2005 to December, 2008. The face to face interview was conducted among those who agreed to participate in the study voluntarily. Structured questionnaire was used to collect the information from the participants regarding age, marital status, and duration of diagnosis of disease. Three mL of blood from each participant was collected for CD4 T cell count. The CD4 T cell count was performed by FACS counting system[11]. During the period of this study, the national guideline for eligibility to start HAART was on the basis of CD4 T cell count of <200/μL[9].

Data was entered in Excel spread sheet and statistical analysis was performed by STATA (Version 12). The measure of association between different explanatory variables and CD4 T cell count (outcome variable) was expressed in terms of odds ratio (OR) with corresponding 95% confidence interval (CI). Chi-square test was used for testing statistical significance between sex and categorical variables and t-test between sex and continuous variables.

The study was approved from the ethics committee of Tribhuvan University, Kathmandu, Nepal. Permission was taken from NPHL before starting the study. Participation was fully voluntary. Informed verbal consent was taken from each participant. Participants were explained about the study and assured about the confidentiality of the collected information.

RESULTS

Of the 1809 HIV infected subjects, 1193 of them (66%) were males, who had a median age of 31 (Inter-quartile range: 26-35) years; the other 616 of them (34%) were females, and their median age was at 29 (Inter-quartile range: 24-35) years. The difference of average age among males and females was found significant. The male to female ratio was 1.9:1. The mean CD4 T cell count of total subjects was 303.5 ± 230.2 cells/μL. The mean CD4 T cell count of males was 287.9 ± 219.2 cells/μL while that of females was 333.9 ± 247.5 cells/μL. Median CD4 T cell count of total subjects was 257 (Q1-Q3, 132-419) cells/μL, of males was 245 (Q1-Q3, 122-403) cells/μL and of females was 276 (156-838) cells/μL. The difference of average CD4 T cell count across sex was statistically significant (P<0.001).

Table 1: Average CD4 T cell count of people Infected with HIV

Variables	No. of Males	No. of Females	Total	P value
Participants	1193 (66%)	616 (34%)	1809 (100%)	
Mean age	30.5 (±9.9)	28.5 (±9.9)	29.8 (±9.9)	<0.001
Median age (Q1-Q3)	31 (26-35)	29 (24-35)	30 (25-35)	
Mean CD4 T cell count (SD)	287.90 (±219.22)	333.91 (±247.47)	303.56 (±230.20)	<0.001
Median CD4 T cell count (Q1-Q3)	245 (122-403)	276 (156-838)	257 (132-419)	

Note: Q1=25th quartile, Q3=75th quartile

Majority of the patients 1172 (64.8%), had CD4 cell count less than 350 cells/μL, comprising of 797 (68%) males and 375 (32%) females. Male participants were 1.4 (OR, 1.36, CI, 1.10-1.67) times more likely to have CD4 T cell count less than 350 cells/μL. Married people were 4.1 (OR, 4.15, CI, 2.95-5.88) times more likely to have CD4 T cell count less than 350 cells/μL than unmarried. CD4 T cell count was found decreased with increased age of the participants. The difference of CD4 T cell count across age group was statistically significant (P<0.001).

Table 2: Demographic factors and CD4 T cell count of HIV infected individuals

Variables	CD4 count <350/ μL	CD4 count <350 /μL	Total	P value	Unadjusted OR(95%CI)
Participants	1172 (64.8%)	637 (35.2%)	1809		
Sex					
Male	797	396	1193	0.012	1.36 (1.10-1.67)
Female	375	241	616		Reference
Marital status					
Married	1113	522	1635	<0.001	4.15 (2.95-5.88)
Unmarried	59	115	174		Reference
Age groups					
≤19	52	102	154		Reference
20-29	381	257	656	<0.001	2.90 (1.98-4.29)
30-39	561	201	762	<0.001	5.47 (3.72-8.09)
40-49	143	47	190	<0.001	5.96 (3.63-9.81)
≥50	35	12	47	<0.001	5.72 (2.61-13.05)

Only 40.8% participants attended for CD4 T cell monitoring within 12 months of diagnosis of HIV. The relation of time duration since the diagnosis of HIV and CD4 T cell count was significant (p<0.001). Longer duration since the diagnosis of HIV was associated with the CD4 T cell count <350 cells/μL. Those who were diagnosed 7-12 months ago were 1.9 times more likely to have CD4 T cell count <350/μL as compared to those who were diagnosed ≤ 6 months ago. In this way, odds of having CD4 T cell count <350/μL was 2.1 times higher among those diagnosed 13-24 months ago, 1.9 times higher among those diagnosed 25-35 months ago and 1.4 times higher among diagnosed ≥37 months ago as compared to those diagnosed ≤ 6 months ago.

Table 3: Duration of diagnosis and CD4+ T cell count of HIV infected individuals

Duration of diagnosis	CD4 count <350 μL	CD4 count ≥350 μL	Total	P value	Unadjusted OR (95%CI
≤ 6 months	244	206	450		Reference
7-12 months	200	89	289	<0.001	1.89 (1.37-2.62)
13-24 months	293	116	409	<0.001	2.13 (1.59-2.86)
25-36 months	182	78	260	<0.001	1.97 (1.40-2.76)
≥ 37 months	253	148	401	0.008	1.44 (1.08-1.92)

DISCUSSION

Of the 1809 HIV infected subjects, 66% were males, who had a median age of 31years; the other 34% were females, and their median age was 29 years. In a study done by Kilaru *et al* with newly diagnosed HIV infection in Barbados, 58.5% were males, who had a median age at presentation of 40 years; the other 41.5% were females, and their median age at presentation was 36 years[4]. In our study, infected individuals are found to be younger.

In the study, mean CD4 T cell count of total subjects was 303.5 ±230.2 cells/μL, of males was 287.9 ±219.2 cells/μL and that of females was 333.9 ±247.5 cells/μL. A study done in Nigeria by Adekunle AE *et al* found slightly less mean value of CD4 T cell count than the finding of our study (i.e. 286.19 ±233.31)[12]. Similarly another study by Ajayi *et al* also found less mean CD4 T cell count than found in our study (i.e. total mean CD4 cell count was 230.7 +/-311.9 cells/μL, of males was 261.0 +/-389.19 cells/μL and of female was 212.17 +/-264.96 cells/μL)[13]. The mean CD4 T cell count of the males was found to be higher than of females which is in contrast with the findings of our study[12,13]. However, a study done by Edathodu J *et al* found that the mean CD4 T cell count to be high among females than in males mean as found out in our study[14]. In our study, median CD4 T cell count of total subject was 257cells/μL, of males was 245ells/μL and of females was 276 cells/μL. A study done in New York found out the median CD4 cell at the time of diagnosis to be 152 cells/μL, which is far less than the findings of our study[15]. It has been observed in the study by Kilaru KR *et al* that the median CD4 cell count at the time of diagnosis was 183 cells/μL, and among males and females was 161 cells/μL and 223 cells/μL respectively which is also less than the findings of our study[4].

In this study, majority of the patients (64.8%) had CD4 T cell count <350 μL. The value indicates that they were already in the stage of requiring commencement of HAART. More than two third of the participants had a CD4+ T Lymphocytes cell count <350 cells/μL (71.8%)[12] and majority of the participants (86.2%) had CD4 cell count <350 cells/μL[13]. This suggests that in our study, less proportion of the participants were in the stage requiring commencement of HAART as compared to the findings by others. However, having about 65% of the participants visiting for assessment of eligibility to HAART who has CD4 T cell count <350 μL is a big challenge in our context. In the study, longer duration since the diagnosis of HIV was associated with the CD4 T cell count <350 cells/μL. As in our study, it had been reported in the study by Stein DS that HIV infected persons with lower CD4 cell counts have been infected for longer periods of time as compared to those with higher CD4+ cell count.

According to Nepal's National Anti-retroviral Therapy Guidelines, 2009, more than three-fifth of the infected individuals are in the stage of beginning of HAART on the basis of CD4 T cell count i.e. <350 cell/μL. Thus, priority must be given to monitor the stage of HIV infected individuals and starting treatment earlier in the course of their illness.

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Bacterial Isolation and Antibiotic Sensitivity Pattern of Urinary Tract Infection in Children in a Tertiary Hospital, Pokhara

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Key words:
Urinary tract infection (UTI), Antibiotic sensitivity pattern, *E. coli.*

ABSTRACT

Objectives: The aim of this study is to find out the causative agents of urinary tract infection (UTI) in children and their antibiotic sensitivity pattern for optimum management of UTI.

Methods: This is a hospital based descriptive study of UTI in children. The data includes both outpatients and inpatients of pediatric department of Gandaki Medical College Teaching Hospital. In this study we have included patients who had history or symptoms suggestive of UTI that were sent for urine culture and sensitivity from April 14th 2012 to Dec 30th 2012.

Results: E. coli was the most common organism 39 (61.9%), followed by *Staphylococcus aureus* 12 (19%), *Klebsiella pneumoniae* 7 (11.1%) and *Proteus* spp. 5 (7.93%). The highest susceptibility was for Nitrofurantoin (100%), Amikacin (95.08%), Norfloxacin (85.18%), and Gentamycin (80%) for all the pathogens isolated. Nalidixic acid and Cefixime showed variable resistance among the organisms isolated.

Conclusions: *E.coli* still remains as the commonest organism isolated in UTI and Nitrofurantoin was the most sensitive antibiotic. Exhibiting the changing drug sensitivity pattern, it is advisable to perform periodic monitoring of antibiotic sensitivity pattern of the bacterial isolates to provide effective treatment.

INTRODUCTION

Urinary tract infection (UTI) in children is one of the most common bacterial infections seen by clinicians[1]. During the first year of life, more boys than girls get UTIs, with a ten fold increased risk for uncircumcised compared to circumcised boys. Recently UTI become more complicated and difficult to treat because of appearance of pathogen with increasing resistance to antimicrobial agents. The diagnosis of UTI in young children is important as it may be the marker of urinary tract abnormalities. Early diagnosis is important to preserve renal function of the growing kidney[2].

The aim of this study is to find out the causative agents of urinary tract infection (UTI) in children and their antibiotic sensitivity pattern in Gandaki Medical College Teaching hospital.

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METHODS

This was a hospital based descriptive study of UTI in children. The data include children of both sexes aged 2 months to 14 years, both outpatients and inpatients of pediatric department of Gandaki Medical College Teaching Hospital. In this study, patients who had history or symptoms suggestive of UTI were selected, specimens were sent for urine culture and sensitivity. It included 216 consecutive patients who had their urine cultured for bacterial growth and for antibiotic sensitivity patterns from April 14th 2012 to Dec 30th 2012.

Bacterial identification was done based on standard bacteriological techniques. All isolates were tested for susceptibility testing as per Kirby Bauer disc diffusion method recommended by National Committee for Clinical Laboratory Standards (NCCLS)[3].

RESULTS

Out of 215 patients whose urine was cultured for bacterial growth, 152 (70.69%) did not show any bacterial growth. Bacterial growth was found in the urine culture of 63 (29.30%) patients (Fig 1). Females 36 (57.14%) were more commonly affected than males 27 (42.80%) with a ratio of 4:3 (Fig 2). The distribution pattern of culture positive samples in different age groups and sexes of children is shown in Table 1. Majority of growth positive cases 24 (38.09%) were in the age group 1 to 5 years.

Fig 1: Status of urine culture

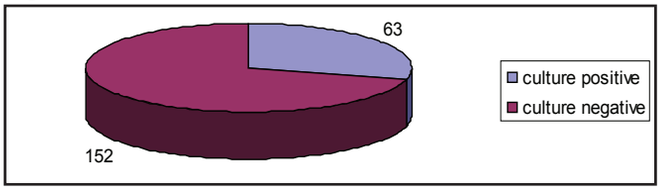
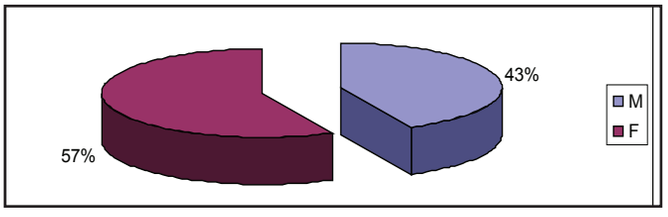


Table 1: Age and Sex distribution of UTI patients

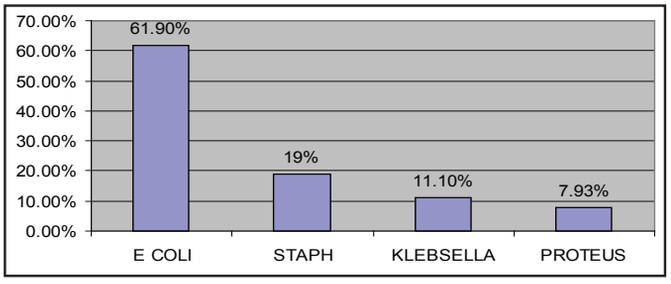
Sex	6 mth-1yr	1 yr-5yr	6 yr-10 yr	10 yr-14yr	Total (%)
Male	5 (15%)	11 (40%)	7 (26%)	4 (13%)	27 (42.80%)
Female	7 (19%)	13 (36%)	10 (28%)	6 (17%)	36 (57.14%)
Total	12 (19.04%)	24 (38.09%)	17 (26.98%)	10 (15.87%)	63 (29.30%)

Fig 2: Sex distribution of UTI patients



E. coli was the most common organism 39 (61.9%), followed by *Staphylococcus aureus* 12 (19%), *Klebsiella pneumoniae* 7 (11.1%) and *Proteus* spp. 5 (7.93%) (Fig 3).

Fig 3: Pattern of bacterial isolation from UTI cases



The highest susceptibility was for Nitrofurantoin (100%), Amikacin (95.08%), Norfloxacin (85.18%), and Gentamycin (80%) for all the pathogens isolated. Nalidixic acid and Cefixime showed variable resistance among the organisms isolated.

E. coli was most sensitive to Nitrofurantoin (100%), followed by Gentamycin (97.29%), Amikacin (89.18%) and resistant to Nalidixic acid 69.23%, and Cefixime 51.72% (Table 2).

Table-2: Antibiotic susceptibility pattern of *E. coli* (n=39)

Antibiotic	No of sensitivity tested	sensitive	Intermediate	resistant
Ofloxacin	33	17 (51.52%)	11 (33.33%)	5 (15.15%)
Norfloxacin	14	11 (78.57%)	1 (7.14%)	2 (14.29%)
Nitrofurantoin	23	23 (100.00%)	0	0
Nalidixic acid	13	4 (30.77%)	0	9 (69.23%)
Ciprofloxacin	36	18 (50.00%)	10 (27.78%)	8 (22.22%)
Amikacin	37	36 (97.30%)	0	1 (2.70%)
Gentamycin	37	33 (89.19%)	0	1 (2.70%)
Cefixime	29	12 (41.38%)	2 (6.90%)	15 (51.72%)
Ceftriazone	26	15 (57.69%)	1 (3.85%)	10 (38.46%)
Azithromycin	12	10 (83.33%)	0	2 (16.67%)
Cefepime	12	10 (83.33%)	0	2 (16.67%)
Ceftazidime	11	8 (72.73%)	0	3 (27.27%)

However, *Staphylococcus aureus* was most sensitive to Nitrofurantoin (100.0%) and Cefepime (100%) followed by Norfloxacin (87.50%), Amikacin (83.33%), and Gentamycin (75%). It was 100% Resistance to Nalidixic acid and Ceftazidime and 80% to Cefixime (Table 3).

Table 3: Antibiotic sensitivity pattern of *Staphylococcus aureus* (n=12)

Antibiotic	No of sensitivity tested	sensitive	Intermediate	resistant
Ofloxacin	11	5 (45.45%)	3 (27.27%)	3 (27.27%)
Norfloxacin	8	7 (87.50%)	0	1 (12.50%)
Nitrofurantoin	3	3 (100.00%)	0	0
Nalidixic acid	2	0	0	2 (100.00%)
Ciprofloxacin	11	5 (45.45%)	3(27.27%)	3 (27.27%)
Amikacin	12	10 (83.33%)	0	2 (16.67%)
Gentamycin	12	9 (75.00%)	2(16.67%)	1 (8.33%)
Cefixime	10	2 (20.00%)	0	8 (80.00%)
Ceftriazone	8	2 (25.00%)	0	6 (75.00%)
Azithromycin	8	5 (62.50%)	1(12.50%)	2 (25.00%)
Cefepime	1	1 (100.00%)	0	0
Ceftazidime	1	0	0	1 (100.00%)

Klebsiella pneumoniae was 100% sensitive to Amikacin and Nitrofurantoin where as 80% resistant to ciprofloxacin (Table 4). *Proteus* spp was 100% sensitive to Nitrofurantoin and Amikacin and 80% sensitive to Gentamycin where as it was 100% resistant to Nalidixic acid, Cefixime and Ceftriazone (Table 5).

Table 4: Antibiotic sensitivity pattern of *Klebsiella pneumoniae* (n=7)

Antibiotic	No of sensitivity tested	sensitive	Intermediate	resistant
Ofloxacin	7	2 (28.57%)	2 (28.57%)	3 (42.86%)

Norfloxacin	5	5 (100.00%)	0	0
Nitrofurantoin	1	1 (100.00%)	0	0
Nalidixic acid	3	2 (66.6%)	0	1 (33.33%)
Ciprofloxacin	5	1 (20.00%)	0	4 (80.00%)
Amikacin	7	7 (100.00%)	0	0
Gentamycin	6	2 (33.33%)	3 (50.00%)	1 (16.67%)
Cefixime	5	1 (20.00%)	1 (20.00%)	3 (60.00%)
Ceftriazone	4	1 (25.00%)	3 (75.00%)	0
Azithromycin	2	1 (50.00%)	1 (50.00%)	0
Cefepime	4	1 (25.00%)	3 (75.00%)	0
Ceftazidime	1	1 (100.00%)	0	0

Table 5: Antibiotic sensitivity pattern of *Proteus* spp. (n=5)

Antibiotic	No of sensitivity tested	sensitive	Intermediate	resistant
Ofloxacin	5	1((20.00%)	1(20.00%)	3(60.00%)
Norfloxacin	0	0	0	0
Nitrofurantoin	4	4 (100.00%)	0	0
Nalidixic acid	1	0	0	1 (100.00%)
Ciprofloxacin	4	1 (25.00%)	0	3 (75.00%)
Amikacin	5	5(100.00%)	0	0
Gentamycin	5	4 (80.00%)	0	1(20.00%
Cefixime	5	0	0	5 (100.00%)
Ceftriazone	2	0	0	2 (100.00%)
Azithromycin	1	1 (100.00%)	0	0
Cefepime	2	0	0	2 (100.00%)
Ceftazidime	1	0	0	0

DISCUSSION

The urinary tract is a common site of infection in the pediatric population. The true incidence of pediatric UTI is difficult to determine because there are varying presentations[4]. But the prevalence varies with the age and sex of children[5]. It occurs in about one percent of boys and three to five percent of girls[6]. In children aged 1 to 5 years, the annual incidence of UTI is 0.9% to 1.4% for girls and 0.1% to 0.2% for boys[7].

In our study, UTI was more common in female children. Male to female ratio was 3 : 4. Other such studies also showed male to female ratio of 1:1.9[8,9] and 1:2[10]. This can be easily attributed to short urethra in females.

Majority of growth positive cases were in the age group of less than six years. This was in agreement with previous report from Iran[11]. This could be because younger children are not well toilet trained and likelihood of ascending infection with fecal flora is more common in this age group[12,13]. Eighty nine percent of the UTI in children was constituted by the age group of less than 6years in one of the studies[14].

The antibiotic sensitivity pattern of organisms changes rapidly over a short period. It is especially true for developing countries where antibiotics are prescribed irrationally not only by the medical practitioners but the antibiotics are also purchased directly from the chemists (medicine shop keepers) without prescription[15]. It has been advised that pediatricians should be aware of the rising resistance of urinary pathogens to commonly prescribed antibiotics as well as the profile of antibiotic resistance within their community[16]. Therefore, periodic evaluation of sensitivity pattern is essential for rational and appropriate use of antibiotics[17].

Likewise other studies[18,19,20], *E. coli* was the most common organism isolated (61.9%) in our study too. In our study, the distribution of pathogens were *E. coli,* the most common organism 39 (61.9%), followed by *Staphylococcus aureus* 12 (19%), *Klebsiella pneumoniae* 7 (11.1%) and *Proteus* spp. 5 (.08%). Our study was consistent with the study conducted by Das R N and team. In that study, the *Enterobacteriaceae* group, namely *E. coli* (59.4%), *Klebsiella* spp. (15.7%), *Enterococcus fecalis* (8.1%), and *Proteus mirabilis* (7.4%), were the most common pathogens isolated, followed by Gram positive cocci, namely *Staphylococcus aureus* (3.4%) and *Staphylococcus saprophyticus* (1.4%)[21].

In our study, most of the organisms isolated were highly susceptibile for Nitrofurantoin (100%), Amikacin (95.08%), Norfloxacin (85.18%), and Gentamycin (80%). A study done in Turkey also reported highest sensitivity of Nitrofurantoin (97.8%) against *E. coli*[22]. Other studies done in Greece and United Kingdom also reported 95.6% 9 and 93.0 % sensitivity of *E. coli* to Nitrofurantoin respectively[23].

Nitrofurantoin showed the greatest effectiveness against *E. coli* isolates, which was different from the study done by Chhetri PK where Ciprofloxacin was most sensitive[18], similar to a study done by Kashanian, *et al*[25]. In our study, *E. coli* was resistant to Nalidixic acid in 69.23%, and Cefixime 51.72%. According to a study done by Chhetri PK, *E. coli* was sensitive to ciprofloxacin in 95.2% followed by Nalidixic acid (60.0%)[18]. This shows a shift in antibiotic susceptibility of *E. coli*, which could be due to the misuse of antibiotics which are easily available over the counter[26]. Other reports have also shown Nitrofurantoin as the most effective drug. However, there may be non-compliance to Nitrofurantoin due to its bitterness.

Staphylococcus aureus also most sensitive (100%) to Nitrofurantoin and Cefepime followed by Norfloxacin (87.5), Amikacin (83.33%), Gentamycin (75%), Ofloxacin (45.48%), Ciprofloxacin (45.45%) and Ceftriazone (25%), while resistant to Nalidixic acid (100%) and Cefixime (80%). But in study done by Malla K showed totally 100% resistance to Gentamycin, Ofloxacin and 100% sensitive to Amikacin, Ciprofloxacin and Norfloxacin. where sensitivity for Nalidixic acid and Cefixime was not done[10].

In our study, *Klebsiella* spp. showed 100% sensitivity to Amikacin, Nitrofurantoin and Norfloxacin where as 80% resistant to Ciprofloxacin and Cefixime but study done by Sharma A showed 100% sensitivity to Ciprofloxacin and Amikacin and 83.3% sensitivity to Ofloxacin and Nitrofurantoin[27]. Sensitivity of *Proteus* spp. was 100% to Nitrofurantoin, Amikacin and Azithromycin where as 100% resistant to Nalidixic acid, Cefixime and Ceftriazone in our study. This finding was comparable to the study done in one of the tertiary centers of Eastern Nepal where *Klebsiella* and *Proteus* spp. were 96.0% and 92.1% sensitive to Amikacin though the percentage of sensitivity to Nitrofurantoin was much lower 33.1%[28].

CONCLUSIONS

UTI in children is common and usually presents with non-specific features. *E. coli* still remains as the commonest

organism isolated in UTI and exhibiting the changing drug sensitivity pattern. It is advisable that pediatricians should be aware of the rising resistance and perform periodic monitoring of antibiotic sensitivity pattern of the bacterial isolates to provide effective treatment. Greater degrees of resistance were seen with Cefixime and Nalidixic acid. This appears to be due to over use and/or misuse of antibiotics.

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Review Article

Neoadjuvant Therapy for Down Staging of Locally Advanced Primary Unresectable Pancreatic Cancer for Radical Surgical Resection

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ABSTRACT

Pancreatic adenocarcinoma is one of the most aggressive and devastating human malignancy with extremely poor prognosis worldwide. Most of the patients present either with locally advanced or metastatic disease at the time of diagnosis. Unresectable locally advanced pancreatic cancer has an extremely poor prognosis and management of locally advanced pancreatic cancer (LAPC) remains controversial. However, there is little evidence available to support treatment options for locally advanced disease. Some studies suggest that locally advanced primary unresectable pancreatic cancer should be treated preoperatively with neoadjuvant therapy; although the optimal algorithm is still under discussion, systemic chemotherapy followed by chemoradiation is a deliberate approach. Although gemcitabine-based systemic chemotherapy with either 5-FU or gemcitabine-based chemoradiation regimens has been used till the date, newer regimens, including FOLFIRINOX, should be evaluated on protocol for its efficacy and toxicity. There is a consistent finding from mostly small and non-randomized studies that neoadjuvant therapy can induce resectability in up to 30%–40% of locally advanced pancreatic cancer patients. This review summarizes and evaluates neoadjuvant therapy strategies, various regimens in the neoadjuvant setting and options for locally advanced primary unresectable pancreatic cancer.

INTRODUCTION

Pancreatic adenocarcinoma is the fourth leading cause of cancer death in USA, with 45,220 new cases in 2013 and estimated 38,460 deaths[1]. Treatment of pancreatic cancer (PC) has become multimodal with chemotherapy, radiation and surgical resection in the hope of long term survival. The only chance for cure and long term survival is microscopic negative margins with R0 surgical resection[2]. However, only 10% to 20 % of patients with pancreatic cancer have resectable disease at the time of diagnosis[1,2,3]. Approximately 30 to 40 percent have locally advanced tumor and another 40 percent will have metastatic disease at the time of diagnosis[3] and thus palliative chemotherapy remains the only option for most of these patients[4]. The overall five years survival probability is less than 5% for all stages combined[1-3,5-7]. Even with advancement in surgical techniques most of the patients undergoing complete surgical resection experience a recurrence[8]. Several autopsy studies suggest that 8%–15% of PC patients die with locally advanced disease and without metastatic spread[9].

Many studies suggest that neoadjuvant therapy has shown

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promising role in down staging of locally advanced primary unresectable pancreatic cancer[10], including other GI malignancies, by shrinking down the visible tumor and removing the cancer cells that cannot be seen with the naked eyes, thus improving resectability and achieving R0 resection[11-13].

Clinical and radiological staging plays most important role to determine if the pancreatic cancer is resectable, borderline resectable or locally advanced. Multiple imaging modalities are involved, including computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography with computed tomography (PET/CT), and endoscopic ultrasound (EUS) for the diagnosis and staging of pancreatic cancer. In the absence of metastatic disease, assessment of vascular invasion is a key aspect in the evaluation of resectability for pancreatic cancer, thus the diagnosis of borderline resectable/ locally advanced primary unresectable pancreatic cancer requires dedicated, high-quality imaging implemented by pancreatic protocol computerized tomography (CT). Before the start of therapeutic interventions, a histological confirmation of pancreatic adenocarcinoma done by EUS-guided fine-needle aspiration (FNA) biopsy is mandatory, the additional use of staging laparoscopy to exclude peritoneal metastasis or patient with risk for disseminated diseases like in locally advanced primary unresectable pancreatic cancer has been suggested by institutions prior to surgery or chemoradiation[15]. This review summarizes neoadjuvant therapy strategies and options for locally advanced primary unresectable pancreatic cancer by reviewing relevant recent literatures.

Definition of locally advanced and borderline resectable pancreatic cancer

Locally advanced disease is considered as the presence of tumor abutment to the celiac trunk/superior mesenteric artery or the involvement or thrombosis of superior mesenteric vein/ portal vein axis greater than 180 degrees[14,15], and categories such as borderline resectable tumors are defined as "those with tumor abutment of <180 degrees (<50%) of the superior mesenteric artery or celiac axis, short segment abutment or encasement of the common hepatic artery typically at the gastroduodenal artery origin superior mesenteric vein/portal vein abutment with impingement and narrowing or segmental venous occlusion with sufficient venous flow above and below the occlusion to allow an option for venous reconstruction"[15,16].

Treatment mode before and after surgery for pancreatic cancer

Due to described overall prognosis for all patients with pancreatic cancer, two ways of treatment has been in use, one prior to surgery (Neoadjuvant therapy) to increase the respectability and proportion of R0 resections and another used following surgical resection (adjuvant therapy) to improve overall survival and locoregional control[17]. The use of adjuvant therapy has been broadly studied but use of neoadjuvant therapy prior to surgery still remains highly controversial. Pancreatic cancer has been relatively resistant to all systemic therapies including chemotherapy and hormonal therapy[18,19]. The poor prognosis of pancreatic cancer is caused by the tumor's characteristic abundant desmoplastic stroma that plays a critical role in tumor growth, invasion, metastasis, and chemoresistance[20].

Biomarkers in the diagnosis, prognosis and management of pancreatic cancer

The role of biomarkers in the management of cancer is very important. Although effective therapies will undoubtedly change the natural history of the disease, effective biomarkers are a promising tool that will likely have a positive impact and will undoubtedly have an important role in the management of patients with pancreatic adenocarcinoma in the future. As evidence of a growing biomarker literature, more than 2,000 biomarker studies already appear in the literature[21]. Serum CA 19-9 is the only FDA approved biomarker recommended for use in the routine management of pancreatic adenocarcinoma. CEA and CA125 are serum antigens that have been investigated as biomarkers in pancreatic adenocarcinoma, but have proved to be less informative than CA 19-9. CA 19-9 has never been shown to be effective as a screening test for pancreatic adenocarcinoma[22]. CA 19-9 serum levels have a sensitivity and specificity of 79-81% and 82-90% respectively for the diagnosis of pancreatic cancer in symptomatic patients[23]. The sensitivity and specificity of CA 19-9 improves substantially in patients with pancreatobiliary disease, and can be manipulated by adjusting the cutoff value[24,25]. In patients with localized pancreatic cancer, preoperative CA 19-9 has limited value as a prognostic marker. Postoperative CA 19-9 levels provide improved prognostic information in patients with localized disease, as compared to preoperative levels[26,27]. Pre-operatively, patients with normal CA 19-9 serum levels (<37 U/ml) have a prolonged median survival (32–36 months) compared to patients with elevated CA 19-9 serum levels (>37 U/ml) (12–15 months). A CA 19-9 serum level of <100 U/ml implies likely resectable disease whereas levels >100 U/ml may suggest unresectablity or metastatic disease[28].

Rationales for neoadjuvant therapy

The rationale behind neoadjuvant therapy is developed from adjuvant therapy. With the suggesting fact that adjuvant therapy is beneficial after surgical resection, different trials and study carried out for adjuvant therapy in last two decades has not showed any significant differences in median survival among different study group even with use of different regimens of adjuvant therapy (Table 1). Correlation of these different phase III trials on adjuvant therapy further shows that the adjuvant approach with these regimens has reached to steady plateau phase. In fact, up to 25% of patients have a complicated course after surgery and are unable to receive the planned adjuvant treatment in time[30]. In patients receiving adjuvant therapy after surgical resection, pancreatic cancer exhibits a prominent tendency to recur locally and to metastasize after a brief median time interval of about 13.4 months from surgery, and risk of recurrent disease can be as high as 74.3%[36]. Early relapse after curative surgery may be explained by the presence of micro-metastases or minimal residual disease not detectable at the time of surgery, or by the spread of cancer that detach from the primary cancer and survive in distant organs due to surgical

manipulation of the tumor[41]. Undoubtedly, several other new drugs and regimens are under study in hope for better median survival after surgical resection in near future. Laterally among experts, their increase in interest of discussion about the theoretical benefits of neoadjuvant therapy prior to surgery and several rationales have been proposed to advocate use of chemotherapy and/or chemoradiation before curative resection, such as:

1. Determine sensitivity to treatment while the tumor remains *in situ*.
2. Complete a full course of treatment, which is more likely to occur in the preoperative than in the postoperative setting.
3. The initiation of adjuvant therapy is delayed due to inadequate recovery from surgery, which delays the control of micrometastasis tumor, and thus, there is need of new preoperative approach of neoadjuvant therapy for early treatment of micrometastasis disease.
4. Potentially curative treatment to patients with primary unresectable locally advanced or borderline disease.
5. Neoadjuvant therapies could potentially downstage locally advanced primary unresectable pancreatic cancer, improving resectability and achieving R0 resection.

Preoperative neoadjuvant therapy for locally advanced primary unresectable pancreatic cancer

Neoadjuvant therapy prior to surgery have shown similar resection frequencies and survival rate to that of patients with primary resected tumors treated with adjuvant therapy, showing no advantage of neoadjuvant therapy for patients with recetable tumors, However in patients with locally advanced primary unresectable tumors and borderline resectable tumors, one third of tumors were resected after neoadjuvant therapy with survival comparable with those patients with initially resectable tumors[2,42].

The California Cancer Surveillance Program for Los Angeles County retrospectively identified 458 patients with nonmetastatic pancreatic cancer who underwent definitive pancreatic resection and received systemic chemotherapy. Using the data of these patients, the neoadjuvant and the adjuvant therapy setting were compared. Out of 458 patients, 39 (8.5%) received neoadjuvant therapy, and 419 (91.5%) received adjuvant therapy. Patients who received neoadjuvant therapy presented significantly lower rate of lymph node positivity (45%) and improved overall survival 34 months compared with adjuvant group of patients 65% and 19 months respectively. This analysis showed a clear benefit for the patients treated with neoadjuvant therapy[43].

Chuong M *et al.* evaluated the rates of pathological complete response in 35 patients after neoadjuvant induction gemcitabine based chemotherapy followed by stereotactic body radiation therapy (SBRT) in borderline resectable pancreatic cancer, This study suggested a survival benefit based on pathological response seen with neoadjuvant gemcitabine based therapy with subsequent stereotactic body radiation therapy[44].

Some studies have demonstrated the potential of neoadjuvant therapy to downstage locally advanced primary unresectable pancreatic cancer. Table 2 lists a summary of neoadjuvant trials for locally advanced primary unresectable pancreatic cancer.

In a meta-analysis by Gillen S *et al.* that compared 111 studies involving 4394 patients in the period from 1980 to 2009 retrospectively and prospectively, no significant difference with respect to the overall survival was found. Considered were neoadjuvant radiochemotherapy, radiotherapy, or chemotherapy, followed by re-staging, and surgical exploration or resection. The group with resectable findings following treated with resection, showed similar survival rates compared to the resected patients who received adjuvant therapy. So no clearly advantage referring to neoadjuvant therapy was found. However, it was shown that one third of patients with initial locally advanced findings had an analogical survival rate after neoadjuvant therapy and resection in comparison to patients with initial resectable tumors[42].

In another meta-analysis which analyzed 14 phase II clinical trials including 536 patients. The patients were divided into two groups: patients with initially resectable tumors (Group A), and patients with borderline/unresectable tumors (Group B). The meta-analysis concluded neoadjuvant treatment appears to have some activity in patients with borderline resectable and unresectable pancreatic adenocarcinoma. Nearly one-third of tumors initially deemed marginal for operative intervention were ultimately able to be resected following treatment. Until more effective targeted chemotherapeutics are developed, the only groups of patients with pancreatic cancer that may benefit from neoadjuvant treatment are those with locally advanced disease[3].

To investigate further on issue the first multicenter randomized trial started to recruit patients with pancreatic cancer to compare neoadjuvant gemcitabine/cisplatin based chemoradiation plus resection with surgery alone for patients with resectable and borderline resectable pancreatic cancer[56].

It is not clear why other phase III randomized trials for neoadjuvant therapy for the treatment of pancreatic cancer have not been initiated. Perhaps the recruitment of a sufficient number of patients is difficult.

Thus, In the future, phase III trials have to be carried out using already established protocols comparing neoadjuvant therapy followed by exploration and possibly resection, with immediate exploration and resection. Certainly, only randomized controlled trials can provide any level of evidence and can prove potential advantages or disadvantages of neoadjuvant therapy for borderline resectable and locally advanced primary unresectable pancreatic cancer.

New approaches and future directions

During last few years some novel agents have been developed, and better understanding of biological mechanisms of disease

have made possible the identification and validation of new targeted agents in pancreatic cancer. A variety of new agents, including monoclonal antibodies and tyrosine kinase inhibitors, are currently under extensive clinical investigation. The different targeted agents that have been developed in treatment of pancreatic cancer include epidermal growth factor receptor (EGFR) inhibitors, vascular endothelial growth factor (VEGF) inhibitors, faenesyle transferase inhibitors and matrix metalloproteinase inhibitors.

So far, little progress has been made in the field of targeted agents in the treatment of pancreatic adenocarcinoma, although several agents are currently under investigation. More clinical trials along with the encouragement of patients to participate in these studies are required in order to produce more definite results for this aggressive and devastating disease.

Up to date, erlotinib remains the only biological agent approved for the treatment of borderline resectable and locally advanced primary unresectable pancreatic cancer. More recently, the combination of 5-fluorouracil, leucovorin, irinotecan, and oxaliplatin (FOLFIRINOX) proved to be superior to single agent gemcitabine, and although associated with higher toxicity, it has been accepted as the preferred first line treatment in selected fit patients[57]. In a retrospective study of neoadjuvant FOLFIRINOX in unresectable or borderline-resectable locally advanced pancreatic adenocarcinoma by Hosein PJ *et al.* concluded that FOLFIRINOX followed by chemoradiotherapy is feasible as neoadjuvant therapy in patients with unresectable locally advanced pancreatic cancer, with promising R0 resection rate of 44%[58].

Hibi T *et al*. evaluated the safety profile and efficacy of a combination regimen of triple chemotherapy with 5-FU, mitomycin C, cisplatin and heparin in addition to a 40 Gy dose of radiation therapy in 24 borderline resectable pancreatic cancer patients to achieve an increase disease free and overall survival. There were significant grade 3-4 hematological toxicities seen although there were no severe gastrointestinal toxicities seen. The 5-year overall survival and disease free survival rates after surgery were 52.6% and 36.3% respectively[59].

Similarly, Moretto R *et al.* evaluated the toxicity and the activity of the FOLFIRI regimen as first-line or second-line chemotherapy in patients with pancreatic or biliary tract tumors and concluded FOLFIRI is feasible and well tolerated in patients with pancreatic or biliary tract tumors; it has a good activity in first line and mostly in patients with pancreatic cancer[60].

Thus, there is an imperative need for molecularly targeted agents with better tolerability, availability for chronic treatment and better selectivity to conventional chemotherapy that will achieve long-term disease control while maintaining an acceptable toxicity profile.

CONCLUSIONS

Pancreatic adenocarcinoma is one of the most aggressive human malignancies. Till the date adjuvant therapy has been accepted widely after surgery. Most of the patients with pancreatic cancer present late and with advance disease and thus they are not suitable for surgery, which has led decrease in overall survival rate of patients. In adjuvant setting 5-FU and gemcetabine based chemotherapy can be considered standard for both locally advanced and advanced pancreatic cancer.

Neoadjuvant therapy prior to surgery have shown similar resection frequencies and survival rate to that of patients with primary resected tumors treated with adjuvant therapy, showing no advantage of neoadjuvant therapy for patients with resectable tumors. However different studies have shown benefit of neoadjuvant therapy in downstaging of tumor in patient with locally advanced primary unresectable and borderline resectable tumors. Studies have demonstrated down staging of tumor after treatment with neoadjuvant chemoradiotherapy, although the use of radiation therapy with or without chemotherapy in both adjuvant and neoadjuvant therapy remains controversial. Despite intensive clinical and pre-clinical research over the last few years, the combination of the anti-metabolite drug gemcitabine with the targeted agent erlotinib, is considered standard of care in the treatment of these patients, with only minimal or modest efficacy. Therefore, novel therapeutic approaches are currently under clinical investigation in an attempt to produce more definite results for this fatal disease. The combination of 5-fluorouracil, leucovorin, irinotecan and oxaliplatin (FOLFIRINOX) proved to be superior to single agent gemcitabine, and although associated with higher toxicity, it has been accepted as the preferred first line treatment in selected fit patients.

The facts above show the potential role of neoadjuvant therapy in downstaging of locally advanced pancreatic cancer. Therefore it is possible to reduce the incidence of margin positivity and to improve the local control in selected patients with pancreatic cancer, and thus a survival benefit will be achieved.

Ultimately, multicenter prospective randomized trials comparing the adjuvant and neoadjuvant approaches must be performed to determine the ideal treatment strategy for pancreatic cancer patients.

Table 1: Adjuvant Therapy phase III clinical trials in pancreatic cancer.

Study	Year	No. of Patients	Regimen	Median Survival(MOS)
GISTG[29]	1985	49	CRT(5-FU bolus)	20
			Surgery alone	11
EORTC[30,31]	1999	218	CRT (5-FU continuous infusion)	17.1
			Surgery alone	12.6
ESPAC-1[32,33]	2001	541	CT(5-FU bolus)	19.5 (CT)
			CRT(5-FU bolus)	14 (non CT)
			CRT+CT	15.1 (CRT)
			Surgery alone	16.1 (non CRT)
RTOG 97-04[34,35]	2008	451	5- FU+CRT	16.9
			Gemcitabine+CRT	20.5
CONKO-001[37,38]	2007	179	Gemcitabine	22.2
		175	Observation	20.2
JSG[39]	2009	58	Gemcitabine	22.3
		60	Observation	18.4
ESPAC-3[40]	2010	1089	5-FU	23
			Gemcitabine	23.6

GISTG- Gastrointestinal Tumor Study Group, EORTC- European organization for Research and Treatment of cancer, ESPAC-European Study Group for Pancreatic Cancer, RTOG 97-04- Radiation Therapy Oncology Group, JSG- Japanese Study Group, CRT- Chemoradiotherapy, CT- Chemotherapy, 5-Fu- 5- Fluorouracil.

Table 2: Neoadjuvant therapy for locally advanced primary unresectable pancreatic cancer

Study	Year	Number		Regimen	Resection Rate	MOS in months	MOS / res. in months
Kamthan *et al*[45]	1997	35		EBRT+5FU+S+CP	5/35	15	31
Sandy *et al*[46]	2000	159	68 Neoadjuvant	EBRT+5FU+S+P	20/68	23.6	32.3
			91 Surgery	-	-	14	-
Aristu *et al*[47]	2003	47		EBRT +5FU±P;CP+5FU;D+Gem	9/47	11	23
White *et al*[48]	2004	88		EBRT +5FU+CP+MMC	18/88	-	23
Pipas *et al.*[49]	2005	24		EBRT +Gem+D	17/24	14	-
Evans *et al*[50]	2008	86		EBRT +Gem	64/86	22.7	34
Varadhachary *et al*[51]	2008	90		CP+Gem+ EBRT +Gem	52/79	17.4	31
Tinkl *et al*[52]	2009	120		EBRT +5FU+MMC or EBRT +Gem+CP	38/120	25	
McClaine RJ *et al*[53]	2010	26		Gem. based CT	12/26	15.5	23.3
Estrella JS *et al*[54]	2011	300	240 Neoadjuvant	Fluoropyrimidine(CRT);Gem(CRT);systemic chemo+ Fluoropyrimidine(CRT); systemic chemo+ Gem(CRT); CT	R 0 - 213/240 R1-26/240 R2-0		33.5
			60 Surgery				26.5
Wang J et al[55]	2012	225		Fluoropyrimidine(CRT);Gem(CRT);systemic chemo+ Fluoropyrimidine(CRT); systemic chemo+ Gem(CRT); CT	R 0 - 198/225 R1-27/225 R2-0		32.2

EBRT- External Beam Radiation Therapy, 5FU- 5-Fluorouracil, S- Streptozotocin, CP- Cisplatin' P- Paclitaxel, D- Docetaxel, Gem- Gemcitabine, MMC- Mitomycin, CT-Chemotherapy, Fluoropyrimidine(CRT)- Fluropyramidine based chemoradition, Gem(CRT)- Gemcitabine based chemoradition, MOS- Median Overall Survival, MOS/res-Median Overall Survival after resection.

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Case Report

Type 2 Diabetes Mellitus in a Nepalese Child: A Case Report

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Key words:
Type-2 diabetes mellitus,
Obese,
Fasting blood sugar,
Nepalese,
Child.

ABSTRACT

Objectives: Type-2 diabetes mellitus initially said to be an adult disease is now reported in children and adolescents in the developed countries because of increased incidence of obesity and sedentary habits associated with westernization and lifestyle changes. There are few reports from Asia but not yet reported from Nepal.

Methods: A 14 year old overweight male with a BMI of 37 kg/m^2 and no family history of DM, presented with weight gain and lethargy. Fasting blood sugar was 229 mg/dl. Urinalysis had +2 of glucose, no ketones. HbA1c of 8.3%, fasting c-peptide of 1.03 mg/dl and postprandial c-peptide of 2.34mg/dl. He was managed with diet and exercise along with metformin 500mg twice daily.

Results: The patient's fasting blood sugar came down to 100 mg/dl, postprandial to 156 mg/dl, HbA1c to 5.6% after 3 months and lost weight by 2 kilograms.

Conclusions: Type-2 diabetes mellitus is being reported in an obese Nepalese child having high socio-economic status. Routine screening of overweight children for DM is recommended.

INTRODUCTION

Before 1980, Type-2 diabetes mellitus (T2DM) was rarely reported, accounting for <2% of all cases of pediatric DM, however a recent increase in incidence in children and adolescents has been documented in several populations.

Recent data from the USA shows rise of pediatric diabetes is 4.9% for Caucasians, 46.1% for Hispanics, 57.8% for African Americans, 69.7% for Asian/Pacific Islanders, and 86.2% for American Indians[1]. In Japan up to 80% of all new cases of pediatric DM are T2DM[2]. Given the rising rates, it is believed that T2DM will be the predominant form of DM among children from a variety of ethnic backgrounds by 2015[3]. In Nepal, T2DM in children is not reported yet.

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CASE REPORT

Nabin Gurung, 14 year old boy from Lekhnath, Kaski, son of retired army officer, presented to Diabetes thyroid and endocrinology care center in Pokhara, Nepal with the complaints of gaining weight and lethargy.

On examination: BP 100/70 mmHg, pulse 92/min, height 149 cm, weight 80 Kg, BMI 37 Kg/m^2.

Laboratory tests: Fasting blood sugar was 229 mg/dl. Urinalysis had +2 of glucose, no ketones. HbA1c of 8.3%, fasting c-peptide of 1.03 mg/dl and postprandial c-peptide of 2.34 mg/dl, FT_3 2.29 pg/ml, FT_4 0.88 ng/dl, TSH 4.94 mIu/L.

Patient was diagnosed as type-2 diabetes and was started with metformin 500mg twice daily and diet and exercise therapy.

Patient was followed up after 3 months, blood sugar came down to fasting of 86 mg/dl, postprandial of 156 mg/dl, HbA1c of 5.1%. There was 1 Kg reduction in his weight but, no significant BMI reduction.

Patient was on regular follow up for 6 months. Blood sugar and HbA1c level was with in satisfactory level.

This boy was confirmed as type-2 diabetes mellitus.

RESULTS

Patient was followed up after 3 months, blood sugar came down to fasting of 86 mg/dl, postprandial of 156 mg/dl, HbA1c of 5.1%. There was 1 Kg reduction in his weight.

Patient was on regular follow up for 6 months. Blood sugar and HbA1c level was with in satisfactory level.

DISCUSSION

Type 2 diabetes mellitus is a relatively new diagnosis in children in the developing countries and seen because of westernization and life style changes. There is an emerging risk associated with T2DM in overweight children[4]. Our patient is a 14 year old overweight male with a BMI of 37 Kg/m^2, and is from high socioeconomic class with sedentary life style and inappropriate eating habits.

The clinical presentation can vary from being asymptomatic to very ill with or without the classical symptoms of polyuria, polydypsia, weight loss, hyperglycemia and glycosuria with or without ketosis[5]. Our patient was asymptomatic.

The preferred screening test is a fasting plasma glucose test, which rarely misses children with asymptomatic or silent T2DM. However it may miss individuals with impaired glucose tolerance and early beta-cell dysfunction[5]. Markers of T1DM namely glutamic acid decarboxylase 65 (GAD65), islet cell antigen 512 (ICA512) and IAA (Insulin autoantibody) may be positive in up to one third of the cases of adolescent T2DM but usually absent in T2DM. The GAD65 and insulin antibody were absent in our patient. Type 2 diabetes mellitus is a chronic and progressive condition if left untreated but has well established treatments which can delay or prevent the consequences of the condition such as neuropathy, blindness or any other blood sugar complications, though the underlying tendency to hyperglycemia may still remain.

Treatment of T2DM in the pediatric population remains challenging because of the difficulty of successfully employing lifestyle changes. The most successful intervention combines dietary changes, exercise, and behavioral modification. Efforts should focus on eliminating high-calorie beverages such as juices, sodas, and energy drinks[5]. The patient has done well on diet and exercise and on metformin.

The only pharmaceutical agents approved for treating T2DM in the pediatric population are metformin and insulin. Metformin can induce mild weight loss in the pediatric population[6].

CONCLUSIONS

Only few cases of Type-2 diabetes are reported from the underdeveloped and the developing world. A high index of suspicion is needed in an overweight child with hyperglycemia and with high socio-economic status. Routine screening of overweight children is recommended.

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