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Editorial

- Physician Burnout- An Unaddressed Issue 01
  Islam MT

Original Article

- Surgical Outcome of Extradural Hematoma in Relation to Preoperative Computed Tomographic Findings 03
  Howlader MRA, Sarker AC, Das S, Rahman MM
- Outcome of Bilateral Orchidectomy Alone in Comparison with Orchidectomy Plus Bicalutamide in the Management of Patient with Bony Metastatic Carcinoma of Prostate 08
  Kabir ASMH, Salam MA, HUDA MN, Mostofa KMI, Alam MO
- Evaluation of Distally Based Superficial Sural Island Flap for Reconstruction of Soft Tissue Defects on Distal Third of Leg, Ankle, Heel and Foot 14
  Kamal AHM, Islam MT
- Effects of Obesity on Peak Expiratory Flow Rate (PEFR) and Forced Vital Capacity (FVC) Among Adult Bangladeshi Medical Students: A Cross-Sectional Study 19
  Sardar MMR, Pervin F, Jolly SS, Das JK, Ali MS
- Bacteriological Profile of Wound Swabs and Their Antimicrobial Susceptibility Pattern at a Tertiary Level Hospital in Bangladesh 24
  Ghosh S, Islam MDU, Pervin S, Biswas RK , Rahman SMM, Alom SMT

Review Article

- Stem Cell Therapy for Ischemic Heart Failure 30
  Kamal MM, Rina MNN

Case Report

- Congenital Hypothyroidism: A Case Report of a 26 Years Old Female 38
  Biswas S, Khanom T, Huda SK

Instructions for Author 42

An Official Organ of Teachers' Association, Khulna Medical College

Editorial

Physician Burnout- An Unaddressed Issue

Physician burnout is a long term stress reaction which is characterized by emotional exhaustion, depersonalization (i.e. lack of empathy for or negative attitudes toward patients) and feeling of decreased personal achievement. It is an epidemic in the U.S. health care system, with nearly 63% of physicians reporting signs of burnout such as emotional exhaustion and depersonalization at least once per week.[1] The COVID-19 pandemic has presented the physicians along with other health care work force with unprecedented challenges leading to psychosocial trauma and burnout.

In Bangladesh, there is no exact statistics although a rising number of physicians are being burnout during their working period. Excessive work load is the main contributor of physician burn out in Bangladesh. According to World health organization (WHO), the current doctor-patient ratio in Bangladesh is only 5.26 per 10,000 population, that places the Bangladesh at the 2nd position from the bottom, among the South Asian countries.[2] In government setup a physician is compelled to do more than 6 physicians work. In addition to care of patients a physician has many academic activities like teaching of medical students and trainees, research activities, attending scientific seminar, conference etc. This creates a huge pressure on the physicians. Physicians have also to manage a large number of attendants, media and political leaders and social workers and sometimes have to face allegations of wrong treatment by them. These excess and unnecessary workloads are the additive factors for physicians burn out in Bangladesh.

In Bangladesh, most of the physicians have to do private practice for long time after their services at govt. hospital. Interns and postgraduate trainee physicians also have long working hours along with their educational activities. This long working hours is important factor of physicians burn out. Specialty choice, frequent call duties (night call or weekend call), comprehensive documentation in electronic medical records, time spent at home for residual work of hospital which disrupts the family are the other important factors for physicians burn out.

Working environment largely contributes to physicians burn out. Most studies suggest that physicians find the loss of autonomy at work, decreased control over the work environment, insufficient use of time for patients due to other administrative activities and loss of support from colleagues. These are the important factors. Inter-cadre disparity, lack of security at physicians working places, fear of being assault by patient's party and arrest by law enforcing agencies, working with less logistic supports are important contributory factors for physicians burnout in Bangladesh. Organizational factors such as negative leadership behaviors, excess work load expectations, insufficient or no rewards, deprivation of due promotion, excess monitoring by the authority, limited interpersonal collaboration, and limited opportunities for improvement with updated knowledge and lack of social support for physicians may also influence burnout.

Personal characteristics associated with burnout include sleep deprivation, over commitment, perfectionism, idealism and work–life imbalance, and an inadequate support from family. Burnout was once thought to be a late-career phenomenon, but the recent studies suggest that younger physicians have nearly twice the risk of stress compared with older colleagues and that onset may be as early as residency training.[3]

Physician burnout can lead to severe personal and professional consequences if left unaddressed. Physicians with burnout can complain of feeling tired, exhausted, fatigued, inattentive, and irritated. Burnout can also put a physician at increased risk of motor vehicle accidents and near-miss events, stroke and myocardial infarction. Psychologically, physician burnout might contribute to increased incidence of stress, disruptive behavior, mood disorders, and a noted correlation with depression. The presence of any of these conditions can severely impact a physician's well-being, disrupting their personal life and decreasing professional efficiency. There is increased incidence of alcohol or odd substances abuse/dependence, especially in surgeons. Most physicians do not acknowledge their symptoms or admit that they can be affected by burnout and refuse to seek help leading to a two-fold increased risk of suicidal ideation. Physicians are at an increased risk of suicide

(28–40 per 100,000) compared to the general population (12.3 per 100,000), especially among specialties which make up the "front-line of care" like emergency, primary, and preventive medicine. Perhaps the professional consequences of physician burnout can contribute to the failure of interpersonal relationships, increased medical errors, increased risk of malpractice, reduced patient satisfaction, and the quality of care and patient outcomes.[3] A physician suffering from burnout is less productive and may even quit the job at some point. Felling of unsafe at working places sometimes make the physicians to refuse treatment or transfer the patient.

Physician burnout is a worldwide significant problem in the medical profession. It has adverse impact on physician well-being, patient care, and the health care system. Doctors who keep working despite of burnout are more likely to have decreased work productivity, exhaustion, poor quality of care and wrong treatment when compared to their earlier careers. Although physician burn out is common, but it is reversible and preventable. Reducing the work overload and clerical job, improving working environment, reducing the inter cadre disparity, ensuring the safety of the physicians at their working place can prevent the physicians burnout. Self-awareness among physicians can help the physicians recognize their vulnerability to burnout, and immediate measures can be taken to overcome and manage it. Institutional psychiatric team can contribute a lot to recognize it earlier. Physicians should reduce their unnecessary workload. They should limit private practice. Combined efforts of physicians, authorities of working place, government and social workers are needed to prevent physicians burn out and ensure a good health care system. It is not possible to prevent the physicians burnout in a day. Although longer time is needed to solve this problem, we should start from today. Otherwise our health care system will be badly affected in future.

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References

1. https://www.ama-assn.org/practice-management/physician-health/what-physician-burnout, updated on Feb 16, 2023.
2. Imdad Kish, Saif AZM. Five decades of growth in the healthcare system. The Daily Star. Last update on: Wed Jan 13, 2021 01:14 AM
3. Patel RS, Bachu R, Adikey A, Malik M, Shah M. Factors Related to Physician Burnout and Its Consequences: A Review. Behav Sci (Basel). 2018 Oct 25;8(11):98. doi: 10.3390/bs8110098. PMID: 30366419; PMCID: PMC6262585.

Original Article

Surgical Outcome of Extradural Hematoma in Relation to Preoperative Computed Tomographic Findings

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Abstract

Background: Extradural hematoma (EDH) is a unique form of traumatic brain injury. Extradural hematoma is a collection of blood between the skull and duramater due to bleeding from meningeal vessels is a common complication of head injury, often fatal if not treated in time. The incidence of EDH among traumatic brain injury patients has been reported to be in the range of 2.7 to 4%. CT was easily and widely used for confirming the diagnosis and location of the hematoma as well as for follow-up after the treatment period.

Aim of the study: To see surgical outcome of extradural hematoma patient in relation to preoperative computed tomographic (CT) findings.

Methods: This prospective study was conducted in the Department of Neurosurgery, Dhaka Medical College and Hospital during the period of January 2016 to December 2017. A total of 98 patients of both sex and any age with EDH who were selected purposively.

Results: Among the total 98 patients age range was 04- 55 years. Majority, 30 (30.60%) patients were from 21- 30 years of age. The mean age was found 25.24±12.2years. 78 (78.55 %) patients were male and 22 (22.44 %) patients were female. A male predominance was observed. It was observed that volume of hematoma (Mean ±SD=43.88±15.82 ml), thickness of hematoma (Mean ±SD=20.14±4.45mm) and Midline shift (Mean ±SD=5.82±2.33mm). Ventricular effacement was present in almost all cases (97.97%). Associated skull fracture was present in 46.92%. Total mortality was 3(3.06%).

Conclusion: Preoperative CT findings is most important prognostic factor of surgically treated EDH patient.

Keywords: Computed Tomographic, Extradural hematoma, GCS.

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Introduction

Extradural hematoma (EDH) is a unique form of traumatic brain injury (TBI). Extradural haematoma (EDH) is a collection of blood between the skull and duramater due to bleeding from meningeal vessels is a common complication of head injury, often fatal if not treated in time1. The incidence of EDH among traumatic brain injury (TBI) patients has been reported to be in the range of 2.7 to 4%.[2-6] The peak incidence of Extradural haematoma (EDH) is in the second decade of life and mean age of patient with EDH in different series is between 20 and 30 years of age[7,8]. Extradural haematoma is very rare in extremes of ages as after 60 years dura is adherent to overlying bone and even in children below 2 years as plasticity of immature calvarium[9,3].

Head injury is a major health problem. The incidence of head injury in India per 100,000 populations per year ranges from 56-430. The overall incidence in US is around 200 per 100,000 per year[10]. Traumatic extradural hematoma (EDH) has been recognized for more than 140

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years. 100 years ago, the mortality rate of EDH was as much as 86%. The overall mortality rate was 14.9% Khaled et al[3] showed patient with GCS of 3 to 5 had a mortality of 36% and patients with GCS of 6 to 8 had a mortality of only 9%.

Until the late 1970s, when angiography was used for diagnosis [the era before computed tomography (CT)], the mortality rate was 30% or high which has reduced now by introduction of CT and proper resuscitative measures and timely surgical intervention to 5 to 12%[11]. CT was easily and widely used for confirming the diagnosis and location of the hematoma as well as for follow-up after the treatment period. It is readily available, relatively inexpensive, and fast. The location of hematoma, ventricular effacement and midline shift was also noted. The presence of any other intradural abnormality was also noted. Data on the patency of basal cisterns, fractures, and hematoma density was also recorded. The "Classic" CT appearance was seen in 84% of the cases and consists of a hyper-dense, biconvex (lenticular) mass adjacent to the skull.[2,6]

Materials and Methods

This prospective study was conducted in the Department of Neurosurgery, Dhaka Medical College and Hospital (DMCH), during the period of January 2016 to December 2017. A total of 98 patients of both sex and any age with EDH who were selected purposively as inclusion and exclusion criteria. Preoperative computed tomography (CT) scan of brain was obtained for all patients where hyper-dense lentiform lesion under skull was identified as a case of extradural hematoma (EDH). After confirming diagnosis rapid thorough general and neurological examination was done and vital signs including GCS score, pupil status, BP, heart rate, O2 saturation etc. were assessed and documented. CT scan finding including site of hematoma, thickness of hematoma, any midline shifting, underlying brain injury, overlying skull fracture also was assessed and documented. Then rapid resuscitation was done and patient was taken to OT for surgical intervention as early as possible in the form of craniectomy or craniotomy with evacuation of hematoma on the basis of the location of hematoma. Post operatively patient was kept in intensive care unit or post-operative ward. Patient follow-up was carried out for a total of 1 month post-operatively. Follow-up of the patients was done on indoor basis up to discharge and on OPD at 1 month. During follow up the patients were assessed using the post-operative GCS, check CT and Glasgow Outcome Scale (GOS) graded with a five-point score. Statistical analyses were carried out by using the Statistical Package for Social Sciences version 22.0 for Windows (SPSS Inc., IBM and New York, USA). Prior to commencement of this study, the "Research Review Committee" & the "Ethical Committee" of DMCH, Dhaka, approved the research protocol.

- **Inclusion Criteria**
  - o Extradural hematoma patients who were admitted intoDMCH of any age and sex.
  - o Extradural hematoma patients who were treated surgically.
- **Exclusion Criteria**
  - o Posterior fossa extradural hematoma patients
  - o Extradural hematoma patient treated conservatively

Results

In this study, 98 patients were included; they were divided into 6 age groups. Age range was 04-55 years. Majority, 30 (30.60%) patients were from 21-30 years of age. The mean age was found 25.24±12.2years (Table I). Among the 98 patients majority, 78 (78.55 %) were male and 22 (22.44 %) patients were female. A male predominance was observed. Majority had a history of motor vehicle accident 44 (44.90 %), 29 (29.60 %) were suffering from assault, 20 (20.40%) patients were fallen from height and other 04 (04.08%) patients had history of fall of heavy wt. overhead (Table II). Among the 98 patients, 82 (83.67%) had vomiting, 72(73.46%) patients had presented with loss of consciousness or altered level of consciousness. 60 (61.22%) patients had headache (Table Ill). Preoperative GCS 14-15 were found in 40 (40.81%) cases, GCS 9-13 were found in 39 (39.79%) cases and GCS 3-8 were found in 19 (19.38%) cases (Table IV). It was observed that majority 25 (25.50%) patients were had parietal lobe involvement. It was observed that volume of hematoma (Mean ±SD=43.88±15.82 ml), thickness of hematoma (Mean ±SD=20.14±4.45mm) and Midline shift (Mean ±SD=5.82±2.33mm) (Table VI). 92 (92.0 %) patients had underwent Craniotomy. Post-operative GCS 14-15 were found in 44 (44.90%) cases in 1st POD, 61 (63.60%) cases in 3rd POD and 85 (88.50%) during discharge. Hospital stay of the study patients, it was observed that majority of patients 78(79.59%) stayed in hospital for 5-8 days. Total mortality was 3(3.06%).

Table I: Distribution of the study patients by age (n=98).

Age in years	Frequency (n)	Percentage (%)
≤10	18	18.36
11-20	24	24.48
21-30	30	30.60
31-40	16	16.36
41-50	8	8.16
51-60	2	2.04
Total	98	100.0
Mean ±SD 25.24±12.2 Min-Max(04-55)		

Table II: Distribution of the study patients by mode of injury (n=98)

Mode of injury	Frequency (n)	Percentage (%)
Motor vehicle accident	44	44.90
Assault	29	29.60
Fall from height	20	20.40
Fall of heavy wt. over head	4	4.08
Unknown	1	1.01
Total	98	100.0

Table III: Distribution of the study patients by clinical presentation (n=98)

Clinical presentation	Frequency (n)	Percentage (%)
Headache	60	61.22
Loss of consciousness/ Altered level of consciousness	72	73.46
Lucid interval	19	19.38
Vomiting	82	83.67
Convulsion	3	3.06

Table IV: Distribution of the study patients by preoperative GCS (n=98)

Preoperative GCS	Frequency of GCS score (n=98)		Mean ±SD	Median
	N	%		
3-8	19	19.38		
9-13	39	39.79	11.53±3.4	12
14-15	40	40.81	7	
Total	98	100.0		

Table V: Distribution of the study patients by location of hematoma (n=98)

Location of hematoma	Frequency (n)	Percentage (%)
Frontal	23	23.46
Parietal	25	25.50
Temporal	5	5.10
Occipital	4	4.08
Temporo-parietal	24	24.48
Fronto-parietal	13	13.26
Parieto-occipital	4	4.08
Total	98	100.0

Table VI: Distribution of the study patients CT scan finding (n=98)

CT scan finding	Frequency (n)	Percentage (%)	Mean ±SD
Volume of hematoma(ml)			
≤30	11	11.22	43.88±15.82
31-60	79	82.65	
90-120	4	4.08	
61-90	4	4.08	
Thickness of hematoma(mm)			
0-10	0	0.0	20.14±4.45
11-20	68	71.42	
21-30	26	26.52	
31-40	4	4.08	
Midline shift(mm)			
0-5	22	22.44	5.82±2.33
6-10	43	43.86	
11-15	11	11.22	
16-20	22	22.44	
Ventricular effacement			
present	97	98.97	
absent	1	1.01	
Skull fracture			
present	46	46.92	
absent	52	53.08	

Discussion

It was observed that the incidence of EDH is highest (30.60%) in the third decade of life (21 to 30 years), followed by 2nd decade of life (11-20years) with a mean age of 25.24±12.2 years and range from 4 to 55 years which is similarly observed by Khaled et al[3]. Emejulu et al9 observed the peak age incidence was 21 to 30 years (42%), with a mean age of 23 years. Aurangzeb et al[7] observed that greatest representation was found in the 21-30 years age groups with 17 patients (47.2%), closely followed by the 11-20 years age group with 7 patients (19.4%).

Majority, 76 (77.55 %) patients were male and 22 (22.44 %) patients were female. Male-female ratio was 3.45:1. A male predominance was observed which reflects male are more exposed to outside world. In one case series in Hong Kong Cheung et al[11] observed male predominance (78.7%). Similar observations regarding the male predominant were also observed by Aurangzeb et al[7], Cheung et al[11], Emejulu et a[l9], Husain et al[12], Khaled et al[3], and Soon et al[13].

In most of the cases the mode of injury was motor vehicle accident 44 (44.88 %) followed by assault 29 (29.58 %) and fall from height 20 (20.40%). Motor vehicle accident was the commonest cause of injury comparable with many other published series Aurangzeb et al[7]; Cheung et al[11]; Emejulu et al[9]; Gurer et al[14]; Khaled et al[3]; Moon et al[5].

Regarding clinical presentation, 82 (83.67%) patients had vomiting, 72 patients (73.46%) presented with altered level of consciousness or with loss of consciousness, 60 patients (61.22%) with headache, 3 patients (3.06%) with history of convulsion. Khaled et al15 observed features altered sensorium (61%), headache/vomiting (56%), seizure (13%). 42.84% patients was found during admission and 40.81% preoperatively within GCS 14-15, 40.81%, 39.78% within GCS 9-13 and 16.32%, 19.38% patients within GCS 3-8 during admission and preoperatively. Mean GCS was 11.83±3.3 and 11.53±3.47 during admission and preoperatively. Gerlach et al16 observed 61.5% patients within GCS 13-15, 15.4% within GCS 8-12 and 23% within GCS 3-8. Khan et al[17] observed presenting GCS in 50%cases within 14-15, 33.3% within 9-13 and, 16.7% within 3-8, which are almost consistent with the current study. According to the CT scan findings location of hematoma was 25.50% in parietal, 23.46% in frontal, 24.48% in temporoparietal, 13.26% in frontoparietal region and only 2% in posterior fossa. Hematoma location was parietal in 49%, frontal in 36%, temporal in 10% and occipital in only 5% observed by Gerlach et al[16]. In another study of 610 cases of EDH, temporo-parietal site was involved in 33.45 % (n = 204) followed by frontal region in 23.28 % (n = 142) and six patients (0.98%) had EDH in posterior fossa Khaled et al[3]. Volume of hematoma (>30 ml) in 88 (89.92%) patients (Mean ±SD=43.88±15.82 ml), thickness of hematoma (Mean ±SD=20.14±4.45mm) and Midline shift (Mean ±SD=5.82±2.33mm). Ventricular effacement present in almost all cases (97.97%). Associated skull fractures were present in 46.92% patients but 62% observed by Khaled et al[15].

Majority, 92 (93.87%) patients had Craniotomy, 5 (5.10%) patients had Craniotomy and only one patients (1.0%) underwent decompressive craniectomy due to peroperative brain swelling that was almost similar with previous study, craniotomy 87%, craniectomy (8.5%) and burr hole trephination (4%) observed by Jeong et al[18]. 79.59% patients were stayed in hospital for 5 to 8 days with mean length 6.57±2.57 days maximum 15 days similar with previous study Bir et al[8] observed mean length of hospital stay 6.45 days and 10.4 days by Cheung et al[11].

Mortality was 3(3.06%), all of them belongs to GCS 3-8. No mortality was found between GCS 9-13 and 14-15. Gerlach et al16 observed 0% mortality. Cheung et al[11] observed that mortality was 4.4% in surgically treated EDH, 3.3% in GCS 3-8 and 1.1% in GCS 13-15. Emejulu et al[9] observed that total mortality was 14.9% among them 2.1% in awake patients, 2.1% in obtunded patients, 10.6% in comatose patients managed both surgically and conservatively. Khan et al[17] observed 3%, 12.5% and 11.5% mortality respectively. The study was limited by population selected from one hospital in Dhaka city in a short period so that the results of the study may not reflect the exact picture of the country.

Conclusion

The availability of computed tomography (CT) has increased the diagnosis of extradural haematoma. The mortality rate reduced now by introduction of CT. Preoperative CT findings is most important prognostic factor of surgically treated EDH patient.

Conflicts of interest : None

References

1. Uzkan U, Kemaloglu S, Ozates M, et al. Analyzing Extradural Haematomas: A retrospective clinical investigation. Dicle Tip Dergisi. 2007; 34(1):14-9.
2. Green MS. Handbook of Neurosurgery. 8th ed. New York:Thieme. 2016.
3. Khaled CN, Raihan MZ, Chowdhury FH, et al. Surgical management of traumatic extradural haematoma: Experiences with 610 patients and prospective analyses. Indian Journal of Neurotrauma. 2008; 5(2):75-9.
4. Kang J, Hong S, Hu C, et al. Clinical Analysis of Delayed Surgical Epidural Hematoma. Korean J Neurotrauma. 2015;11(2):112-17.
5. Moon RDC, Abdulla MAH, Kolias AG, et al. The impact of major trauma centre implementation on the pathways and outcome of traumatic intracranial extradural haematoma in a regional centre. British Journal of Neurosurgery. 2016;30(5):541-44.
6. Ramamurthi, Tandon PN. Text book of Neurosurgery. 3rd ed. New Delhi:Jaypee brothers medical publishers ltd.2012.
7. Aurangzeb A, Ahmed E, Maqbool S, et al. Burr Hole Evacuation of Extradural Hematoma in Mass Trauma. A Life Saving and Time Saving Procedure:Our Experience in the Earthquake of 2005. Turk Neurosurg. 2016; 26(2):205-08.
8. Bir SC, Maiti TK, Ambekar S, et al. Incidence, hospital costs and in-hospital mortality rates of epidural hematoma in the United States. Clinical Neurology and Neurosurgery. 2015;138:99-103.
9. Emejulu JKC, Uche EO. The Challenges of Managing Acute Extradural Hematoma in a NigerianNeurosurgical Center - Still a Long Way to Go. World Neurosurgery. 2014;82(6):969-73.
10. Nath HD, Tandon V, Mahapatra AK, et al. Outcome of head injury in unknown patients at Level-1 apex trauma centre. Indian Journal of Neurotrauma. 2011;8(1):11-6.
11. Cheung PSY, Lam JMY, Yeung JHH, et al. Outcome of traumatic extradural haematoma in Hong Kong. Injury, Int. J. Care Injured. 2007;38:76-80.
12. Husain M, Ojha BK, Chandra A, et al. Contralateral motor deficit in extradural hematoma: Analysis of 35 patients. Indian Journal of Neurotrauma. 2017;4(1):41-4.
13. Soon WC, Marcus H, Wilson M. Traumatic acute extradural haematoma – Indications for surgery revisite. British Journal of Neurosurgery. 2016;30(2):233-34.
14. Gurer B, Kertmen H, Yilmaz ER, et al. The Surgical Outcome of Traumatic Extraaxial Hematomas Causing Brain Herniation. Turk Neurosurg. 2017;27(1):37-52.
15. Khaled CSMNK, Islam KMT, Mahmood E, et al. Extradural Haematoma in Children:Surgical Experiences and Prospective Analysis of 170 Cases. Turkish Neurosurgery. 2012;22(1):39-43.
16. Gerlach R, Dittrich S, Schneider PW, et al. Traumatic Epidural Hematomas in Children and Adolescents Outcome Analysis in 39 Consecutive Unselected Cases, Pediatric Emergency Care.2009;25:164-69.
17. Khan MB, Riaz M, Javed G, et al. Surgical management of traumatic extra dural hematoma in children: Experiences and analysis from 24 consecutively treated patients in a developing country. Surgical Neurology International. 2013;4:103.
18. Jeong YH, Oh JW, Cho S. Clinical Outcome of Acute Epidural Hematoma in Korea: Preliminary Report of 285 Cases Registered in the Korean Trauma Data Bank System. Korean J Neurotrauma. 2016;12(2):47-54.

Original Article

Outcome of Bilateral Orchidectomy Alone in Comparison with Orchidectomy Plus Bicalutamide in the Management of Patient with Bony Metastatic Carcinoma of Prostate

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Abstract

Background: Prostate cancer is the most common urological malignancy in elderly male. It has been recognized that androgen have a key role in the control of growth and function of the prostate. Suppression of androgen represents the main thrust of androgen deprivation treatment for prostate cancer. To combat adrenal androgens anti-androgen are added to conventional gonadal suppression.

Objective: To compare the outcome of bilateral orchidectomy alone and bilateral orcchidectomy plus bicalutamide in treating the patient of bony metastatic prostatic carcinoma.

Methods: This study was carried out in the Department of urology at Dhaka Medical College Hospital, Dhaka, from January 2014 to December 2017. All patients of bony metastatic prostate carcinoma got admitted in the department of urology were selected as study population. Total 80 patients were included in this study, of which 40 patients were in group A, those treated with bilateral orchidectomy alone and rest 40 patients were in group B, those treated with bilateral orchidectomy plus bicalutamide. At least six months follow up was done in each patient of both groups. Follow up of patients was done at first, third and sixth month following initiation of therapy.

Results: The mean ± SD of age of the patients was 75.16 ± 8.33 years and 77±6.06 years in group A and group B respectively (p>0.05). In group A, the mean ± SD of serum PSA was 2.78 ±0.75, In group B, the mean ± SD of serum PSA was 2.52 ±0.76 (p>0.05).In group A mean±SD of bone pain was 1(3.3), in group B it was 0(0.0) (p>0.05). In this study 9(30%) patients and 12(40%) patients had complete response in group A and in group B respectively (p>0.05).In this study 5(16%) patients and 8(26%) patients had complete disappearance of bone scan hot spot in group A and in group B respectively(p>0.05). In this study 1(3.3%) patient and 0(0.0%) patients had voiding symptoms in group A and in group B respectively (p>0.05).In this study 1(3.3%) patients in group A and in group B 9(30%) patients had nausea (p<0.05). In group A, Mean ± SD of Qmax was 14.06 ± 3.10 sec where in group B it was 14.36 ± 3.33 sec. (p>0.05).

Conclusion: The addition of bicalutamide after bilateral orchidectomy does not improve the outcome of the treatment of patient with bony metastatic prostatic carcinoma, rather more adverse effects and costly in case of combined androgen blockade.

Keywords: Bilateral orchidectomy, Orchidectomy plus bicalutamide, Bony metastatic carcinoma of prostate.

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Introduction

Though we have less authentic data in our country, prostate cancer is the most common urological malignancy in elderly male patient and second leading cause of death among male after lung cancer in the United States[1,2]. Early prostate cancer usually has no symptoms or non-specific clinical features[1]. Advanced disease may present with obstructive or irritative voiding symptoms of LUTS (lower urinary tract symptoms), such as haematuria, UTI and features of metastasis[2,3]. At diagnosis, 20-30% of patients present with advanced or metastatic disease and approximately 25% patients die from their disease within 2 years[1,4]. For many years it has been recognized that androgen have a key role in

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the control of growth and function of the prostate[2,5]. Suppression of androgen represents the main thrust of androgen deprivation treatment for prostate cancer[5]. To combat adrenal androgens, anti-androgen are added to conventional gonadal suppression[6]. Some recent studies suggest that the beneficial effects of anti-androgen in metastatic prostatic carcinoma; however, tremendous controversy has been seen in most of the studies regarding this issue[7,8]. This study was conducted to compare the outcome of bilateral orchidectomy alone and bilateral orchidectomy plus bicalutamide in treating the patient with of bony metastatic prostatic carcinoma.

Materials and Methods

This comparative study was carried out in the Department of urology at Dhaka Medical College Hospital, Dhaka, from January 2014 to December 2017. Patients were evaluated by taking detailed history, physical examinations, and investigations like- Urine for R/M/E & C/S, CBC, Serum creatinine, S.PSA, Ultrasonography of whole abdomen with special attention to KUB and prostate region, Histopathological examination of prostate, Isotope bone scan, Uroflowmetry, X-ray chest and Liver function test. All patients of bony metastatic prostate carcinoma got admitted in the department of urology were selected as study population. Total 80 patients were included in this study, of which 40 patients were in group A, those treated with bilateral orchidectomy alone and rest 40 patients were in group B, those treated with bilateral orchidectomy plus bicalutamide. At least six months follow up was done in each patient. Patients were re-evaluated at 1st, 3rd and 6th month after primary treatment. Follow up were included patient's clinical evaluation and investigations. Clinical evaluation includes history & examination to evaluate the bone pain, voiding symptoms and adverse effects and investigations include S. PSA, Uroflowmetry, and Isotope bone scan. Voiding symptoms were graded by IPSS score[1]. Pain was assessed by using pain score[6]. All the collected data were recorded in the pre-designed data collection sheets and subjected to statistical analysis.

Results

In both groups, maximum patients were in age group 71-80 years. In group A, 22.5% patient were 70 or less than 70 years old, 45.0% patients were between 71-80 years and rest 32.5% were more than 80 years. In group B, 15.0% patient were 70 years or less than years old, 50.0% patients were between 71-80 years and rest 35.0% were more than 80 years. There was no statistical significant difference in age between the groups (Figure-1).

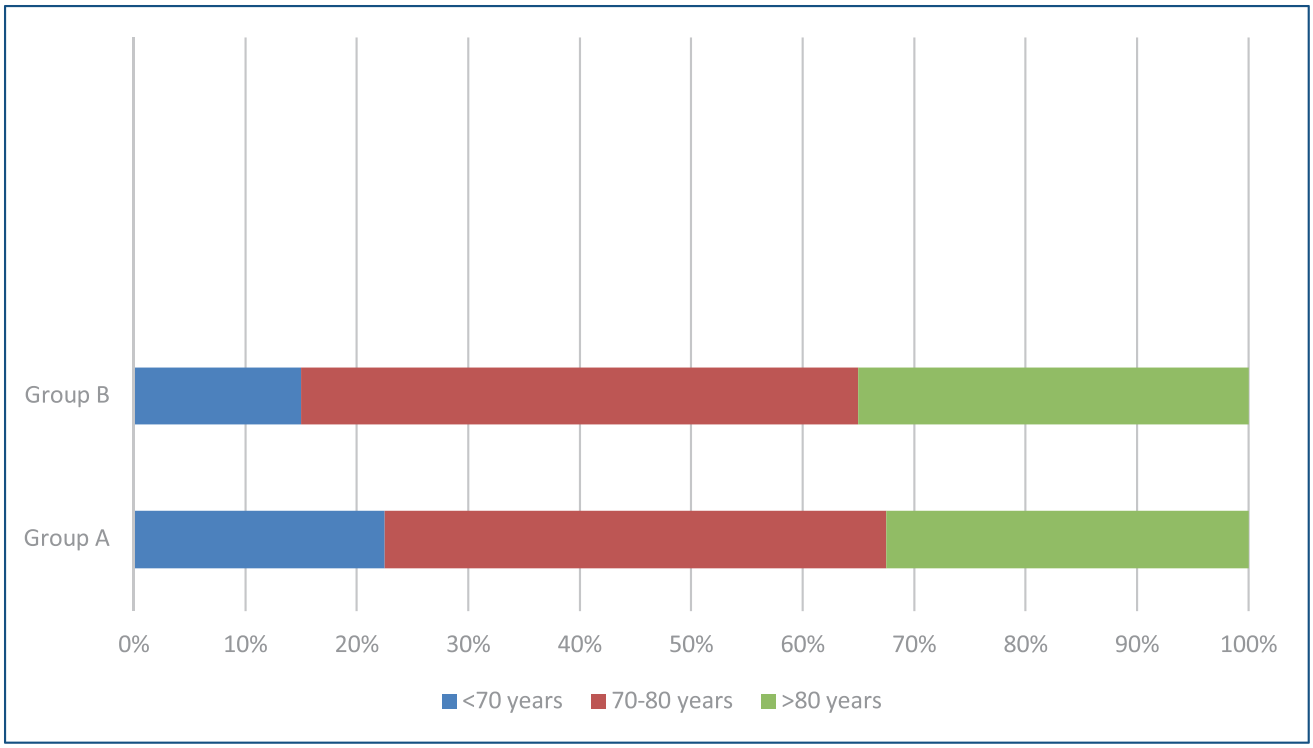

Fig-1: Distribution of patients according to age in two groups

Table I: Comparison of bone pain between two groups at baseline and follow up

Bone pain	Group		p value
	Group A (n=40)	Group B (n=40)	
At baseline			
● Mild	16 (40.0)	17 (42.5)	
● Moderate	10 (25.0)	11 (27.5)	
● Severe	4 (10.0)	4 (10.0)	0.973
● Intractable	1 (2.5)	2 (5.0)	
● None	9 (30.0)	6 (15.0)	
1 month after operation			
● Mild	12 (30.0)	11 (27.5)	
● Moderate	6 (15.0)	6 (15.0)	0.995
● Severe	2 (5.0)	2 (5.0)	
● Intractable	0 (0.0)	0 (0.0)	
3 months after operation			
● Mild	7 (17.5)	6 (15.0)	
● Moderate	5 (12.5)	3 (7.5)	0.694
● Severe	0 (0.0)	0 (0.0)	
● Intractable	0 (0.0)	0 (0.0)	
6 months after operation			
● Mild	5 (12.5)	3 (7.5)	
● Moderate	3 (7.5)	1 (2.5)	0.313
● Severe	0 (0.0)	0 (0.0)	
● Intractable	0 (0.0)	0 (0.0)	

In group A, 16 (40%), 10 (25%), 4 (10%) and 1 (2.5%) patients had mild, moderate, severe and intractable bone pain respectively. In group B, 17 (42%), 11 (27%), 4 (10%), 2 (5%) and (3.3%), patients had mild, moderate, severe and intractable bone pain respectively. Evaluation of the subjects in terms of bone pain shows that 12 (30%), 6 (15%) and 2 (5%) in group A and 11 (27%), 6 (15%), and 2 (5%) in group B had mild, moderate and severe bone pain respectively after 1 month of operation which reduced to 7 (17.5%) and 5 (12%) in group A and 6 (15.0%) and 3 (7.5%) in group B had mild and moderate pain respectively after 3 months of the operation and after 6 month of operation 5 (12%) and 3 (7.5%) in group A and 3 (7.5%) and 1 (2.5%) had mild and moderate bone pain respectively (Table-I). There was no statistical significant difference in between the groups with respect to bone pain. Here bone pain was assessed by using pain score.

Table II: Comparison of voiding symptoms between two groups at baseline and follow up

Voiding symptoms	Group		p value
	Group A (n=40)	Group B (n=40)	
At baseline			
● Mild	14 (35.0)	14 (35.0)	
● Moderate	15 (37.5)	14 (35.0)	0.947
● Severe	11 (27.5)	10 (25.0)	
● None	0 (0.0)	2 (5.0)	
1 month after operation			
● Mild	10 (25.0)	8 (20.0)	
● Moderate	9 (22.5)	7 (17.5)	0.735
● Severe	6 (15.0)	5 (12.5)	
3 months after operation			
● Mild	7 (17.5)	6 (15.0)	
● Moderate	5 (12.5)	4 (10.0)	0.906
● Severe	3 (7.5)	2 (5.0)	
6 months after operation			
● Mild	4 (10.0)	3 (7.5)	
● Moderate	3 (7.5)	2 (5.0)	0.818
● Severe	0 (0.0)	0 (0.0)	

Table II shows voiding symptoms of the patients in two groups. In group A 14 (35.%), 15 (37.5%), and 11 (27.5%) patients and group B 14 (35%), 14 (35%) and 10 (25%) had mild, moderate, and severe voiding symptoms respectively. 1 month after operation 10 (25%), 9 (22%) and 6 (15%) in group A and 8 (20%), 7 (17%) and 5 (12%) patients had mild, moderate and severe voiding symptoms respectively which reduced to 7 (17.5%),5 (12.5%) and 3 (7.5%) in group A and 6 (15.0%), 4 (10%) and 2 (5%) in group B had mild ,moderate and severe voiding symptoms respectively after 3 month of operation and after 6 month of operation 4 (10%) and 3 (7.5%) in group A and 3 (7.5%) and 2 (5%) in group B had mild and moderate voiding symptoms respectively ($p>0.05$). There was no significant difference between the groups with respect to voiding symptoms throughout the whole period of observation.

Table III: Comparison of serum PSA between two groups

Serum PSA (ng/ml)	Group		p value
	Group A (n=40) [Mean ± SD]	Group B (n=40) [Mean ± SD]	
At baseline	100.75 ± 24.31	107.40 ± 28.46	0.265
1 month after operation	4.74 ± 1.21	4.39 ± 1.82	0.316
3 months after operation	2.97 ± 1.11	2.95 ± 0.89	0.944
6 months after operation	2.73 ± 0.72	2.54 ± 0.73	0.263

The serum PSA level of the patients at baseline and at the time of different follow ups. Mean serum PSA was 100.75 ± 24.31 ng/ml in group A and 107.40 ± 28.46 ng/ml in group B at baseline. After 1 month of intervention, the serum PSA dropped 4.74 ± 1.21 ng/ml and 4.39 ± 1.82 ng/ml in group A and group B respectively and after 3 months of intervention the values decreased to 2.97 ± 1.11 ng/ml and 2.95 ± 0.89 ng/ml, while after 6 months, the values became 2.73 ± 0.72 ng/ml and 2.54 ± 0.73 ng/ml in group A and group B respectively. The differences between the groups in terms of changes in PSA level throughout the observation were not significant (p >0.05).(Table-III)

Table IV: Comparison of adverse effects between two groups

Adverse effects	Group		p value
	Group A (n=40)	Group B (n=40)	
Nausea	1 (2.5)	9 (22.5)	0.007
Vomiting	3 (7.5)	10 (25.0)	0.034
Diarrhoea	1 (2.5)	3 (7.5)	0.305
Hot flash	8 (20.0)	16 (37.5)	0.084
Gynaecomastia	0 (0.0)	1 (2.5)	0.314

Adverse effects was significantly lower in group A than those in group B. Table IV shows follow up findings of adverse effects. In group A, 01 patient exhibited nausea, 03 vomiting, 01 diarrhoea and 08 hot flash but in group B, 09 patients exhibited nausea, 10 vomiting, 03 diarrhoea, 16 hot flash and 01 gynaecomastia. Nausea and vomiting were quiet significant (p<0.05) and other were not.

Table V: Comparison of bone scan hot spot between two groups

Bone scan hot spot	Group		p value
	Group A (n=40)	Group B (n=40)	
Complete disappearance	13 (32.5)	11 (27.5)	
Partial disappearance	27 (55.0)	29 (67.5)	
Total	40 (100.0)	40 (100.0)	0.496

Table V shows evaluation of bone scan hot spot. Complete disappearance of hot spot were seen in 13 (32.5%) and 11 (27.5%) patients in group A and group B respectively. Partial disappearance of hot spot were seen in 27 (55.0%) and 29 (67.5%) patients in group A and group B respectively. There was no statistical significant difference between two groups (p>0.05).

Table VI: Comparison of maximum urine flow rate (Qmax) between two groups

Maximum urine flow rate (ml/sec)	Group		p value
	Group A (n=40) [Mean ± SD]	Group B (n=40) [Mean ± SD]	
At base line	10.77 ± 2.39	11.00 ± 5.47	0.812
1 month after operation	12.12 ± 2.27	13.00 ± 3.76	0.213
3 months after operation	13.85 ± 2.97	14.05 ± 3.49	0.784
6 months after operation	13.92 ± 2.95	14.37 ± 3.21	0.517

Table VI shows peak flow rate of the patients in two groups. The mean peak flow rate in group A and group B were 10.77 ± 2.39 ml/sec and 11.00 ± 5.47 ml/sec respectively at baseline which increased to 12.12 ± 2.27 ml/sec and 13.00 ± 3.76 ml/sec respectively after 1 month, 13.85 ± 2.97 ml/sec and 14.05 ± 3.49 ml/sec after 3 month, 13.92 ± 2.95 ml/sec and 14.37 ± 3.21 ml/sec respectively after 6 months of operation. There was no statistical significant difference between two groups (p>0.05).

Discussion

In this study mean ± SD of age was 75.40±7.79 and 76.52±6.11 years in Group A and B respectively. Majority of the patients were in age group of 71-80 years. In group A, 22.5% and 15.0% patients were 70 or less than 70 years

old in respective groups. 32.5% patients in group A and 35.0% patients in group B were more than 80 years. P value suggests statistically non-significant result here (P=0.475). Majority of the researches suggest that the incidence of prostatic carcinoma (with bony metastasis) was significantly higher after the age of 75-80 years[6].

In this study, bone pain was evaluated by using the pain score[6]. In group A, 16 (40%), 10 (25%), 4 (10%) and 1 (2.5%) patients had mild, moderate, severe and intractable bone pain respectively. In group B, 17 (42%), 11 (27%), 4 (10%), and 2 (5%) patients had mild, moderate, severe and intractable bone pain respectively. Evaluation of the subjects in terms of bone pain shows that 12 (30%), 6 (15%) and 2 (5%) in group A and 11 (27%), 6 (15%), and 2 (5%) in group B had mild, moderate and severe bone pain respectively after 1 month of operation which reduced to 7 (17.5%) and 5 (12%) in group A and 6 (15.0%) and 3 (7.5%) in group B had mild and moderate pain respectively after 3 months of the operation and after 6 month of operation 5 (12%) and 3 (7.5%) in group A and 3 (7.5%) and 1 (2.5%) had mild and moderate bone pain respectively. There was no statistical significant difference in between two groups with respect to bone pain.(P>.05),which correlates with the studies of Zalcberg et al[3], Robinson et al[4], Eisenberger et al[7].

In group A 14 (35.%), 15 (37.5%), and 11 (27.5%) patients and group B 14 (35%), 14 (35%) and 10 (25%) had mild, moderate, and severe voiding symptoms respectively. one month after operation 10 (25%), 9 (22%) and 6 (15%) in group A and 8 (20%), 7 (17%) and 5 (12%) patients had mild, moderate and severe voiding symptoms respectively which reduced to 7 (17.5%),5 (12.5%) and 3 (7.5%) in group A and 6 (15.0%), 4 (10%) and 2 (5%) in group B had mild ,moderate and severe voiding symptoms respectively after 3 month of operation and after 6 month of operation 4 (10%) and 3 (7.5%) in group A and 3 (7.5%) and 2 (5%) in group B had mild and moderate voiding symptoms respectively (p>0.05). There was no significant difference between two groups with respect to voiding symptoms throughout the whole period of observation. Result same as most of the studies like Zalcberg et al[3], Robinson et al[4], Samson et al[5], Eisenberger et al[6], but Ansari and Gupta[7] had more improvement in combination therapy (80% vs 50%),(p< 0.05) which was statistically significant.

In this study, the mean serum PSA was 100.75 ± 24.31 ng/ml in group A and 107.40 ± 28.46 ng/ml in group B at baseline. After 1 month of intervention, the serum PSA declined to 4.74 ± 1.21 ng/ml and 4.39 ± 1.82 ng/ml in group A and group B respectively and after 3 months of intervention the values decreased to 2.97± 1.11 ng/ml and 2.95 ± 0.89 ng/ml, while after 6 months, the values became 2.73 ± 0.72 ng/ml and 2.52 ± 0.73 ng/ml in group A and group B respectively. The differences between the groups in terms of changes in PSA level throughout the observation were not significant.(p>0.05), which correlates with the studies of Zalcberg et al[3], Robinson et al[4], Samson et al[5], Ansari and Gupta[6], but in the study of Eisenberger et al the percentage of S.PSA response was significantly higher among combination therapy.(74% vs 61%)[7].

In group A, 01 patient exhibited nausea, 03 vomiting, 01 diarrhoea and 08 hot flash but in group B, 09 patients exhibited nausea, 10 vomiting, 03 diarrhoea, 16 hot flash and 01 gynaecomastia. Nausea and vomiting were quiet significant (p<0.05) and other were not.

On follow up bone scan hot spot, Complete disappearance of hot spot was seen in 13 (32.5%) and 10 (25.0%) patients in group A and group B respectively. Partial disappearance of hot spot was seen in 22 (55.0%) and 27 (67.5%) patients in group A and group B respectively. There was no statistical significant difference between two groups (p>0.05). Findings were similar to studies done by Zalcberg et al[3], Robinson et al[4], Eisenberger et al[7].

The mean peak flow rate in group A and group B were 10.77 ± 2.39 ml/sec and 11.00 ± 5.47 ml/sec respectively at baseline which increased to 12.12 ± 2.27 ml/sec and 13.00 ± 3.76 ml/sec respectively after 1 month, 13.85 ± 2.97 ml/sec and 14.05 ± 3.49 ml/sec after 3 month, 13.92 ± 2.95 ml/sec and 14.37± 3.21 ml/sec respectively after 6 months of operation.Though improvement in peak flow rate a bit higher in Group B but it is not statistically significant (p> 0.05) but in the study of Ansari and Gupta[6] have found statistically significant improvement in peak flow rate in combination therapy.

Labrie[8] reported a high response rate (90%) and long term survival in advanced carcinoma prostate with combined androgen blockade. But similar results were not achieved by others. Several randomized studies in the early nineties demonstrated better results with combined androgen blockade[9,10].

In the studies of Janknegt et al[11]; Robinson et al[4] showed that combined androgen blocked is only effective in patients with good performance status and a low volume disease. EORTC phase three prospective trial Comparing orchiectomy to orchiectomy plus cyproterone acetate and diethyl stillbestrol (DES), it was shown that there was no difference in progression and survival in all three arms[4].

In an open, multicenter, randomized study it was concluded that both short term or continuous addition of cyproterone acetate to buserline, a LHRH agonist did not improve treatment results compared to orchiectomy only[12].

Another multicentre, randomized trial comparing zoladex with zoladex plus flutamide in advanced carcinoma prostate showed no statistical differences in objective response between the two groups, 67% in zoladex group and 65% in combination group. Also there was no difference in time to treatment failure and time to progression between the two treatment groups[13].

In a most recent review by Ansari and Gupta, Lukka et al, Attar, using various combinations of androgen deprivation data does not support routine use of antiandrogens in combination with medical or surgical castration as first line hormonal therapy in patients with metastatic prostatic carcinoma.[6,14,15] It was also evident that quality of life-benefit resulting from orchiectomy in patients with metastatic prostate carcinoma appeared to be offset by the addition of bicalutamide, primarily because of an increased incidence of adverse effects.[14-16] In our study, nausea and vomiting were significantly high in Group B patients (P>0.05%) and other adverse effects are not significant.

Conclusion

The result of this study has demonstrated that the addition of bicalutamide after bilateral orchidectomy does not improve the outcome of the treatment of bony metastatic carcinoma of prostate.

Conflicts of interest: None.

References

1. Huggins C, Stevens RE, Hodges CV. Studies on prostatic cancer: II. The effects of castration on advanced carcinoma of the prostate gland. Arch Swg. 1941; 43: 209-223.
2. Denmeade SR, Lin XS, Isaacs JT. Role of programme (apoptotic) cell death during the progression and therapy for prostate cancer, Prostate 1996; 28: 251-265.
3. Zalcberg JR. Bilateral orchidectomy and flutamide versus orchidectomy alone in newly diagnosed patient with metastatic carcinoma of prostate-an Australian multicentre trial. British journal of urology. 1996;77:865-896.
4. Robinson MRG. The final analysis of the EORTC Genito-urinary Tract Cancer Co-operative group phase 3 clinical trail (protocol 30805) comparing orchidectomy, orchidectomy plus cyproterone acetate and low dose stilboesterol in the management of metastatic carcinoma of the prostate. Eur Urol. 1995;28:273-283.
5. Samson J. Systematic review and meta-analysis of monotherapy compared with combined androgen blockade for patients with advanced prostate carcinoma. American cancer society. 2002;95:361-376.
6. Eisenberger M. Btlateral orchiectomy with or without flutamide for metastatic prostate cancer. NEngl JMed. 1998;339: 1036-1042.
7. Ansari MS. Orchidectomy versus combined androgen blockade in the management of advanced carcinoma prostate, Indian j urol. 2001;18:52-56.
8. Labrie F. Cornbination therapy with flutamide and castration (LHRH agonist or orchidectomy) in advanced prostate cancer: a marked improvement in response and survival, J Steroid Biochem. 1985; 23: 833.
9. Keuppens FP. Orchiectomy versus Goserline plus Flutamide in patients with metastatic prostatic cancer. Cancer. 1993;72: 3863.
10. Keuppens F. Zoladex R and Flutamide versus bilateral orchiectomy: a randomized phase III Vial EORTC 30853 study. Cancer 1990; 66: 1045-1057.
11. Jank'negt RA. Total androgen blockade with the use of orchiectomy and nilutamide (Andron) or placebo as treatment of metastatic prostate cancer. Cancer 1993; 72:3874.
12. Klijn J. Short term versus long term addition of cyproterone acetate to buserline therapy in comparison with orchidectomy in the treatment of metastatic prostate carcinoma. Cancer. 1993; 72:3858-3862.
13. Tyrrell CJ, Kaisary AV, Iversen P. A randomized comparison of Casodex (bicalutamide) 150 mg monotherapy versus castration in the treatment of metastatic and locally advanced prostate cancer. Eur Urol. 1998;33:447-456.
14. Lukka H. Maximum androgen blockade in the treatment of metastatic prostatic cancer- a systematic review. Curr Oncol. 2006;13: 81-93.
15. Attar FS. comparative study between orchidectomy and orchidectomy with hormone therapy (combined) androgen blockade for patients with advanced carcinoma of prostate. Barsal journal of surgery. 2010; 22: 95-100.
16. Laufer M, Denmeade SR, Eisenberger MA. Complete androgen blockade for prostate cancer: What went wrong? J Urol. 2000; 164: 3-9.

Original Article

Evaluation of Distally Based Superficial Sural Island Flap for Reconstruction of Soft Tissue Defects on Distal Third of Leg, Ankle, Heel and Foot

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Abstract

Background: Reconstruction of soft tissue defects on distal third of leg and foot is always a difficult problem to tackle. Various methods of reconstruction to cover such defects include cross-leg flaps, local cutaneous, fascial flaps, fascio-cutaneous flaps, distally based muscle flaps and free flaps. Local flaps have short size and limited arc of rotations. Free flaps are superior to other options but they have some disadvantages such as requirement of well-trained microsurgical team, sophisticated equipment, long operating time, high cost etcetera. The reverse flow superficial sural island flap (SSIF) has become the favourite option among reconstructive surgeons due to more advantages.

Objective: The general objective of this prospective study was to evaluate the outcome of distally based SSIF for reconstruction of soft tissue defects on distal leg, ankle, heel and foot.

Materials and Methods: This prospective study was carried out at the Department of Burn and Plastic Surgery in Khulna Medical College Hospital and some private hospitals in Khulna from September 2016 to March 2017. Thirty patients with soft tissue defects on distal third of leg, ankle, heel and foot were included in this study. Distally based SSIFs were used for coverage in all cases and its survivability, successful reconstruction of the defect, flap tip necrosis, flap loss, and donor site morbidity were studied. Data were collected by a structured case record form, a check list and a master data sheet.

Results: The SSIFs survived in all patients. Marginal loss at the distal edge of the flap was noticed in six patients and partial necrosis was found in three cases.

Conclusion: The distally based superficial sural island flap is a versatile and reliable flap for resurfacing soft tissue defects on the distal lower extremity. This can be performed as a single stage procedure with easy dissection, short operating time, and minimal morbidity.

Key Words: Sural island flap, Reconstruction, Outcome

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Introduction

Soft tissue defects on the distal third of the leg, ankle, heel and foot remain a difficult problem to solve. Most open fractures of lower third of tibia are associated with soft tissue defects because tibia is subcutaneous bone with almost no muscles around its lower third, tight skin, and deficient circulation. Heel is another problem site because of its weight bearing property, hence it needs a durable skin cover. Moreover, the dorsal surface of foot has less subcutaneous tissue.[1,2]

Several reconstructive procedures are available to repair soft tissue defects in these regions, including local skin flaps, fascio-cutaneous flaps, muscle flaps and free flaps as well.

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These modalities have their own indications, advantages, and disadvantages. An ideal flap should be technically easy to harvest and reliable; it should also have a high success rate with minimal donor site morbidity. Free tissue transfer could be the treatment of choice, but it requires a team approach and needs prolonged operative time with a risk of about 0.08% failure rate. Moreover, non-availability of microsurgical expertise at peripheral centers, the cost, and the patient-related factors might preclude the option of free flap.[3,4] Although free tissue transfer plays an important role in limb salvage, regional flap designs would sometimes provide easier and more cost effective alternatives for soft tissue coverage of the injured lower extremity.[5,6]

Loco-regional flaps for lower leg and ankle defects such as the peroneal artery flap, anterior tibial artery flap and posterior tibial artery flap have the disadvantage of sacrificing a major artery in already traumatized limb. Supra-malleolar flap is another option but its reliability is questionable in compromised vascularity.[7,8] Morbidity and operative times are increased in technically demanding microvascular surgeries.[9]

Ideal flap thickness and quality, minimal donor site morbidity, minimum functional deficit, short recovery time, the wide arc of rotation, and safe vascularity are the significant advantages of the reverse sural artery flap. Masquelet et al introduced the sural flap in 1992 and after their work, distally based superficial sural island flaps have become the mainstay in the reconstruction of the distal leg, ankle, heel and foot defects.[16] Over the past decade several modifications have been reported to improve flap viability and to solve a myriad of reconstructive needs.[10] A study conducted by Newaz MM et al. at NITOR, Dhaka, Bangladesh from 2003 to 2005 shows that the sural island flap is an effective coverage option for wounds at the lower third of leg and foot.[11] The aim of this study was to evaluate the outcome of distally based superficial sural island flap (SSIF) for reconstruction of soft tissue defects on distal third of leg, ankle, heel and foot, which were performed at a tertiary level hospital named Khulna Medical College Hospital.

Materials and Methods

This prospective observational study was conducted at the Burn and Plastic Surgery Department of Khulna Medical College Hospital and some private hospitals in Khulna from September 2016 to March 2017. The sample size was thirty and was collected from the population by qualitative purposive technique. The patients with soft tissue defects on the distal leg, ankle, heel, and foot were included in this study and those who disagreed to participate were excluded. Distally based superficial sural island flap (SSIF) was used for reconstruction of soft tissue defects in all cases.

This SSIF was based on the median superficial sural artery, a branch of the superficial sural artery arising from the popliteal or sural artery and was anatomically nourished by the lowermost perforating branch of the peroneal artery. The axis of flap lied over short saphenous vein. The standard flap skin paddle was planned in the middle third of leg as per the defect size and the flap was islanded. The pedicle of this flap was composed of superficial fascia, deep fascia, sural nerve, lesser saphenous vein and accompanying vessels, and the median superficial sural artery; the flap proper included the skin island, subcutaneous tissue, and the fascia.

Preoperatively, hand held Doppler ultrasound was performed in all cases as a part of essential clinical examination to locate the cutaneous perforators. During the procedure having kept the patient in prone position, the SSIF was outlined at the posterior aspect of junction of upper and middle thirds of the leg along the axis of the sural nerve and small saphenous vein. The pivotal point of the pedicle was within 6 cm above the lateral malleolus. Skin incision was made from the proximal margin of the flap at the junction of upper third and middle third of the leg. The skin flap was then elevated with the deep fascia, along with the small saphenous veins. The neurovascular pedicle was 3-4cm in width. At the proximal margin of the flap the vein was ligated and severed and the nerve and the accompanying vessels were also cut. Then the flap was rotated 180° and was passed through a subcutaneous tunnel to reach the defect. The SSIF was islanded to cover the defect by suturing its edges to the edges of the defect. The donor site was repaired with split thickness skin graft.

The ankle was immobilized post operatively for 14 days. Interrupted skin sutures were removed on 7th postoperative day and the rest sutures were removed on 14th postopera

tive day. Flap survivability, successful reconstruction of the defect, flap tip necrosis, flap loss and donor site morbidity were observed. Postoperatively the flap survivability was monitored clinically on the basis of skin color, skin temperature, skin turgor, capillary refill, color of blood and pin prick. These assessments were done 6 hourly for first 24 hour and then 8 hourly for next 4 days. All the patients were followed up weekly in the first month and then monthly afterwards. During the follow up, the flap progression and its outcome were recorded including photographs. Cosmetic outcome was assessed based on three parameters namely flap thickness, color match, and appearance of the donor site defect. 30 patients were followed up for 2 months or more. Data were collected by using a structured case record form, a check list, and a master data sheet. The data analysis was done with the help of SPSS (statistical package for social science).

Results

In this study, thirty cases were included. Age of the patients in this series ranged from 12-60 years and the mean age was 33 years. The majority of cases was in 20-29 years group (Table-I). In this study, particular areas of distal leg and foot were exposed due to soft tissue loss. Exposed sites were medial malleolus, ankle joint, lateral malleolus, tendoachilles, heel, and lower part of tibia (Table-II). Soft tissue loss was higher over the part of lower tibia (36.67%). 21 flaps (70.00%) survived completely without necrosis, which was highest in percentage. Ischemic complications occurred in 9 (30%) cases (Table-III). Outcome were measured as excellent, good and fair on the basis of soft tissue healing, tip necrosis, partial necrosis, total necrosis and infection (Table-IV). Majority (60%) flaps had excellent outcome (Figure-1). Outcome considered excellent where there were no flap necrosis, no infection, satisfactory aesthetic outcome of the flap, and no donor site morbidity. Good outcome referred to no flap necrosis with minor infection or, patchy loss of donor site skin graft, which was healed by secondary intention. Fair outcome was defined as tip necrosis or, partial necrosis of the flap with or, without minor infection.

Table I: Age distribution of patients

Age group	Percent (%)
10-19	10.0
20-29	40.0
30-39	20.0
40-49	20.0
50-59	6.7
60-69	3.3

Table II: Area distribution of soft tissue defects

Exposed part	Frequency	Percent (%)
Lateral malleolus	1	3.33
Lower tibia	11	36.67
Heel	4	13.33
Medial malleolus	3	10.00
Tendoachilles	10	33.33
Ankle Joint	1	3.33

Table III: Survivability of flap

Condition of flap	Number	percent (%)
No Necrosis	21	70.0%
Tip Necrosis	6	20.0%
Partial Necrosis	3	10.0%
Total necrosis	0	0%

Table IV: Clinical outcome

Grading	Criteria	Frequency	Percent (%)
Excellent	No flap necrosis, no infection, satisfactory aesthetic outcome of the flap with no donor site morbidity	18	60.00
Good	No flap necrosis with minor infection or, patchy loss of donor site skin graft, which was healed by secondary intention	03	10.00
Fair	Tip necrosis or, partial necrosis of the flap with or, without minor infection	09	30.00

1(a) 1(b) 1(c)

Figure-1: Sural island flap for coverage of heel defects and exposed tendoachilles

Discussion

Several procedures have been described for coverage of soft tissue defects on the distal third of the leg and foot with their own pros and cons.[12] The advent of neurocutaneous flaps by Masquelet has led to a new tremendous approach to this kind of clinical problem, which is considered a great challange for reconstructive surgeons who are not particularly familiar to microvascular free flaps. Moreover, septocutaneous perforators of the peroneal artery in the distal third of the calf are constant, reliable and well documented. Distally based superficial sural island flap (SSIF) provides a simple, safe, and reliable flap to cover medium size defects in any part of the distal third of the leg, ankle, and proximal foot. Ease of elevation, pedicle length, and arc of rotation of the flap are magnificent advantages of the SSIF. Lin SD et al have mentioned some disadvantages of this procedure such as prone position during surgery, sural hypoesthesia, unsightly postoperative scar on the donor site etcetera.[13]

This study reveals the fact that SSIF is indeed a reliable modality for resurfacing soft tissue defects considering its good functional outcome and minimal donor area morbidity. The study outcomes are consistent with some studies performed in developed countries.[14]

Few clinical researches illustrate that sural flaps are used to cover defects secondary to road traffic accidents, non-healing skin wounds, chronic venous ulcers, chronic osteomyelitis in diabetics, contractures, gangrene, unstable scars, cancer resections, and electrical burns.[15] In sample patients, road traffic accident is major cause of defects, similar to some other studies.[16] All SSIFs survive in this research. Regarding complications of the procedure, there is no complete loss of flap but partial flap necrosis occurs in three cases.

There are several ways to reconstruct the wounds over the distal third of the leg namely local flap, axial flap, and free flap. In this study eight patients with soft tissue lose over the lower leg was covered with superficial sural island flap. Among these patients, three individuals have experienced partial loss of the flap due to pressure over the pedicle due to tight bandage. The wound has been dressed regularly and skin grafting has been done over the granulated wound. Another five flaps have survived but infection in one case have been controlled with appropriate antibiotic. Seven heels have been reconstructed in this series with SSIFs and excellent results are obtained with no complication. Flap survival is comparable to other study series.

Superficial sural island flap is fascio-cutaneous in nature but very versatile in terms of movement and vascularity. Its arc of rotation is 1800 and provides adequate coverage of proximal and distal heel without kinking of the vascular pedicle. The shortcoming of this flap regarding heel

coverage is that it is insensate and tissue type is not similar to that of the heel. Adaptive alteration overcomes this limitation. It requires about one to one and half year to gain adaptive changes of weight bearing heel and protective sensation. Moreover, it is a simple procedure which can be done in any centre with an average technical expertise. In a comparative study between medial plantar flap and SSIF for heel coverage, it has revealed no significant difference in flap survival. The only difference is early weight bearing in case of medial plantar flap.

One clinical study depicts that venous congestion is the most significant reason for flap necrosis.[17] One patient experiences venous congestion postoperatively in this study. The methods reported to improve venous outflow are exteriorizing the pedicle, intermittent drainage of short saphenous vein, leaches, and the supercharging of the flap by anastomosing the proximal end of the lesser saphenous vein to a vein in the recipient defect. During the procedures, the pedicles have been exteriorized and the sleeve of deep fascia around pedicle have been preserved that maintain the integrity of arterial and venous channels and reduce this complication.

The limitations of this study include the time constraint, small sample size, the limited theatre facilities, and skilled manpower. As the study group is small in size, the findings may not be representative to the reference population.

Conclusion

Among the several operative treatment modalities for the reconstruction of soft tissue defects on the distal third of lower extremity, the SSIF is a simple, safe, and single stage procedure with easy dissection, short operating time, and minimal morbidity. It provides a sensate and durable coverage with reasonable aesthetic result. Hence, the distally based superficial sural island flap is a versatile and reliable flap for resurfacing soft tissue defects on the distal lower extremity.

Conflicts of interest: None

References

1. Isaraj S, Nardi K, Ina K. Reconstruction of Defects of the Lower Third of the Leg and Foot with a Reverse Sural Island Flap. J Surg Res. 2020;3(1): 031-042.
2. Alam M, Shaheen M, Hossain S, Anam S, Rahman S. Sural Island Flap - A Good Option for Coverage of the Exposed Heel (Tendo-Achillis). J Dhaka Med Coll. 2010;19(1):19-24.
3. Muppireddy S, Srikanth R. Distally based reverse sural artery flap as an interpolation flap. Int J Res Orthop 2017; 3(1):61-65.
4. Parajuli NP, Shrestha D, Panse N. Distally Based Sural Faciocutaneous and Fascial (Adipo-fascial) Flap for Reconstruction of Distal Leg, Ankle and foot defects. Kathmandu Univ Med J 2014; 46(2):126-31.
5. Maazil AA. Distally Based Sural Fasciocutaneous Flap for Soft Tissue Reconstruction of The Distal Leg, Ankle and Foot Defects. Kufa Med Journal 2012; 15(1): 232-238.
6. Opara KO, Nwagbara IC, Jiburum BC. Reverse sural island flap elevated from the proximal third of the leg: its reliability and versatility in distal leg and foot reconstruction. European Journal of Plastic Surgery. 2010; 34(4): 273–278.
7. Sugg KB, Schaub TA, Concannon MJ, Cederna PS, Brown DL. The Reverse Superficial Sural Artery Flap Revisited for Complex Lower Extremity and Foot Reconstruction. Plast Reconstr Surg Glob Open. 2015; 3(9):519.
8. Fathi HR, Fathi M, Javid MJ. S-Shaped Reverse Sural Flap for Reconstruction of Tissue Defect on Heel. Burns & Trauma. 2013; 1(1): 2321-3868.
9. Ciofu RN, Zamfirescu DG, Popescu SA, Lascar I. Reverse sural flap for ankle and heel soft tissues reconstruction. Journal of Medicine and Life. 2017; 10(1): 94-98.
10. Isenberg JS. The reversal sural artery neurocutaneous island flap in composite lower extremity wound reconstruction. The Journal of Foot and Ankle Surgery. 2000; 39(1): 44-48.
11. Newaz MM et al. Sural Island Flap-The Effective Coverage of Wound at the Lower Third of Leg and Foot. Journal of Bangladesh Orthopaedic Society 2008; 23(2): 73-76.
12. Lu TC, Lin CH, Lin YT, Chen RF, Wei FC. Versatility of the pedicled peroneal artery perforator flaps for soft-tissue coverage of the lower leg and foot defects. Journal of Plastic, Reconstructive and Aesthetic Surgery 2011; 64(3): 386-393.
13. Maffi TR, Knoetgen J, Turner NS, Moran SL. Enhanced survival using the distally based sural artery interpolation flap. Annals of Plastic Surgery 2005; 54(3): 302-305.
14. Wee JT. Reconstruction of the lower leg and foot with the reverse-pedicled anterior tibial flap: preliminary report of a new fasciocutaneous flap. Br J Plast Surg 1986; 39: 327-37.
15. Young IH, Hwan JC, Chang YC, Yong BK. Reconstruction of the Soft Tissue Defect of the Lower Leg by Distally Based Superficial Sural Artery Fasciocutaneous Island Flap Using Supercharged Vein. Arch Plast Surg. 2008; 35(2):208-213.
16. Masquelet AC, Romana MC, Wolf G. Skin island flaps supplied by the vascular axis of the sensitive superficial nerves: anatomic study and clinical experience in the leg. Plast Reconstr Surg 1992; 89: 1115-1121.
17. Mehtab AP, Saeed S, Yunis HS. Distally based sural artery flap: A workhorse to cover the soft tissue defects of lower 1/3 Tibia and Foot. Pak J Med Sci 2007; 23(1): 103-107.

Original Article

Effects of Obesity on Peak Expiratory Flow Rate (PEFR) and Forced Vital Capacity (FVC) Among Adult Bangladeshi Medical Students: A Cross-Sectional Study

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Abstract

Background: Obesity is defined as increase in body weight due to excess accumulation of body fat. It is a major reason of morbidity and mortality as well as many non-communicable diseases. Limited data is present about effects of obesity on pulmonary function of young healthy adults.

Objectives: The objective of this study was to observe the effect of obesity on peak expiratory flow rate (PEFR) and forced vital capacity (FVC) of young adult Bangladeshi medical students.

Methods: A cross sectional analytical study was carried out in the Department of Physiology, Khulna Medical College from January 2022 to December 2022. Study population was 48 young healthy Bangladeshi medical students, out of them 28 were male and 20 were female in the age group of 18-21 years. Study subjects were categorized on the basis of body mass index into normal male, overweight and obese male, normal female, overweight and obese female. PEFR was measured by mini-Wright's peak flow meter and FVC was measured by Student's spirometer. The test of significance was calculated by using unpaired student-t test and correlation was done by Pearson correlation test. P value at or below 0.05 was considered as significant.

Results: PEFR (liter/min) and FVC (liters) of normal male had no significant difference with overweight and obese male. PEFR (liter/min) and FVC (liters) of normal female had no significant difference with overweight and obese female. Body mass index (BMI) showed negative correlation with PEFR and positive correlation with FVC in both male and female group.

Conclusion: No significant difference in lung's function was observed between young adult normal group and young adult overweight, obese group. It indicates that massive body fat deposition is needed to reduce the lung's function. However, PEFR and FVC of healthy adult Bangladeshi medical students were near lower limit of normal range. It indicates the ethnic variation of lung's function and the necessity to establish reference range of lung's function for the Bangladeshi people. It was also observed that the effect of increased BMI was greater on peak expiratory flow rate than vital capacity. However, it was a cross-sectional study with small sample size. Longitudinal studies with larger sample size should be conducted in future for better exploration of the effect of obesity on Lung's function.

Key words: Obesity, PEFR, FVC, BMI, BSA

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Introduction

Obesity is the most common metabolic disease in the developed countries as well as in developing countries. It is an important cause of mortality and morbidity across the world.[1] Obesity decreases the expansibility of the lungs and chest wall. It reduces the strength of respiratory muscles, thereby decreases exercise capacity. Obesity affects ventilation by decreasing movement of the Diaphragm and ribs. Adipose tissue secrets large number of cytokines and chemical mediators which increases the risk of asthma, atopy and responsiveness of the airways.[2] Peak expiratory flow rate (PEFR) is the peak flow of air during single forceful expiration after a maximum forceful

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inspiration. It is expressed in Liters/minute. It is a cheap and a simple test which is widely used to diagnose and classify obstructive airway disease. It is used to evaluate the degree of airway obstruction during acute asthma attack and often a more reliable indicator than the patient's history and examination findings.[3]

Vital capacity (FVC) is the maximum volume of air which can be expired forcefully after a maximum forceful inspiration. Vital capacity depends on lungs compliance, Chest wall compliance, airway resistance and the strength of the respiratory muscles.[4] It is 20-25% lower in female than male and the difference is due to smaller lung size in female. Vital capacity is affected by age, sex, height and ethnicity.[5] Reference values of pulmonary function are usually based on populations having European background.[4] Effect of obesity on lung function was verified previously but there is limited data regarding young population and ethnic variation.[1] As a result, the objective of the present study was to observe the effect of obesity on peak expiratory flow rate and vital capacity of young healthy adult Bangladeshi male and female medical students.

Methods

This cross-sectional comparative study was done in Khulna Medical College, Bangladesh from January 2022 to December 2022. A total of 48 young healthy adult Bangladeshi medical students were randomly selected. Among them, 28 were male and 20 were female study subjects. Inclusion criteria were healthy adults of both gender, age between 18-21 years who do not have any comorbidity. Underweight, athletes, smokers, alcoholics and pregnant students were excluded from the study. Known case of cardiovascular and respiratory disease, Hypertension, Diabetes mellitus and any endocrine disease, hyperlipidemia, oral contraceptive pills and anti-hyperlipidemic drug users and patients having any chronic illness were excluded from the study. Before recruitment, aim, procedure and benefit of the study was explained and informed written consent was taken from each study subject. Standing Height was recorded without shoes in centimeters using standard height scale fixed to the wall with moving head piece. Weight was recorded in kilograms using standard weighing scale with minimal clothing. Body Mass Index (BMI) was calculated by dividing the body weight in kilograms with height in square meters. Body surface area (BSA) was recorded by Dubois's body surface are chart.

Peak expiratory flow rate was measured using mini-Wright's peak Flowmeter which was expressed as Liters per minute. To avoid diurnal variations, measurement was done between 9 am to 11 am. The subjects were asked to sit comfortably and then to inspire forcefully, followed by to expire forcefully into the instrument's mouthpiece with nostrils closed. Each subject made three PEFR measurement and the highest value was considered. Vital capacity was recorded by Student's Spirometer. The subjects sat comfortably facing the spirometer and was asked to inspire forcefully to fill the lungs. Then the nostrils closed with a nose clip and the mouthpiece held firmly between the lips. Then the subject was asked to expire forcefully all the air with maximum effort into the student's spirometer. Thereby the forced vital capacity was recorded in Liters.

The study subjects consisted of 18-21 years old healthy male and female, assigned into four groups: Group-I (male, normal BMI: 18.5-24.99), Group-II (male, overweight, BMI: ≥ 25.00-29.99 and obese, BMI: ≥30.00), Group-III (female, normal BMI: 18.5-24.99) and Group-IV (female, overweight, BMI: ≥25.00-29.99 and obese, BMI: ≥30.00). Overweight and obese were mentioned in the same group due to small sample size. Data was analyzed by computer using SPSS software program. The test of significance was calculated by using unpaired student-t test and correlation was done by Pearson's correlation test. P value less than 0.05 was considered as significant.

Results

Comparison of demographic variables between male and female subjects by weight in kg, height in meter, BMI in kg/m^2 and BSA in m^2. Besides BMI, all the variables were significantly higher in male than female. Comparison of Peak expiratory flow rate (liters/minute) and forced vital capacity (liters) between male and female subjects. All the variables were significantly higher in male than female. (Table I)

Comparison of demographic variables between Group-I (normal male) and Group-II (overweight and obese male) subjects by weight in kg, height in meter, BMI in kg/m^2 and BSA in m^2. Besides height, all the variables were significantly higher in overweight and obese male than normal male. PEFR (liters/min) showed no significant difference between Group-I (normal male) and Group-II

(overweight and obese male). FVC (liters) showed no significant difference between Group-I (normal male) and Group-II (overweight and obese male). (Table II)

Comparison of demographic variables between Group-III (normal female) and Group-IV (overweight and obese female) subjects by weight in kg, height in meter, BMI in kg/m2 and BSA in m2. Besides height, all the variables were significantly higher in overweight and obese female than normal female. PEFR (liters/min) showed no significant difference between Group-III (normal female) and Group-IV (overweight and obese female). FVC (liters) showed no significant difference between Group-III (normal female) and Group-IV (overweight and obese female). (Table III)

BMI showed negative correlation with PEFR and positive correlation with FVC in both male and female group. (Table IV).

Table I: Comparison of demographic data and pulmonary functions among male and female subjects (N=48)

Variables	Male (n=28)	Female (n=20)	P value
Weight (Kg)	70.54±12.52	57.75±12.43	0.001^{HS}
Height (cm)	1.69±0.08	1.54±0.09	0.0001^{HS}
BMI (Kg/m2)	24.59±4.15	23.73±3.45	0.45^{NS}
BSA (m2)	1.80±0.17	1.56±0.18	0.0001^{HS}
PEFR (Liters/minute)	491.79±77.61 (300-600)	342.25±77.40 (100-430)	0.0001^{HS}
FVC (Liters)	2.87±0.52 (1.6-3.7)	1.93±0.28 (1.5-2.4)	0.0001^{HS}

Data were expressed as mean ± SD. Range is mentioned inside parenthesis.

The test of significance was calculated using unpaired t-test. P-value at or below 0.05 considered as significant. S = Significant, HS=highly significant, NS = not significant.

N = total number of study subjects. n = number of study subjects in each group.

BMI = Body mass index. BSA= Body surface area.

PEFR = Peak expiratory flow rate. FVC = Forced vital capacity.

Table II: Demographic data and pulmonary functions of male subjects (N=28

Variables	Group-I (n=16)	Group-II (n=12)	p-value
Weight (kg)	61.88±6.72	82.08±8.28	0.0001^{HS}
Height (meter)	1.68±0.09	1.69±0.07	0.70^{NS}
BMI (Kg/m2))	21.62±0.75	28.55±3.41	0.0001^{HS}
BSA (m2)	1.70±0.14	1.94±0.10	0.0001^{HS}
PEFR (Liter/minute)	499.38±66.88 (350-600)	481.67±92.13 (300-660)	0.56^{NS}
FVC (Liter)	2.83.50±0.49 (1.6-3.5)	2.93±0.57 (1.6-3.7)	0.64^{NS}

Data were expressed as mean ± SD. Range is mentioned inside parenthesis.

The test of significance was calculated using unpaired t-test. P-value at or below 0.05 considered as significant. S=Significant, HS=highly significant, NS= not significant.

N=total number of study subjects. n=number of study subjects in each group.

BMI=Body mass index. BSA= Body surface area.

PEFR=Peak expiratory flow rate. FVC= Forced vital capacity.

Table III: Demographic data and pulmonary functions of female subjects (N=20)

Variables	Group-III (n=12)	Group-IV (n=08)	p-value
Weight (kg)	51.17±3.07	70.13±10.26	0.0001^{HS}
Height (meter)	1.54±0.05	1.55±0.13	0.71^{NS}
BMI (Kg/m2))	21.25±0.41	27.45±2.41	0.0001^{HS}
BSA (m2)	1.48±0.06	1.68±0.23	0.01^{S}
PEFR (Liters/minute)	345.42±93.89 (100-430)	337.50±48.62 (250-400)	0.82^{NS}
FVC (Liters)	1.83.33±0.31 (1.5-2.3)	2.07±0.16 (1.8-2.4)	0.06^{NS}

Data were expressed as mean ± SD. Range is mentioned inside parenthesis.

The test of significance was calculated using unpaired t-test. P-value at or below 0.05 considered as significant. S=Significant, HS=highly significant, NS= not significant.

N=total number of study subjects. n=number of study subjects in each group.

BMI=Body mass index. BSA= Body surface area.

PEFR=Peak expiratory flow rate. FVC= Forced vital capacity.

Table IV: Correlation of Body mass index (Kg/m2) with pulmonary function parameters in male and female subjects (N=48)

Gender	Variables	Correlation coefficient	p-value
Male (n=28)	PEFR	-0.291	0.13^{NS}
	FVC	+0.045	0.82^{NS}
Female (n=20)	PEFR	-0.093	0.69^{NS}
	FVC	+0.382	0.95^{NS}

Correlation coefficient was calculated by Pearson correlation test. + indicates positive correlation and – indicates negative correlation.

P-value at or below 0.05 was considered as significant. NS=Not significant.

N=total number of study subjects, n=number of study subjects in each group.

PEFR=Peak expiratory flow rate. FVC= Forced vital capacity.

Discussion

Obesity increases the risk of hypertension, metabolic disorders, cardiovascular diseases and Lung problems. Fat deposition in the chest wall decreases the expansibility of the Lungs and chest wall. It also affects the function of the intercostal muscles, thereby ribs movement. Fat deposition around the abdomen decreases the descent of the Diaphragm during inspiration. Decrease lungs and chest wall compliance causes increase work of breathing.[2] However limited date is present about the effect of obesity on lung function among young healthy adult Bangladeshi male and female. As a result, the objective of the present study was to assess the effect of obesity on pulmonary function among healthy adult Bangladeshi male and female medical students.

In the present study, total forty-eight young healthy adult male and female Bangladeshi medical students were randomly selected and categorized into Group-I (male, normal BMI), Group-II (male, overweight and obese), Group-III (female, normal BMI) and Group-IV (female, overweight and obese). Overweight and obese were included in the same group due to shortage of adequate number of study subjects in this group. Body mass index (BMI) was used to identify the normal, overweight and obese because BMI reflects the obesity. It represents both fatty mass and lean tissue mass.[2] Peak expiratory flow rate was measured by mini-Wright's peak flowmeter because it is cheap and user-friendly instrument which can assess the degree of airflow.[3,6] Vital capacity was measured by student's spirometer because it is widely used screening test for lung function.[4] In the present study, it was observed that the male had higher height, weight and body mass index in comparison to female. Moreover, peak expiratory flow rate and forced vital capacity were higher in male in comparison to female. This finding is in agreement with Mishra et al, 2013.6. It may be due to the fact that the male sex hormone increases both the muscle mass and the muscular strength.

The normal Value of PEFR for the healthy adult male is 360-900 L/min and for female is 168-600 L/min.[7] Vital capacity of a healthy adult is in between 3 to 5 liters[8]. In the present study, PEFR and FVC of the study subjects were near lower limit of normal range. It may be due to the fact that lung function widely varies among different ethnic groups.[9] It indicates the necessity to establish reference range for Bangladeshi people. Peak Expiratory Flow Rate (PEFR) was introduced by Adornin in 1942 and was recognized as an index of lung function in 1949. In the present study, it was observed that the PEFR were higher in male in comparison to female. This finding is compatible with Babu et al, 2015[10]. It may be due to the fact that male have more muscle mass and muscular strength which increases PEFR. On contrary, female have higher body fat and lower body surface area which decreases PEFR. Moreover, normal male medical students had non-significantly higher PEFR in comparison to overweight and obese male. Similarly, normal female medical students had non-significantly higher PEFR in comparison to overweight and obese female. It may be due to the fact that obesity increases airway resistance, thereby reduces airflow.[11]

In the present study, it was observed that FVC was higher in male in comparison to female. This finding is compatible with Choudhuri D and Choudhuris S, 2013.[12]. It may be due to the fact that the strength of the respiratory muscles are greater in male in comparison to female. It is also reported that women have lower lung volumes.[5] In the present study, forced vital capacity of normal male group showed no significant difference with that of overweight and obese male group. So, it is our assumption that only massive central fat deposition around the abdomen reduces the FVC by hampering the descent of the Diaphragm.[11] In the present study, FVC of normal female group showed no significant difference with that of overweight and obese female group. It may be due to the fact that female type of fat deposition around breast, hip and thigh do not affect the lung's function.

In the present study, it was observed that BMI had negative correlation with PEFR in case of both male and female. It indicates that obesity reduces the air flow. However, in the present study, BMI showed positive correlation with the forced vital capacity in case of both male and female. BMI of all the study subjects of the present study were less than 30 kg/m^2 and all the study subjects were young healthy adults who belonged to 18-21 years. None of them had any comorbid condition or risk factors. So, all of them had good muscular strength. As a result, the findings indicate that only massive fat deposition around the lungs and chest wall due to obesity decreases the FVC by reducing the expansibility of the lungs and chest wall.

One of the strengths of the study was enrollment of all healthy adult BMI groups belong to same age18-21 years. Moreover, the study subjects of different BMI groups had no comorbid condition. Furthermore underweight study subjects were excluded from the study for better interpretation of the results. On contrary, the limitation include small sample size, specifically in overweight and obese group. Moreover lung volumes and capacities were not recorded. In addition, the relation of pulmonary function with other markers of obesity like waist circumference, waist to hip ratio was not explored. So, there is a need for conduction of longitudinal studies with larger sample size, considering the percentage and the distribution of body fat.

Conclusion

Present study showed that the PEFR and FVC were lower in female than male. However, no significant difference in lung's function was observed between young adult normal group and overweight, obese group. It indicates that only massive body fat deposition during ageing reduces lung's function. Moreover, healthy adult Bangladeshi medical students had PEFR and FVC near lower limit of normal range which indicates the ethnic variation of lungs function. It also indicates the necessity to establish reference range of lungs function for the Bangladeshi people. It was observed that the effect of increased BMI was greater on PEFR than FVC. Due to limited information's regarding the effect of obesity on lung's function among Bangladeshi people, this study may be considered as an important baseline data for further research with larger sample size.

Conflicts of interest: None.

References

1. Nowreen N and Ahad F. Association of body mass index with pulmonary function in overweight young adults. National Journal of Physiology, Pharmacy and Pharmacology. 2019; 9(1): 12-15.
2. Sushil MI, Bhagat B, Singhne R, Kumari R. Effect of obesity on spirometry tests among healthy male adults. IOSR-JDMS. 2019; 18(1): 63-65.
3. Dharamshi HA, Faraz A, Ashraf E, Alam SS, Amar A, Osama S. Variation of PEFR with Height, Weight and Waist-Hip Ratio in medical students. International archives of Medicine.2015; 8(84):1-6.
4. Munawar F, Niazi RAK, Mumtaz A, Khan S, Ansar A, Ahmed S Nawaz R. Predicted and recorded vital capacity in students of Shalamar medical and dental college, Lahore. Pak J Physiol. 2011; 7(2): 50-52.
5. Alghadir A, Aly F, Zafar H. Sex based differences in lung functions of Saudi adults. J. Phys. Ther. Sci. 2012; 24: 5-9.
6. Mishra J, Mishra S, Satpathy S, Manjareeka M, Nayak PK, Mohanty P. Variations in PEFR among males and females with respect to anthropometric parameters. IOSR-JDMS. 2013; 5(1): 47-50.
7. Ebomoyi MI and Iyawe VI. Variations of peak expiratory flow rate with anthropometric determinants in a population of healthy adult Nigerians. Nigerian Journal of Physiological Sciences. 2005; 20(1-2): 85-89.
8. Pandey A, Shankar P, Singh AK, Kaur R, Dixit RK. Predicted vital capacity versus recorded vital capacity in students of Desh Bhagat dental college, Sri Muktsar Sahib Punjab. 2014; 3(2): 3368-3375.
9. Memon MA, Sandial MP, Ahmed ST. Pulmonary function tests in a cohort of older Pakistani population. Pak J Physiol. 2006; 2(1): 1-4.
10. Babu RK, Mohit M, Kolekar D. A comparative study of PEFR and BMI in male and female medical students. IJHSR. 2015; 5(8): 273-278.
11. Dayananda G. The effects of obesity on lung functions. JBPS. 2009; 22(2): 17-20.
12. Choudhuri D and Choudhuris S. Effect of gender and body mass index on pulmonary function tests in adolescents of tribal population of a north eastern state of India. Indian J Ohysiol Pharmacfol. 2014; 58(2): 170-173.

Original Article

Bacteriological Profile of Wound Swabs and Their Antimicrobial Susceptibility Pattern at a Tertiary Level Hospital in Bangladesh

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Abstract

Background: Wound infection is a major health problem that results in prolong hospital stay, increased treatment cost and responsible for significant mortality and morbidity worldwide.

Objective: The aim of the present study was to isolate and identify the bacterial pathogens causing wound infection and to determine their antimicrobial susceptibility profile.

Methods: This cross sectional study was conducted at the Department of Microbiology, Khulna Medical College, Khulna from April 2018 to December 2020. 300 wound swab samples were collected and inoculated into appropriate culture media. The bacterial pathogens were identified by using standard microbiological methods. Antimicrobial susceptibility test were performed using disc diffusion technique following Kirby-Bauer method.

Results: In this study 228 bacterial isolates were recovered from 300 samples showing an isolation rate of 76% , 212(93%) were Gram-negative organisms and 16 (7%) were Gram-positive organisms. Majority (28%) of culture positive cases were in age group51-60 years and 52.6% were male. The predominant bacteria isolated from infected wounds were Pseudomonas 82 (35%) followed by Klebsiella 59 (26%), Escherichia coli 35 (15%),Proteus 27 (12%). The Gram negative isolates showed sensitivity to imipenem (93.54%) amikacin (83.87%)gentamicin and piperacillin- tazobactum while they were least sensitive to third and fourth generation cephalosporin.

Conclusion: Pseudomonas was the most frequently isolated pathogen from wound swab and the antibiotic sensitivity pattern of various isolates help to assist the clinician in appropriate selection of empirical antibiotics against wound infection.

Keywords: Antimicrobial susceptibility, Bacterial pathogen, Wound infection

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Introduction

A wound is an injury that breaks the skin or other body tissue. Exposure of subcutaneous tissue following a loss of skin integrity (i.e. wound) provides a moist, warm, and nutritious environment that is conducive to microbial colonization and proliferation[1]. The wound can be colonized by a wide array of organisms and is influenced by factors such as a type, depth, location, and level of tissue perfusion and also the host immune status. Wound infection is a major health problem that results in sepsis, prolong hospital stay, increased treatment cost and are responsible for significant mortality and morbidity worldwide[2]. Wound infection can be caused by variety of organisms like bacteria, virus, fungi and protozoa and may co-exist as poly microbial communities.Organisms commonly found

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in infected wounds include Gram positive cocci such as S. aureus, Streptococcus spp, Gram negative bacilli mostly Acinetobacter, E. coli, Proteus spp , Klebsiella spp , Pseudomonas aeruginosa and anaerobic bacteria such as Propionibacterium spp[3] . Regional and local variations occur among causative microorganisms of wound infection. Thus clinician should be aware of causative agents and their antimicrobial susceptibility profile in their locality.

Antibiotic resistance among bacteria is becoming more and more serious problem throughout the world. This is particularly worse in resource poor countries where sale of antibiotics is under poor control. The widespread and prolonged use of antibiotics lead to the emergence of resistant bacterial pathogens in wound infections contributing to high morbidity and mortality rates[4]. Antibiotic resistance emerges commonly when patients are treated with empiric antimicrobial drugs. Monitoring of resistance patterns in the hospital is needed to overcome these difficulties and to improve the outcome of serious infections in hospital settings[5].

The antibiotics resistant pathogens are acquired from either health care setting environment, health care personnel, or inpatients . If the local antimicrobial susceptibility data are not available, the chances of haphazard use of antibiotics will be high. As a result, the rate of drug resistance will increase causing a serious problem. Information on bacterial pathogens including their antibiotic sensitivity pattern from inpatient is limited in Khulna Medical college hospital. Hence the present study was carried out to identify the causative agent of wound infection and antibiotic susceptibility pattern of the isolates, which will be beneficial as guidance for medical practitioners to select empirical antimicrobial therapy and on the implementation of infection control measures that plays an important role in minimizing the emergence rate of antimicrobial resistance.

Materials and Methods

This cross sectional study was carried out in the department of Microbiology, Khulna Medical College, Khulna from April 2018 to December 2020. Total 300 specimens consisting of wound swabs, pus, purulent exudates or wound discharge were collected from indoor patients of various clinical wards of Khulna Medical College Hospital. Clinically diagnosed patients of all ages and of both sexes having wound infection with pus or discharge draining from infection site or wounds having any signs of infection (pain or tenderness, localized swelling, redness or heat) or the wound that has not healed within ten days after the injury were included in the study. Swab of wound secretion/pus, purulent exudates, or wound discharge was aseptically collected using sterile cotton swab from each study participant and then swab was taken in a sterile test tube and transported immediately to the microbiology laboratory. The samples were inoculated into Blood agar media, MacConkey agar media and Nutrient agar media[6]. All the plates were incubated aerobically at 370C for 18-24 hours. Isolation and identification of different bacteria were done by standard microbiological procedures, including colony morphology, Gram staining and biochemical tests[7].

Antimicrobial susceptibility testing was carried out by Kirby-Bauer disc diffusion technique using Mueller Hinton agar media and zone of inhibition were measured as recommended by the Clinical and Laboratory Standard Institute. (CLSI) guidelines 2018[8]. The reliability of the findings was guaranteed by implementing quality control measures throughout the whole processes of the laboratory work. The reference strains used as control were E. coli (ATCC 25922), P. aeruginosa (ATCC 27853), and Staphylococcus aureus (ATCC 25923).[9]

The following antibiotic discs from Oxoid Ltd. UK, were used, Azithromycin (15µg), Ceftriaxone (30μg), Ceftazidime (30μg), Cefepime (5μg), Ciprofloxacin (5μg), Amoxyclav (30µg), Gentamicin (10μg), Amikacin (30μg), Imipenem(10μg) , Vancomycin (30 μg) , linezolid (30 μg) and piperacillin+tazobactum (10 μg). Data were compiled and analyzed with SPSS version 20 statistical software. Before starting the study ethical clearance was obtained from the concerned authority of Khulna Medical College.

Results

Among 300 samples from wound infection, 228(76%) yielded bacterial growth, and remaining 72(24%) were culture negative (Figure 1).Both female (47.4%) and males (52.6%) had nearly comparable infection rates(Figure 2).Out of these culture positive cases, majority 64(28%) were in the age group of 51-60 years (Table 1). The most frequently isolated bacteria were Pseudomonas spp .80(35%), followed by Klebsiella 59(26%), Escherichia coli 35 (15%), Proteus spp. 27 (12%), Staphylococcus aureus 14 (6%), Acinetobacter 11(5%) and Enterococci 2(1%)(Table II.) Pseudomonas showed lowest sensitivity to almost all of the drugs except imipenem which was 82% sensitive, followed by piperacillin-tazobactum 73%, amikacin 47% and aztreonam 48%. Klebsiella showed 71% sensitivity to imipenem and 38% sensitivity to Amikacin, and 33% sensitive to gentamicin, The sensitivity of Escherichia coli to imipenem was 71%, amikacin 71%, gentamicin 62% and low level of sensitivity was found to aztreonam (28%) and ciprofloxacin (28%). Imipenem was the most sensitive drug for Proteus 77% and Acinetobacter 61%.Other drugs like ceftriaxone, cefepime, ceftazidime showed lowest sensitivity below 10% to Acinetobacter (Table III). Among the Gram positive isolates Staphylococcus aureus were found highly sensitive to linezolid (92%), vancomycin (85%), amikacin (78%), and gentamicin (78), doxycycline (71%) and low sensitivity were found in commonly used antibiotics like ciprofloxacin (35%), amoxyclav (21%) and azithromycin (7%). Enterococci showed highest sensitivity to linezolid (100%), vancomycin (100%) and also clindamycin (100%). Lowest sensitivity was found to ciprofloxacin (0%) and azithromycin (0%). (Table IV)

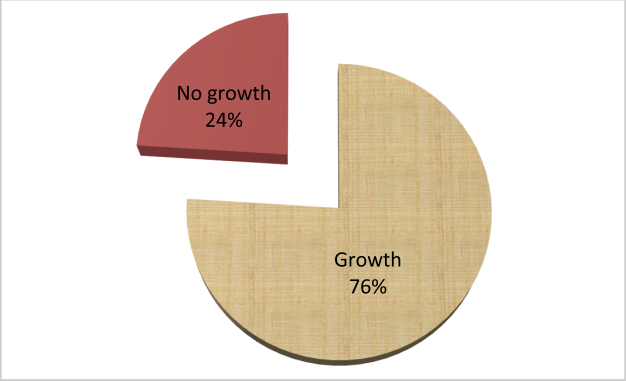

Figure 1: No growth and growth distribution (N=300)

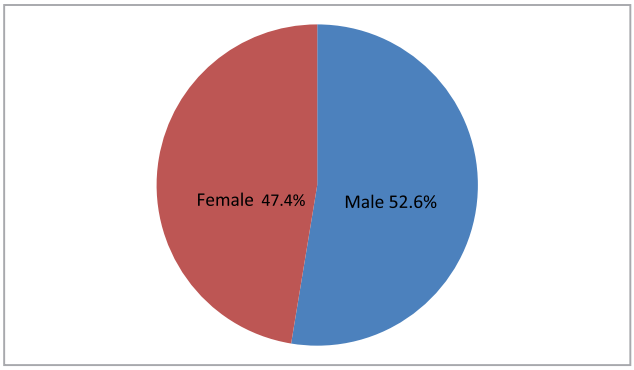

Figure 2: Male and female distribution

Table I: Age distribution and frequency of positive growth (N=228)

Age distribution in yrs	Number of patient	Percentage
0-10	01	0.4
11-20	11	4.8
21-30	23	10.08
31-40	34	14.9
41-50	50	21.9
51-60	64	28.07
61-70	33	14.4
71-80	09	3.9
81-90	02	0.8
91-100	1	0.4

Table II: Organisms isolated from wound swab (N = 228)

Gram negative isolates		Gram positive isolates isolates	
Name	Number (%)	Name	Number (%)
Pseudomonas	80(35%)	Staphylococcus aureus	14(6%)
Klebsiella	59(26%)	Enterococci	02(1%)
Escherichia coli	35(15%)		
Proteus	27(12%)		
Acinetobacter	11 (5%)		
Total	212(93%)	Total	16(7%)

Table III: Antibiotics sensitivity pattern of Gram negative bacteria (n=212)

Antibiotics	Pseudomonas (n=80)	Klebsiella (n=59)	E.coli (n=35)	Proteus (n=27)	Acinetobacter (n=11)
IPM	66(82%)	42(71%)	25(71%)	21(77%)	6(61%)
AK	38(47%)	23(38%)	25(71%)	5(18%)	2(18%)
AT	39(48%)	2(3%)	10(28%)	4(14%)	2(18%)
AZM	11(13%)	4(6%)	3(8%)	1(3%)	3(27%)
CPM	24(30%)	5(8%)	5(14%)	6(22%)	0(0%)
CIP	26(32%)	7(11%)	12(28%)	4(14%)	1(9%)
AMC	1(1%)	4(6%)	2(5%)	1(3%)	0(0%)
CRO	4(5%)	2(3%)	6(17%)	2(7%)	0(0%)
TZP	59(73%)	13(22%)	10(28%)	8(29%)	0(0%)
GEN	23(28%)	20(33%)	22(62%)	3(11%)	1(9%)
CAZ	21(26%)	3(11%)	13(37%)	2(7%)	1(9%)

Table IV: Antibiotic sensitivity pattern of Gram positive bacteria (n=16).

Antibiotics	S.aureus (n=14)	Enterococci (n=2)
Vancomycin	12(85%)	2(100%)
Linezolide	13(92%)	2(100%)
Ciprofloxacin	5(35%)	0(0%)
Doxycycline	10(71%)	1(50%)
Clindamycin	8(62%)	2(100%)
Penicillin	0(0%)	0(0%)
Azithromycin	1(7%)	0(0%)
Amoxyclav	3(21%)	1(50%)
Amikacin	11(78%)	1(50%)
Gentamycin	11(78%)	1(50%)

Discussion

Wound infections are underestimated problems that result into a chronic disease. The control of wound infections is becoming difficult due to widespread bacterial resistance to antibiotics. A changing pattern of isolated organisms and their antimicrobial sensitivity varies from hospital to hospital and region to region is a usual feature.

In the present study, 228(76%) bacterial pathogens were isolated from300 samples. Almost similar isolation rate was reported by Afroz et al(2020)72.4% and Dhakal et al(2017) 78.1%[10,11]. In our study, Gram negative bacilli was the most predominant pathogenic bacteria from wound sample which was similar to the other studies done by Abedin et al(2022) & Omoyibo et al(2018)[12,13]. This high rate of Gram-negative and low rate of Gram-positive isolates from wound may be due to high number of cases included from inpatients in the present study compared to outpatients. This may probably contribute high number of Gram-negatives than Gram-positives.

In this study, the most common bacterial isolates were P. aeruginosa, which is similar to the findings of Pondei et al (2013) and Deboral et al(2020)[14,15]. Another studies in Bangladesh done by Sultana et al (2015)& Alam et al (2021) showed that the most frequently isolated bacteria were Staphylococcus aureus[16,17]. This difference may be due to variation in common nosocomial pathogens inhabitant in different hospital set up. The organisms most frequently involved in surgical infections change from time to time, and also vary with hospital settings. The incidence of Pseudomonas aeruginosa in postoperative wound infection is becoming more serious in developing countries because of relaxation in general hygienic measures, mass production of low quality antiseptic and medicinal solutions for treatment, difficulties in proper definition of the responsibility among the hospital staff. High prevalence of P. aeruginosa in the clinical samples of our study may be due to the fact that the type of samples (swabs samples of the site of infection) and health care managements is different with those of other investigations. In fact, the presence of environmental pollution, especially in the hospital environment as well as lack of optimal disinfection of instruments and equipments of hospitals may be the reasons for the high prevalence of P. aeruginosa (35%) in wound swab of our study. In our hospital due to lack of adequate bed, most of the patient have to stay in floor, which may be the cause of spread of these bacteria in hospital personnel.

In this study, majority (28%) of wound infection cases were within the age group of 51-60 years. This is in agreement with a study done by Azzah S(2022)[18] . This may be due to age related alterations in both arm of immunity, the

innate and adaptive immune systems, which reduce their ability to combat infection[19].

The bacteria Pseudomonas (35%), was the most predominant isolates were found in our study that exhibited the highest sensitivity to imipenem (82%) , piperacillin+tazobactum (73%) and aztreonam (48%) and amikacin (47%), while showed the lowest sensitivity to antibiotics, amoxyclav (1%), ceftazidime(26%),ciprofloxacin (32%), similar with Ranjan,et al[20]. Klebsiella showed highest sensitivity to imipenem(71%), amikacin(38%), gentamicin (33%) and piperacillin+ tazobactum(22%), on the other hand reduced sensitivity to ciprofloxacin(11%), ceftriaxone (3%), ceftazidime(11%) and amoxyclav (6%) which which was in line with study done by Tarana et al[21]. In our study, Gram negative rods showed reduced sensitivity to fourth & third generation cephalosporins like cefepime (0-30%) ceftriaxone (0-6%) and ceftazidime (1-21%) , which coincided with findings of Shahidullah et al[22]. Among the b-lactams, high resistance was seen by gram-negative bacteria to even fourth-generation cephalosporins whereas carbapenems are still sensitive. Cephalosporin resistance among Gram-negative bacilli can be the result of induction of chromosomal β-lactamases after exposure to the antibiotic. This may be due to the fact that third and fourth generation cephalosprins have been used for long period in this country. So due to indiscriminate and overuse of these drugs over this organisms have developed resistance. High resistance rate was also observed for ciprofloxacin. The most effective antibiotics in this study were imipenem, amikacin and gentamicin.

In this study, Staphylococcus aureus showed 92% sensitive to linezolid, 85% to vancomycin, 78% to amikacin, gentamicin followed by 71% to doxycycline and less sensitivity were found in ciprofloxacin (35%), amoxyclav (21%) and azithromycin(7%).The high sensitivity of Gram positive bacteria to vancomycin , linezolid , doxycycline and gentamicin has also been reported by other authors as well[23]. Remarkable susceptibility of Staphylococcus aureus to vancomycin, linezolid, amikacin and gentamicin may be due to lesser use of these antibiotics as a result of their less availability, cost and toxic effect.

Such high antimicrobial resistance is probably promoted due to selective pressure exerted on bacteria due to numerous reasons like non adherence to hospital antibiotic policy, excessive and indiscriminate use of broad-spectrum antibiotics, lack of infection control policy.

We acknowledged certain limitations of our study. Firstly, anaerobic cultures were not done due to lack of equipment and funds. Thus, anaerobic bacteria, which are also important in wound infections, could not be isolated. Secondly, current CLSI guidelines recommend colistin susceptibility testing by estimation of MIC because the disc diffusion test does not detect low -level resistance. So colistin susceptibility could not be detected in our study due to lack of facility.

Conclusion

The findings of this study showed that Pseudomonas was found to be the predominant among all of the isolates of wound infections and showed highest sensitivity to imipenem, amikacin followed by piperacillin-tazobactum. Among the Gram negative bacilli Escherichia coli , Klebsiella are the most common bacteria causing wound infection. Most of the Gram negative isolates were highly sensitive to imipenem, amikacin, gentamycin. So this knowledge of the most likely causative organisms and prevailing drug susceptibility pattern of this study may be helpful in deciding empirical therapy to reduce mortality and morbidity in wound infections. Therefore, periodic surveillance of microbial profile and their antimicrobial sensitivity pattern in the study region is essential for efficient wound infection management with appropriate antibiotics, in attempt to contain antimicrobial resistance.

Conflicts of interest: None

References

1. Felgueiras HP, Amorim MT. Functionalization of electrospun polymeric wound dressings with antimicrobial peptides. Colloids and Surfaces B. Biointerfaces. 2017; 1(156):133-148.
2. Bowler PG, Duerden BI, Armstrong DG. Wound microbiology and associated approaches to wound management. Clinical Microbiology Reviews. 2001;14(2):244-69.
3. Taiwo SS, Okesina AB, Onile BA . In-vitro antimicrobial susceptibility pattern of bacterial isolates from wound infection in university of Ilorin Teaching Hospital. Afr. J. Clin. Exp. Microbiol 2002; 3(1): 6-10.
4. Rengaraj R , Velu P, Gurumurthy H, Ali SM . Aerobic Bacterial Pathogens and their Antimicrobial Susceptibility Pattern in a Tertiary Care Centre from Kanchipuram District, Tamil Nadu, India- A Retrospective Study National Journal of Laboratory Medicine. 2021; 10(1): 5-8.
5. Khanam RA, Islam MR, Sharif A, Parveen R, Sharmin I, Yusuf MA. Bacteriological profiles of pus with antimicrobial sensitivity pattern at a teaching hospital in Dhaka City. Bangladesh J Infect Dis. 2018;5(1):10-14.
6. Collee JG, Marr W. Specimen collection, culture containers and media. In: Collee JG, Duguid JP, Fraser AG, Marmion BP eds. Mackie & McCartney Practical Medical Microbiology, Vol. 2, 14th ed. Churchill Livingstone, New York; 1996: 85-111.
7. Cheesbrough M . District laboratory practice in tropical countries Vol 2. 2nd ed. Cambridge University Press, India 2006.
8. Clinical and Laboratory standards Institute. Performance standards for antimicrobial testing; twenty eighth international supplement. CLSI document M100-S 28, Clinical and Laboratory Standards Institute, Wayne, PA.2018.
9. Leite-Sampaio NF, Gondim CNFL, Martins RAA, Siyadatpanah A, Norouzi R, Kim B et. al. Potentiation of the Activity of Antibiotics against ATCC and MDR Bacterial Strains with (+)-α-Pinene and (-)-Borneol. Biomed Res Int. 2022; doi: 10.1155/2022/8217380&7.Rohamed Ali
10. Sadia Afroz1, Dipika Sarkar , Khadeza Khatun , Tarek Mahbub Khan , Shikha Paul. Bacterial pathogens in wound infection and their antimicrobial susceptibility pattern in a medical college hospital, in Dhaka, Bangladesh. Int J Res Med Sci. 2020 ;8(6):2105-2109.
11. Dhakal A, Raman R. Antimicrobial Susceptibility Pattern of Bacterial Isolates Obtained From Wound Infections at a Tertiary Care Hospital of Nepal. Int J Med Res Prof. 2017;3(6):319-23.
12. Abedin MZ, Muhammad II,Helal HB, Sultana S, Farnaz NE, Afrin MN et a.,Bacteriological profiles and multi-drug susceptibility patterns of wounds infecting bacterial isolates in rural hospital of Bangladesh. Public H Open Acc .2022: 6(1): 000196.
13 Omoyibo EE, Oladele A O, Ibrahim MH, and Adekunle O. Antibiotic Susceptibility of Wound Swab Isolates in a Tertiary Hospital in Southwest Nigeria.Ann Afr Med. 2018 ; 17(3): 110–116.
14. Kemebradikumo Pondei, Beleudanyo G. Fente, and Oluwatoyosi Oladapo. Current Microbial Isolates from Wound Swabs, Their Culture and Sensitivity Pattern at the Niger Delta University Teaching Hospital, Okolobiri, Nigeria. Trop Med Health. 2013 ; 41(2): 49–53.
15. Deboral A, Bhosale NK, Umadevi S. Aerobic Bacteriological and Antibiotic Susceptibility Profile of Pus Isolates from A Tertiary Care Hospital, Puducherry. J Pure Appl Microbiol. 2020;14(3): 1961-1966.
16. Shahin Sultana, Nurunnahar Mawla, Shamima Kawser,Nayareen Akhtar, Md. Khoybar Ali Current Microbial Isolates from Wound Swab and Their Susceptibility Pattern in a Private Medical College Hospital in Dhaka city. Delta Med Col J. 2015;3(1):25-30
17. AlamMM,Islam M N , Hawlader MD, Ahmed S, Wahab A, Islam M, Uddin KM , Hossain A.Prevalence of multidrug resistance bacterial isolates from infected wound patients in Dhaka, Bangladesh: A cross-sectional study. International Journal of Surgery Open . 2021; 28 : 56-62.
18. Azzah S. Alharbi. Bacteriological profile of wound swab and their antibiogram pattern in a tertiary care hospital, Saudi Arabia. Saudi Medical Journal. 2022; 43 (12): 1373-1382
19. Bajaj V, Gadi N, Spihlman AP, Wu SC, Choi CH, Moulton VR. Aging, immunity, and COVID-19: how age influences the host immune response to corona virus infections? Front Physiol. 2021; 11: 14-16
20. K Prabhat Ranjan, Neelima Ranjan, Satish K Bansal, and D R Arora J Lab Physicians.Prevalence of Pseudomonas aeruginosa in Post-operative Wound Infection in a Referral Hospital in Haryana. J Lab Physicians. 2010 ; 2(2): 74–77 .
21. Tarana MN, Fardows J, Farhana N, Khatun R, Akter S. Bacteriological Profile of Wound Swab and Their Antimicrobial Susceptibility Pattern in Shaheed Suhrawardy Medical College, Dhaka. J Shaheed Suhrawardy Med Coll. 2019; 11(1): 65-68 .
22. Shahidullah, M. Yusuf, Z. Khatun, U. Ara, M. Mitul Antibiotic sensitivity pattern of bacterial isolates from different clinical specimens: experience at NICVD, Dhaka. Cardiovasc J. 2012; 5: 67-72.
23. Nabina Maharjan, BS Mahawal .Bacteriological Profile of Wound Infection and Antibiotic Susceptibility Pattern of Various Isolates in a Tertiary Care Center, J. Lumbini. Med. Coll. 2020; 8(2): 218-225

Review Article

Stem Cell Therapy for Ischemic Heart Failure

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Abstract

Patients having ischemic heart failure are at risk of development of heart failure with reduced ejection fraction. Now a days regenerative medicine is getting interest at regenerating and repairing ischaemically damaged myocardium through stem cell therapy. Stem cells are traditionally isolated from bone marrow and demonstrate excellent safety in clinical practice. Stem cell-based therapy is currently tested in several clinical trials of ischemic heart failure suggest that stem cell therapy become an important new tool in heart failure management.

Key words: Stem cell therapy, Heart failure.

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Introduction

Ischaemic heart disease is a major health problem worldwide. The prevalence and incidence of ischaemic heart disease is increasing day by day. Patients having coronary artery disease, vulvular heart disease, myocardial and other cardiac disorders are at risk of development of heart failure with reduced ejection fraction. Despite numerous pharmacological interventions and invasive therapeutic techniques, therapeutic options for end stage heart failure remain limited to left ventricular assist device and organ transplantation. So the patients and physicians are seeking an alternative treatment strategy. Regenerative medicine may bring hope here.

The pathology of heart failure includes intrinsic defects of contracticity of cardiac muscle due to the molecular pathology, defect in energy production, extrinsic defects to cardiac musle cells, such as interstitial fibrosis affecting the compliance of the heart and myocyte loss unmatched by myocyte replacement. The ischemic loss of myocardium initiates a detrimental cascade of events including formation of a noncontractile scar, ventricular wall thickening, haemodynamic overload, ventricular remodeling, heart failure and eventually death.

Therefore, new and more efficient heart failure therapies are headed including those with the ultimate goal of restoring function by regenerating and repairing damaged myocardium. Stem cell therapy offers the most promise in this regard.

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Stem-Cell Types

Stem cells are defined as cells that are clonogenic (capable of producing exact duplicates), self-renewing (capable of dividing indefinitely), and potent (capable of differentiating into multiple cell lineages).6 Several generations of stem cells can be distinguished, according to their potential for differentiation, as being totipotent, pluripotent, multipotent, or unipotent.7Stem cells in the very early stages of embryonic development are often referred to as totipotent, or omnipotent. Totipotent cells can give rise to any type of cell: cells of the trophoblast and cells of the 3 germ layers (endoderm, mesoderm, and ectoderm), all of which are necessary for complete embryonic development. Stem cells that can give rise to cells of all 3 embryonic germ layers but not to trophoblasts are considered pluripotent. Three types of pluripotent stem cells can be derived from the mammalian embryo: embryonic stem (ES) cells, embryonic germ (EG) cells, and embryonic carcinoma (EC) cells. The ES cells are derived from the inner cell mass of the blastocyst at day 5 post-fertilization. The EG cells are derived from embryonic genital ridges at 9.5 to 12.5 days post-coitus. Both ES and EG cells can develop into cells of the 3 germ layers. The EC cells emerge from undifferentiated parts of germ cell tumors; they are also less able to differentiate, are usually aneuploid (that is, having varying amounts of DNA), and are malignant in laboratory animals.[8,10] Stem cells that give rise to cells of different lineages within a single germ layer are considered multipotent. However, when injury occurs, this small pool of stem cells can no longer produce sufficient amounts of tissue-specific cells. This has led to the hypothesis that bone marrow stem cells (BMSCs) are mobilized from the bone marrow (central pool) and directed to the injured tissue or organ. Tissue-specific progenitor (unipotent) stem cells arise from multipotent cells. After a limited number of divisions, unipotent stem cells begin to differentiate and give rise to cells of specific tissue types. These tissue-specific cells then impart function and structure to tissues and organs by becoming their integral units.[11]

Stem-Cell Differentiation

At present, there are 4 accepted theories to explain the differentiation of adult stem cells into tissue-specific cells. None of them are mutually exclusive. The 1st theory posits a putative primordial equivalent of the embryonic stem cell (the so-called “stem cell of all stem cells”); the antigenic signature of this cell has recently been defined as CD34–, CD44–, CD45–, c-kit–, and major-histocompatibility-complex (MHC) classes I and II.[6] This primordial equivalent can be found in bone marrow and peripheral blood and can give rise to various lineage-restricted stem cells.[6,11] The 2nd theory posits several types of circulating lineage-restricted adult stem cells. The 3rd theory is grounded on the assumption that already differentiated tissue-specific cells regain the properties of a stem cell through a process of dedifferentiation and subsequent redifferentiation into new cells of another tissue.6 This theory goes against the long-held belief that adult stem cells are tissue-specific cells that can differentiate only into cells of the tissues in which they reside.The 4th theory, which is supported by most experimental and clinical data, suggests that circulating hematopoietic stem cells (HSCs) predestined to become primarily hematopoietic cells can, under certain circumstances, deviate from that predestined pathway in a process called transdifferentiation.[6,10,11] The molecular mechanisms involved in this process remain very obscure and are the focus of intensive research efforts, but further discussion of these mechanisms lies beyond the scope of this review.Although it is theoretically possible for hybrid tetraploid cells to somehow regain the tetraploid karyotype in a diploid state (thus masking the occurrence of cell fusion), the fact remains that cell fusion has a very low estimated frequency of 1:10,000 to 1: 100,000. Therefore, it is highly unlikely that cell fusion would account for the extensive tissue regeneration that has been achieved with stem-cell therapy.10Therapeutic stem-cell transplantation is founded on 2 principal assumptions: first, as already mentioned, that heart failure is due to the irreversible loss of a critical number of cardiomyocytes; and second, that the function of the infarcted heart can be improved by repopulating areas of dead myocardium with new contractile cells.[1] Unfortunately, spontaneous multiplication of cardiomyocytes in areas surrounding an infarct cannot completely compensate for lost cells,[2] and the conversion of in-scar fibroblasts to contractile cells requires a complicated, time-consuming process of genetic manipulation that, to date, has not been shown to result in the generation of functional myocytes that can integrate themselves into the surrounding viable myocardium. Therefore, obtaining contractile cells from an exogenous pool and engrafting them into post infarction myocardial scar tissue seems to be the best solution.[1,16]

Potential Sources of Cardiac Stem Cells

To restore function to nonviable infarcted myocardium, optimal stem-cell transplantation (also called cell cardiomyoplasty) should generate contractile cells that integrate both functionally and structurally into the surrounding viable muscle. This integration occurs via the formation of cell-to-cell contacts such as cardiac-specific intercalated discs consisting of desmosomes and gap junctions. The desmosomes give myocardial tissue the necessary physical strength; the gap junctions, which consist of the cardiac muscle-specific protein connexin, enable communication between cardiomyocytes that results in coordinated and synchronous contraction of myocardial tissue. The contractility of engrafted cells can occur naturally (for example, in the case of fetal cardiomyocytes or skeletal myoblasts) or be induced by transdifferentiation (for example, in the case of adult stem cells). Endothelial cells and fibroblasts have also been used to restore function to nonviable myocardium, but the results have been substantially inferior to those achieved with contractile cells.[1,2,8,10]

Embryonic Stem Cells

Embryonic stem cells are very conducive to stem-cell transplantation therapy, mainly because they are pluripotent. These cells are also weakly immunogenic, since they express only moderate amounts of MHC class I and no MHC class II proteins, and they can readily differentiate into nearly any cell in the body.[10,17] In vitro differentiation of ES cells into cardiomyocytes occurs in embryoid bodies. This differentiation can be divided into 3 stages: early, intermediate, and terminal. In the early stage, pacemaker-like cells are produced, and in the intermediate stage, atrial and ventricular cells and cells of the heart conduction system develop. During the terminal stage, well-organized bundles of myofibrils can be observed with clearly distinguishable A, I, and Z bands, and intercalated discs that contain desmosomes and gap junctions. Cardiomyocytes derived from terminally differentiated ES cells respond to β-adrenergic stimulation in vitro.[8]

Fetal and Neonatal Cardiomyocytes

Fetal and neonatal cardiomyocytes are not true stem cells, since they are already differentiated and do not, in practical terms, divide. Nevertheless, they can be used for cell cardiomyoplasty in ischemic myocardium. These cells are obtained from fetal and neonatal hearts, respectively, and then grown in tissue cultures. In animal models of myocardial infarction (MI), the cells have been successfully engrafted through epicardial injection into ischemic myocardium. These cells have also been shown to connect with host cardiomyocytes through intercalated discs containing desmosomes and gap junctions—a sign of their structural and functional integration into the host myocardium.

Skeletal Myoblasts

Histologically, skeletal myoblasts (SMs) are committed progenitors of skeletal muscle cells. Normally, they reside under the basement membrane of skeletal muscle fibers, where they remain quiescent until recruited for repair or regeneration of damaged muscle tissue. Skeletal myoblasts were the 1st potential cardiac stem cells to be explored extensively because of their autologous origin, high proliferative potential, commitment to a myogenic lineage, and resistance to ischemia. The last property is an especially important one for cells intended for implantation in the hypoxic environment of a postinfarction scar.[1,21,22] Studies in rats and human beings confirmed that implanted SMs could repopulate scar tissue, resulting in ventricular wall thickening, elevated ejection fraction, and improved contractility.[5,21–23] However, as shown by fluorescent studies, the engrafted cells also developed a peculiar phenotype of hyperexcitable myotubes with contractile activity that was completely unaffected by neighboring cardiomyocytes.[24] Other investigators found that SM-derived cardiomyocytes did not necessarily integrate into the surrounding host myocardium, as evidenced by the normal expression in vitro versus downregulated expression in vivo of 2 key proteins involved in electromechanical cell integration N-cadherin and connexin 43.[25] Therefore, the contribution of SM-derived cardiomyocytes to improved cardiac function cannot be explained in terms of electromechanical integration.[24]

Bone Marrow Stem Cells

Bone marrow is composed of various types of cells of specific phenotypes and function. Bone marrow cells can be transplanted either as total, unfractionated bone marrow or as a well-defined subpopulation of BMSCs.[1,27] Bone marrow has recently gained attention as a potential source of multipotent stem cells for cell cardiomyoplasty, particularly because of its easy accessibility, autologous origin, and ability to transdifferentiate into either myocardial or vascular cells.Total unfractionated bone marrow is usually aspirated

from the iliac crest and immediately injected into damaged myocardium. Although this approach seems very simple, feasible, and straightforward, it is not effective. Studies in sheep showed no improvement in regional or global cardiac function after injection of unfractionated bone marrow into scar tissue1 and no hemodynamic improvement after injection into infarcted myocardium. Another, slightly more complicated method is to inject a well-defined sub population of multipotent BMSCs into damaged myocardium. Preclinical results suggest that this approach is effective, although hematopoietic subpopulations appear to be more effective than nonhematopoietic subpopulations[29,30]: in a mouse model of MI, a nonhematopoietic subpopulation of BMSCs (CD34–, c-kit+, Sca-1+) known to re-generate the hematopoietic system was shown histologically to regenerate and revascularize cardiac tissue. In other mouse studies,[31] a hematopoietic subpopulation of BMSCs (CD34+, lin–, c-kit+), containing both short-term repopulating progenitor cells and long-term repopulating HSCs, was shown to regenerate ischemic myocardium. It is currently believed that long-term repopulating HSCs can transdifferentiate into cardiomyocytes and endothelial cells, making them capable of mediating the regeneration of damaged myocardium.[31] In 1 study,[32] fluorescently labeled CD34+, lin–, c-kit+ HSCs were injected into healthy myocardium adjacent to an infarct that had been induced several hours earlier by left coronary artery occlusion. Nine days later, a new band of myocardium occupying 68% of the infarcted area and extending across the entire infarct had appeared in 40% of the experimental cases. Further histologic analysis of the new myocardium revealed small fetal-like cardiomyocytes that were positive for A-actinin (a protein specific for cardiac and skeletal muscle); cardiac-specific myosin; several transcription factors known to promote stem-cell differentiation and activate cardiac gene programs (GATA-4, MEF2, and Csx/Nkx 2.5); and connexin 43.[31,32] Thirty-six percent of the fluorescently stained cardiomyocytes were also positive for BrdU, a sign that the HSC-derived cardiomyocytes were at 1 point mitotically active. Nineteen percent of fluorescent cells were also positive for Ki-67, a marker of active cell cycling.[32] The investigators also identified fluorescent endothelial and smooth muscle cells in the new myocardial tissue, indicating that revascularization accompanied myocardial regeneration. Improved cardiac function was confirmed by hemodynamic studies that showed a 30% to 40% improvement in left ventricular systolic and diastolic pressures after HSC injection. As further proof that HSCs were responsible for the therapeutic effects, it was shown that the lin–, c-kit+ subpopulation could not reconstitute bone marrow in irradiated animals and therefore does not contain HSCs.[12,29,31,32] The mobilization of HSCs from bone marrow can apparently be enhanced by cytokine factors, as shown by studies in a rat model of MI.[28,31,33] Treatment with cytokine stem-cell factor (SCF)—which binds to the c-kit tyrosine kinase receptor, and granulocyte colony-stimulating factor (G-CSF) led to a 250-fold increase in circulating HSCs. This in turn resulted in a band of new myocardium that occupied 76% of the infarct, a 61% reduction in 30-day mortality (from 78% to 17%), and substantially improved cardiac function. The phenotypes of engrafted cells included developing cardiomyocytes, endothelial cells, and smooth muscle cells. These results, together with those discussed above, suggest that lin–, c-kit+ cells can improve both short- and long-term outcomes of ischemic cardiomyopathy by transdifferentiating into physically and functionally integrated cardiomyocytes and vascular cells. Recently, multipotent mesenchymal stem cells (MSCs) have gained attention for their therapeutic potential. Also known as bone marrow stromal cells, MSCs are self-renewing clonal precursors of nonhematopoietic tissues derived from mesodermal germ layer. They are relatively easy to obtain from autologous bone marrow, to expand in vitro without sacrificing multipotency, and to cryopreserve for future use. At the Texas Heart Institute, allogeneic MSC injections were performed in a canine model of chronic ischemia induced by ameroid constriction. The MSCs differentiated into smooth muscle cells and endothelial cells, which resulted in increased vascularity and improved cardiac function both at rest and under stress. These results suggest that the ischemic burden of the left ventricle decreased after cell therapy.

Other Stem Cells

In addition to the stem cells already discussed, other sources of cardiac stem cells are currently under investigation. These include peripheral blood CD34+ cells, endothelial progenitor cells, fibroblasts, and cardiac progenitor cells.

Procedure

Stem cells can be delivered into the ischemic myocardium either by invasive or by noninvasive means. Invasive epicardial injection is done on a surgically exposed heart. Then, depending on the protocol used, cardiac stem cells are injected into the infarction itself or into the viable myocardial tissue surrounding it. However, in light of the

trend toward less invasive diagnostic and therapeutic procedures, percutaneous approaches are under investigation. Catheter-based trans-endocardial injection, which is technically feasible and functionally efficient, has been widely confirmed to be accurate for delineating and identifying scarred and viable myocardium and for differentiating degrees of infarct transmurality. The electromechanical mapping platform offers a benefit over surgical and intracoronary approaches, because the viability of the site can be determined before each injection. Injections can then be limited to targeted, viable areas of hibernating myocardium. Many treated sites in patients with ischemic heart failure are in areas of totally occluded epicardial vascular beds, making intracoronary delivery impossible. Furthermore, potential ischemia provoked by coronary manipulation is avoided with use of this method. This approved procedure seems safer for these chronically ill, high-risk patients because it avoids associated surgical morbidity and mortality. Catheter-based infusion through the coronary sinus is under study but is currently limited in its clinical application. There have been sporadic reports of successful intracoronary injections of stem cells during open-heart revascularization procedures, but larger trials are needed. Also under consideration are noninvasive methods of targeting the ischemic myocardium with stem cells that take advantage of endogenous mechanisms. Recent studies in a rat model showed that endogenous signaling via cytokines can enhance mobilization, homing, and trans-differentiation of stem cells.[11] Two possible explanations for this have been proposed. In the 1st mechanism, cytokines are released into the blood in response to cellular necrosis in the injured myocardium; from there, they mobilize BMSCs to enter the peripheral circulation. The mobilized stem cells then home in on adhesive receptors presented by the injured tissue and, once there, begin to differentiate into tissue-specific cells (that is, cardiomyocytes). In the 2nd mechanism, stem cells from the bone marrow continually circulate throughout the body, constantly traveling through all kinds of tissues. When myocardial injury occurs, the stem cells exit the circulation at the injury site and infiltrate. Both mechanisms assume that stem cells originate in a common pool (that is, the bone marrow), as discussed above.[11] Despite their relatively high efficiency, all of the above-mentioned delivery methods are hampered by a major limitation of cell cardiomyoplasty, namely, cell death. As many as 90% of transplanted cells die shortly after implantation as a result of physical stress from the implantation procedure itself, myocardial inflammation, or myocardial hypoxia. This does, however, suggest ways to improve the timing of cell cardiomyoplasty. Therapy too soon after an ischemic episode, when the damaged tissue is still inflamed, may increase the risk of cell death; therapy too late may decrease the chances of reverse myocardial remodeling.[1]

Researches about stem cell therapy for ischemic heart failure

Early results from phase I human trials of stem-cell therapy for ischemic heart disease are beginning to emerge. In 1 trial, 10 patients who had experienced MI were treated by bypass surgery and were also injected with skeletal myoblasts derived from the musculus vastus lateralis into the post infarction scar. The combined therapy resulted in ventricular wall thickening across 60% of the treated ischemic myocardium and improved systolic function. In general, this combined therapy was also safe and effective, although 4 patients did have some ventricular tachycardia that was apparently due to the stem-cell transplantation. No definite conclusions can be drawn about the benefits of the stem-cell therapy itself until larger, multicenter, randomized, controlled studies that do not involve concomitant revascularization can be done. In another trial,[31] 6 patients who had experienced MIs underwent implantation of autologous BMSCs into peri-infarction regions during a coronary artery bypass grafting procedure. After 9 to 16 months of follow-up, the patient-reported exercise capacity and the mean ejection fraction had noticeably improved in all cases, and no ventricular arrhythmias had occurred. In 5 patients, myocardial perfusion scans showed significant improvement in cardiac function (mean ejection fraction increased from 0.37 to 0.48).In a controlled trial,[10] patients who had suffered an acute MI were treated with BMSCs that were delivered to infarcted areas by a high-pressure balloon catheter 5 to 9 days after the ischemic event. The delay between MI and treatment was due to the time required to aspirate, separate, harvest, and culture the stem cells. When compared with untreated control patients at 3-month follow-up, the treated patients showed no change in ejection fraction. However, they did have a significant reduction in infarct size and a significant increase in stroke volume. No adverse effects were reported.

In the largest clinical trial of its kind so far, 21 high-risk patients with end-stage ischemic heart disease were enrolled in a prospective, nonrandomized trial of autologous mononuclear BMSCs. After thorough baseline evaluation, 14 patients received stem-cell treatment and 7 patients (controls) did not. In brief, autologous mononuclear BMSCs were injected trans-endocardially into viable myocardium identified by electromechanical mapping. At the 2-month follow-up visit, treated patients showed a significant reduction in total reversible defect and a significant increase in global left ventricular function. At 4 months, treated patients showed improved left ventricular ejection fraction (from 0.20 at baseline to 0.29) and reduced end-systolic volume. This technique appears to be feasible, safe, and effective. Several other clinical trials of stem-cell therapy for ischemic heart failure are under way in the United States. Their therapeutic results have not yet been published.

Research in Bangladesh

Zaman et al. observed that intracoronary administration of autologus BM derived stem cell therapy at least 2 months after ischemic attack is well tolerable and safe with modest improvement in exercise capacity, LVEF at 6months follow up. This study demonstrated a significant improvement in 6MWD, SpO2, BROG scale, LVEF by echocardiography with no mortality in SCT group compared to control group. The echocardigraphic evaluation of this study revealed a significant increased in LVEF at 6 months follow up in both control and SCT group (29.5± 0.8 to 34±1.6)% and (28.7±1.3 to 40+_ 2.5)% respectively, P=0.04. But SCT group showed more significant improvement at 6 months from the baseline than GDMT only group (P=0.02 vs P=0.07).[33]

Research in Egypt

Madathil et al. (2022) stated that cell therapy for cardiac regeneration has been examined over two decades and thus the safety of such approaches is established in clinical studies. Recent approaches using hESCs and iPSC derived cardiomyocyte have significantly increased our understanding of mechanisms governing cardiovascular differentiation and the modeling of adult onset disease phenotype.

Shiba et al. showed that hESC derived cardiomyocytes can electrically couple and protect against arrhythmia.[34]

Zhu et al. observed that in vivo hESC derived graft soon disappeared and the modest LV functional improvement was due to ongoing paracrine mechanisms. Similar observations were noted by other investigators in different settings.[35]

Research in USA

Tehzeeb et al. (2019) observed that stem cell therapy has been considered as a promising alternative to conventional treatments. The use of stem cells for the replacement of damaged heart tissues can help improve functioning. In addition, these cells have shown a beneficial role in stimulating neovascularization and preventing myocardial cell death and thereby preventing heart failure.[36]

Patel et al. (2005) did a randomized control trial (RCT) in 20 patients with ischemic HF and left ventricular ejection fraction (LVEF) documented as less than 35% of normal. Stem cells were delivered to subpericardial areas of the patients in the experimental group. It showed an increase in LVEF from a pretreatment value of 29.4% of normal to 46.1% in the patients with ischemic HF receiving autologus SCT plus coronary artery bypass grafting (CABG), as opposed to an increase from 30.7% to 37.2% in the control group that received only CABG. No adverse effects were observed in either group. Clinically, this was a notable finding in favor of SCT.[37]

Another clinical trial "The Acute and Long-term effects of Intracoronary Stem Cell Transplantation in 191 patients with Chronic Heart Failure: the STAR heart study" involved intracoronary injections of stem cells in patients with ischemic HF and low LVEF. The cells were obtained from bone marrow of the same patients to whom they were delivered (autologous). Data analysis at upto five years after the initiation of this treatment showed that SCT led to an increase LVEF, dercease in left ventricular preload, end systolic volume (ESV), systolic wall stress, area of infract and long term mortality was noted in New York Heart Association (NYHA).[38]

Conclusion

Stem cell therapy for ischemic heart failure is very promising. Clinical trials found SCT to be safe and beneficial in heart failure patients, improve cardiac performance and increase left ventricular formation like LVEF.

References

1. Poss KD, Wilson LG, Keating MT. Heart regeneration in zebrafish. Science 2002;298:2188-90.
2. Pasumarthi KB, Nakajima H, Nakajima HO, Soonpaa MH, Field LJ. Targeted expression of cyclin D2 results in cardiomyocyte DNA synthesis and infarct regression in transgenic mice.Circ Res 2005;96:110-8.
3. Oh H, Wang SC, Prahash A, et al. Telomere attrition and chk2 activation in human heart failure. Proc Natl Acad Sci USA 2003; 100:5378-83.
4. Losordo DW, Dimmeler S. Therapeutic angiogenesis and vasculogenesis for ischemic disease:part I. angiogenic cytokines. Circulation 2004;109:2487-91.
5. Olson EN, Schneider MD. Sizing up the heart: developmentredux in disease. Genes Dev 2003;17:1937-56.
6. Smith RR, Barile L, Cho HC, Leppo MK, Hare JM, MessinaE, et al. Regenerative potential of cardiosphere-derived cells expanded from percutaneous endomyocardial biopsy specimens.Circulation. 2007 Feb 20;115:896-908.
7. Hu S, Liu S, Zheng Z, Yuan X, Li L, Lu M, Shen R, Duan F, Zhang X, Li J, Liu X, Song Y, Wang W, Zhao S, He Z, Zhang H, Yang K, Feng W, Wang X. Isolated coronary artery bypass graft combined with bone marrow mononuclear cells delivered through a graft vessel for patients with previous myocardial infarction and chronic heart failure: a single-center, randomized, double-blind, placebo-controlled clinical trial. J Am Coll Cardiol. 2011;57:2409–15.
8. Kupatt C, Hinkel R, Lamparter M, et al.: Retroinfusion of embryonic endothelial progenitor cells attenuates ischemia- reperfusion injury in pigs. Role of phosphatidylinositol 3- kinase/AKT kinase.Circulation. 2005, 112:117-22.
9. Kupatt C, Horstkotte J, Vlastos GA, et al.: Embryonic endothelial progenitor cells expressing a broad range of proangiogenic and remodeling factors enhance vascularization and tissue recovery in acute and chronic ischemia.
10. Gepstein L. Derivation and potential applications of human embryonic stem cells. Circ Res 2002;91:866–76.
11. Orlic D, Hill JM, Arai AE. Stem cells for myocardial regeneration. Circ Res 2002;91:1092–102.
12. Orlic D. Adult bone marrow stem cells regenerate myocardium in ischemic heart disease. Ann N Y Acad Sci 2003;996: 152–7.
13. Ying QL, Nichols J, Evans EP, Smith AG. Changing potency by spontaneous fusion. Nature 2002;416:545–8.
14. Wang X, Willenbring H, Akkari Y, Torimaru Y, Foster M, Al-Dhalimy M, et al. Cell fusion is the principal source of bone-marrow-derived hepatocytes. Nature 2003;422:897–901.
15. Vassilopoulos G, Wang PR, Russell DW. Transplanted bone marrow regenerates liver by cell fusion. Nature 2003;422: 901–4.
16. Etzion S, Barbash IM, Feinberg MS, Zarin P, Miller L, Guetta E, et al. Cellular cardiomyoplasty of cardiac fibroblasts by adenoviral delivery of MyoD ex vivo: an unlimited source of cells for myocardial repair. Circulation 2002;106 (12 Suppl 1):I125–30.
17. Min JY, Yang Y, Converso KL, Liu L, Huang Q, Morgan JP, Xiao YF. Transplantation of embryonic stem cells improves cardiac function in postinfarcted rats. J Appl Physiol 2002; 92:288–96.
18. Leor J, Patterson M, Quinones MJ, Kedes LH, Kloner RA. Transplantation of fetal myocardial tissue into the infarcted myocardium of rat. A potential method for repair of infarcted myocardium Circulation 1996;94(9 Suppl):II332–6.
19. Scorsin M, Hagege AA, Marotte F, Mirochnik N, Copin H, Barnoux M, et al. Does transplantation of cardiomyocytes improve function of infarcted myocardium? Circulation 1997;96(9 Suppl):II-188–93.
20. Li RK, Jia ZQ, Weisel RD, Mickle DA, Zhang J, Mohabeer MK, et al. Cardiomyocyte transplantation improves heart function. Ann Thorac Surg 1996;62:654–61.
21. Tambara K, Sakakibara Y, Sakaguchi G, Lu F, Premaratne GU, Lin X, et al. Transplanted skeletal myoblasts can fully replace the infarcted myocardium when they survive in the host in large numbers. Circulation 2003;108(Suppl 1):II259–63.
22. Goodell MA, Jackson KA, Majka SM, Mi T, Wang H, Pocius J, et al. Stem cell plasticity in muscle and bone marrow. Ann N Y Acad Sci 2001;938:208–20.
23. Pagani FD, DerSimonian H, Zawadzka A, Wetzel K, Edge AS, Jacoby DB, et al. Autologous skeletal myoblasts transplanted to ischemia-damaged myocardium in humans. Histological analysis of cell survival and differentiation. J Am Coll Cardiol 2003;41:879–88.
24. Leobon B, Garcin I, Menasche P, Vilquin JT, Audinat E, Charpak S. Myoblasts transplanted into rat infarcted myocardium are functionally isolated from their host. Proc Natl Acad Sci U S A 2003;100:7808–11.
25. Reinecke H, MacDonald GH, Hauschka SD, Murry CE. Electromechanical coupling between skeletal and cardiac muscle. Implications for infarct repair. J Cell Biol 2000; 149:731–40.
26. Scorsin M, Hagege A, Vilquin JT, Fiszman M, Marotte F, Samuel JL, et al. Comparison of the effects of fetal cardiomyocyte and skeletal myoblast transplantation on postinfarction left ventricular function. J Thorac Cardiovasc Surg 2000;119:1169–75.
27. Horwitz EM. Bone marrow transplantation: it's not just about blood anymore! Pediatr Transplant 2003;7 Suppl 3:56–8.

28. Bel A, Messas E, Agbulut O, Richard P, Samuel JL, Bruneval P, et al. Transplantation of autologous fresh bone marrow into infarcted myocardium: a word of caution. Circulation 2003;108 Suppl 1:II247–52.

29. Stamm C, Westphal B, Kleine HD, Petzsch M, Kittner C, Klinge H, et al. Autologous bone-marrow stem-cell transplantation for myocardial regeneration. Lancet 2003;361: 45–6.

30. Jackson KA, Majka SM, Wang H, Pocius J, Hartley CJ, Majesky MW, et al. Regeneration of ischemic cardiac muscle and vascular endothelium by adult stem cells. J Clin Invest 2001;107:1395–402.

31. Orlic D, Kajstura J, Chimenti S, Bodine SM, Leri A, Anversa P. Bone marrow stem cells regenerate infarcted myocardium. Pediatr Transplant 2003;7 Suppl 3:86–8.

32. Orlic D, Kajstura J, Chimenti S, Bodine DM, Leri A, Anversa P. Transplanted adult bone marrow cells repair myocardial infarcts in mice. Ann N Y Acad Sci 2001;938:221–30.

33. Zaman SMM , Khaled MFI , Dey BP , Begum M , Ahmed SM, Islam MA , Banerjee SK , Hoque MH. Pilot study of Stem Cell Therapy in Heart Failure Patients. University Heart Journal 2020; 16(2): 52-58.

34. Shiba Y, Fernandes S, Zhu WZ, Filice D et al. Human ES-cell-derived cardiomyocytes electrically couple and suppress arrhythmias in injured hearts. Nature. 2012;489(7415):322-325. doi: 10.1038/nature11317. PMID: 22864415; PMCI

35. Zhu K, Qiang Wu, Cheng Ni, Zhang P et al. Lack of Remuscularization Following Transplantation of Human Embryonic Stem Cell-Derived Cardiovascular Progenitor Cells in Infarcted Nonhuman Primates. Circulation Research.2018; 122(7):958-969.

36. Tehzeeb J, Manzoor A, Ahmed MM. Is Stem Cell Therapy an Answer to Heart Failure: A Literature Search. Cureus. 2019;11(10):e5959. doi: 10.7759/cureus.5959. PMID: 31803548; PMCID: PMC6874291.

37. Patel AN, Geffner L, Vina RF, et al. Surgical treatment for congestive heart failure with autologous adult stem cell transplantation: a prospective randomized study. J Thorac Cardiovasc Surg. 2005;130:1631–1638.

38. Strauer BE*, Yousef M, and Schannwell CM. The acute and long-term effects of intracoronary Stem cell Transplantation in 191 patients with chronic heartt failure: the STAR-heart study. European Journal of Heart Failure. 2010;12: 721–729. doi:10.1093/eurjhf/hfq095

Case Report

Congenital Hypothyroidism: A Case Report of a 26 Years Old Female

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Abstract

Congenital hypothyroidism (CH) results from thyroid hormone deficiency present since birth, with a worldwide incidence of 1: 3000 - 4000 infants. It may manifest either in neonatal period or early infancy. Newborn screening has dramatically reduced rates of untreated CH. However, in low-income nations where newborn screening programs do not exist, untreated CH remains a significant health and societal challenge. Untreated children present with profound mental retardation and severe growth restriction. This is a case report of a 26 year old female who presented with severe breathlessness along with poor growth, speech and learning difficulties.

Key Words: Congenital hypothyroidism, Thyroid hormone, Mental retardation, Growth restriction

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Introduction

Congenital hypothyroidism (CH) is a common and preventable cause of irreversible intellectual disability (ID)[1]. Laboratory screening allows prompt initiation of treatment during the first month of life [2]. CH is a partial or complete loss of function of the thyroid gland (hypothyroidism) that affects infants from birth (congenital)[3]. CH is the most common neonatal endocrine disorder, and this can occur because of an anatomic defect in the gland, an inborn error of thyroid metabolism or iodine deficiency[4]. Historically, thyroid dysgenesis was thought to account for approximately 80% of cases. The incidence of CH, as detected through newborn screening, is approximately 1 per 4000 births[5]. Thyroid hormone is very essential for the normal development of brain growth and myelination and for the maintenance of neuronal connections. Thyroid hormone plays its most critical role in the first few months of life, especially for brain development[6].

Significant mental retardation is considered the most serious complication of untreated congenital hypothyroidism. Severe impairment of linear growth and bone maturation also occurs[3]. Decreased levels of serum thyroid hormone (total or free T4) and elevated levels of thyroid-stimulating hormone (TSH) aid in the establishment of the diagnosis of congenital hypothyroidism[7]. Thyroid scanning (using technetium-99m or iodine-123) may be useful in defining the cause of CH and may help in genetic counseling[8]. Moreover, thyroid scans can demonstrate the presence of an ectopic thyroid, such as a lingual or sublingual gland. Ultrasonography may be a reasonable alternative or addition to scintigraphy but may fail to reveal some ectopic glands[8]. The main obstacle in the management of CH is early diagnosis and thyroid hormone replacement[9].

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Case report

Miss Taslima, 26 years old female hailing from Bagerhat, Bangladesh got admitted into Khulna Medical College Hospital on 19/10/2022 with the complaints of growth retardation, delayed achievements of milestones of development, progressive abdominal swelling and breathlessness for last 3 months. According to her parents, though Taslima is 26 years old, she has failed to attain adequate growth like other children since her childhood which became more noticeable after 03 years of her age. Since then she had poor appetite and used to pass stools two to three times weekly which were hard most of the times. She also had cold intolerance and was not as active as her siblings. Her mother had no significant illness and pregnancy was uneventful while carrying her. She was delivered at term by normal vaginal delivery (NVD) with a birth weight of 2700gm and did not have any history of prolonged jaundice, poor feeding or lethargy. She was exclusively breast fed for 6 months. Her milestones of development were at the lower limit of normal and lagged behind her siblings. After 03 years of age development became very sluggish. Her mother did not have neck swelling nor used anti-thyroid medication. Her siblings did not have similar problem. She has been suffering from gradual abdominal distension and respiratory distress for the last 2 months. Her menarche started at the age of17 years. Menstrual cycle is irregular happening at 4-5 months interval with heavy flow and menstrual period is average 10-15 days. She had completed her immunization as per EPI schedule.

On examination, she was dyspnoeic at rest with propped up position, moderately anaemic, had coarse, puffy facial appearance with depressed nasal bridge and a protruding tongue, periorbital swelling, baggy eyelids, loss of both lateral eyebrows. Skin was dry, rough, coarse and hair was dry, sparse. There was bipedal non-pitting oedema and JVP was raised. She had short, broad hand with short fingers. Her anthropometry was like under 5 child proportion with a height of 105 cm, weight of 20 kg; BMI was 18 kg/m2 (Figure 1). There was no goiter. Abdomen was distended with clinically evident ascites with umbilical hernia but no other organomegaly. Heart sounds were muffled. Her concentration and memory was poor and intelligence below average. She had hypotonia with delayed relaxation of ankle jerk. Vision and hearing was intact but voice was hoarse. Other systemic examination including respiratory system was normal.

Figure 1: Photographs of the patient (with permission from patient)

Laboratory investigations showed hemoglobin -5.2 gm/dl, ESR-50 mm in 1st hour, WBC-8500/cu mm with 54% polymorph, 41% lymphocytes. PBF -normocytic, normochromic and macrocytic RBC. Her thyroid profile was suggestive of hypothyroidism: S TSH > 150 miu/ml [Normal 0.4 - 4] with undetectable FT3 and FT4. USG of thyroid was normal. Chest X-ray showed enlarged cardiac shadow and. ECG showed low voltage tracing with sinus rhythm. A 2D echocardiography revealed moderate pericardial effusion with features of impending cardiac temponade. Fasting lipid profile was total cholesterol -168 mg/dl, T.G -170 mg/dl, HDL -38 mg/dl, LDL -96 mg/dl. Serum Electrolytes : Sodium -140.8 mmol/l, Potasium -3.80 mmol/l, Chloride -96.2 mmol/l. Thus she was diagnosed as congenital hypothyroidism with pericardial effusion, most likely due to dyshormonogenesis. Thyroxin was started at a dose of 50μ/day with other supportive treatment and for urgent pericardiocentesis she was referred to Shahid Sheikh Abu Naser Specialised Hospital, Khulna.

Discussion

CH is a partial or complete loss of function of the thyroid gland (hypothyroidism) that affects infants from birth (congenital)[10]. The thyroid gland is a butterfly-shaped tissue in the lower neck. It makes iodine-containing hormones that play an important role in regulating growth, brain development, and the rate of chemical reactions in the body (metabolism). People with CH have lower-than-normal levels of these important hormones. CH occurs when the thyroid gland fails to develop or function properly[11]. In 80 to 85 percent of cases, the thyroid gland is absent, severely reduced in size (hypoplastic), or abnormally located. These cases are classified as thyroid dysgenesis[12]. In the remainder of cases, a normal-sized or enlarged thyroid gland (goiter) is present, but production of thyroid hormones is decreased or absent. Most of these cases occur when one of several steps in the hormone synthesis process is impaired; these cases are classified as thyroid dyshormonogenesis[13].

If the hypothyroidism developed early during fetal life, the effect might appear in certain

organ systems, including the central nervous system and skeleton. However, most infants with CH are normal at birth. The diagnosis of hypothyroidism at birth based on clinical evidence is rarely possible[14]. The diagnosis of CH is not always easy to make due to nonspecific symptoms. Usually specific symptoms do not appear in newborns, so most infants are diagnosed by the neonatal screening program. The specific clinical signs are prolonged jaundice, lethargy, feeding problems, constipation, hypothermia, mottling and dry skin, umbilical hernia, macroglossia, anterior and posterior open fontanels, hoarse cry, and delayed relaxation of ankle jerk. The physical development is usually retarded, such as delayed sitting, standing, and talking ages. The degree of physical and mental retardation increases with the age of diagnosis and treatment. The child is stunted in growth.

In developed countries, where neonatal screening is done routinely, the prognosis for affected infants has improved dramatically. However, this is not routinely done in our country, so her diagnosis was not made at birth. Furthermore, in the case highlighted, she appeared normal to her parents until about three years of age when she practically stopped growing and subsequently could not read or write like her peers. This patient unlike most others did not have obvious features in infancy; the delay in overt manifestation in this case is due to the transplacental transfer of moderate amounts of maternal T4, coupled with the function of the hypoplastic gland. This late onset of symptoms is in keeping with thyroid gland hypoplasia. The outlook for patients whose onset is after two years is much better even in the face of delay in diagnosis and treatment.

The consequences of untreated CH, constitute a great burden to the family and nation at large particularly when it comes in terms of severe mental retardation and growth restriction. The cost of special education and institutionalization of these affected children is surely at least many folds than the cost of the screening program.

Conclusion

In a summary it can be stated that birth screening program can aid in early diagnosis and management of CH to a large extent. As implementation of this large-scale screening program requires multilevel planning, approval and finance so at present at least we should decrease the threshold for suspicion. Otherwise, we will miss lots of cases.

References

1. Grosse SD, Van Vliet G. Prevention of intellectual disability through screening for congenital hypothyroidism: how much and at what level? Archives of disease in childhood. 2011;96(4):374–9.
2. Rose SR, Brown RS, Foley T, Kaplowitz PB, Kaye CI, Sundararajan S. American Academy of Pediatrics; Section on Endocrinology and Committee on Genetics, American Thyroid Association; Public Health Committee, Lawson Wilkins Pediatric Endocrine Society. Update of newborn screening and therapy for congenital hypothyroidism. Pediatrics. 2006;117(6):2290–303.
3. Gomella TL, Cunningham MD, Eyal FG, Tuttle DJ. Neonatology: management, procedures, on-call problems, diseases, and drugs. McGraw-Hill Education Medical New York, NY; 2013.
4. The Lecturio Medical Concept Library. Hypothyroidism | Concise Medical Knowledge [Internet]. 2022 [cited 2023 May 2]. Available from: https://www.lecturio.com/concepts/hypothyroidism/
5. Hershey AD, Migraine Kliegman RM, Stanton BF, Schor NF, St Geme JW, Behrman RE. Nelson Textbook of Pediatrics. 19th Edit. Saunders, Philadelphia; 2011.
6. Kurinczuk JJ, Bower C, Lewis B, Byrne G. Congenital hypothyroidism in Western Australia 1981–1998. Journal of paediatrics and child health. 2002;38(2):187–91.
7. Hertzberg V, Mei J, Therrell BL. Effect of laboratory practices on the incidence rate of congenital hypothyroidism. Pediatrics. 2010;125(Supplement_2):S48–53.
8. Eugster EA, LeMay D, Zerin JM, Pescovitz OH. Definitive diagnosis in children with congenital hypothyroidism. The Journal of pediatrics. 2004;144(5):643–7.
9. Perry RJ, Maroo S, Maclennan AC, Jones JH, Donaldson MD. Combined ultrasound and isotope scanning is more informative in the diagnosis of congenital hypothyroidism than single scanning. Archives of Disease in Childhood. 2006;91(12):972–6.
10. Klett M. Epidemiology of congenital hypothyroidism. Experimental and Clinical Endocrinology & Diabetes. 1997;105(S 04):19–23.
11. Rastogi MV, LaFranchi SH. Congenital hypothyroidism. Orphanet journal of rare diseases. 2010;5(1):1–22.
12. Harris KB, Pass KA. Increase in congenital hypothyroidism in New York State and in the United States. Molecular genetics and metabolism. 2007;91(3):268–77.
13. Olney RS, Grosse SD, Vogt RF. Prevalence of Congenital Hypothyroidism—Current Trends and Future Directions: Workshop Summary. Pediatrics [Internet]. 2010 May 1 [cited 2023 May 2];125(Supplement_2):S31–6. Available from: https://publications.aap.org/pediatrics/article/125/Supplement_2/S31/29827/Prevalence-of-Congenital-Hypothyroidism-Current
14. Medda E, Olivieri A, Stazi MA, Grandolfo ME, Fazzini C, Baserga M, et al. Risk factors for congenital hypothyroidism: results of a population case-control study (1997–2003). eur j endocrinol [Internet]. 2005 Dec [cited 2023 May 2];153(6):765–73. Available from: https://academic.oup.com/ejendo/article/153/6/765/6695196

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It will include statement of the problem with a short discussion of its importance and significance, short review of the literature related to the problem with pertinent reference and lastly objectives/ rationale/ benefits expected will be stated in 1-2 paragraph.

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