Robotic surgery in urology

Thrombocytopenia in the emergency department

Barriers to tobacco smoking in dental students

Phenotypic mapping in autism spectrum disorders
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ABSTRACT
Urology as a subspecialty of surgery is always driven by rapid adaptation of technological advances, from open surgery to endoscopic surgery and laparoscopy. Arrival of robotic system marked a new era in urology. In this comprehensive systemic review we analysed current status of robotic system in urology as well what we can expect in future. Robotic surgery is now widely use in urologic oncology and reconstructive urology with excellent outcomes. High initial installation costs with high disposable cost per surgery combined with lack on insurance are current reasons for slow progression of robotic surgery is India. Advent of new systems may end monopoly and can bring down cost of robotic systems in future.

Keywords: Robotic surgery, robotic urology.

INTRODUCTION
What Hippocrates told to diagnose the diseases holds true for technology in medicine as well

“Declare the past, diagnose the present, and foretell the future.”

We all know that the only one thing certain in universe is “change”. Advent of robotic surgery marked a new era in Robotic urology. As it provided better ergonomics, optimal magnification of the operative field, surgeon dexterity, and precision of surgical manipulation, it overcame many difficulties associated with pure laparoscopy. Robotic assisted prostatectomy and robot-assisted partial nephrectomy have been widely considered as minimally invasive alternatives to open surgery with equivalent oncological and probably better functional outcome. After success in above procedures robotic surgery is now commonly used in other genitourinary diseases such as bladder cancer, upper tract urothelial cancer, ureteropelvic junction obstruction, adrenal surgery and reconstructive urology. Expanding evolving indications for Robotic urologic surgery also focus on pelvic organ prolapse and Microsurgery in Male Infertility and Andrology.

METHODOLOGY
A comprehensive literature search focusing on the management of role of robotic surgery in urology was done. All articles in PUBMED, Medline, EMBASE and the Cochrane Libraries were reviewed. Final selection of articles was limited to studies representing high levels of evidence such as prospective comparative studies, randomised controlled trials, systemic reviews and meta-analysis. Review of past and current robotic system also included product monograph and details from various websites of relevant companies.

Time line of robotic assisted surgery, from past to future.

High initial installation cost and high disposable cost per surgery are major hindrance for wider adaptation in the Indian subcontinent. With upcoming newer systems the cost of robotic surgery may go down making it accessible to many parts in Indian subcontinent. In future it may replace laparoscopic surgery with similar costs and better outcomes for patients and comfort of ergonomic position for surgeon. India is predicted to become second largest centre for robotic surgery center in world after USA².

The earliest form of Robot involved in a surgical procedure goes back to 1985 when the PUMA 560 robotic arm was used to perform a brain biopsy. Following which, in 1987, was used for cholecystectomy. The da Vinci (Intuitive Surgical Inc., Mountain View, CA, USA) got FDA approval in 2000 and at present there are around 80 da Vinci system working in India with over 1.7 million robotic assisted procedure performed worldwide till now². Intuitive surgical is world leader in robotic surgical systems for over 18 years and have grown by 237% over the last 5 years as per ISRG’s stock report³. Historically they have updated systems every 4 to 6 years with da Vinci Si, X, Xi are common models currently in use in India. da Vinci SP is recently launched in USA and initial reports of successful adaptation in urology is coming up. da Vinci has evolved as a comprehensive system with integrated intraoperative ultrasonography (USG), infrared imaging with indocyanine green and energy sources such as ultrasonic shears and tissue sealers developed over time, helping surgeons to perform complex minimally invasive surgeries.

Alternative to da Vinci systems: The other robots.

REVO I Robotic Surgical System (Meere Company, South Korea)
The REVO-I system is a master slave system similar to the Da Vinci system. They developed the current model (after working for over 20 different systems) the MSR-5000 REVO-I which was introduced in 2015. Clinical trail for performing cholecystectomy and prostatectomy
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was successful, following which it got Korean FDA approval in August 2017.6,5

**Senhance Surgical Robotic System (Transenterix, USA)**

Initially developed by the Italian company called Sofar, as ALF-X robotic system. The system was later bought by US-based Transenterix Company later renaming it as Senhance Surgical Robotic System. It has advantages of being compatible with any 3D vision cart system and with use of laparoscopy instruments helping in significant reduction of cost. All available data is from gynaecological or colorectal procedures.7,8

**Hugo RAS** - the newly launched Robot from Medtronics Company was unveiled recently and carries more flexibility in usage of arms. The Hugo system has 3 components – central tower, console and multiple cart-based rolling robotic arms. The advantage is cost effectiveness being comparable to conventional laparoscopy. The system has incorporated the current standards of vision magnification and 3D vision. The system is aiming at CE and FDA approval around 2021 – first quarter.9

**The Versius robot** by CMR Company is a machine system from Cambridge, UK, similar to Hugo RAS mentioned above. The company has received ISO certification in September 2018 for further use of its system for practical use. This system has individual robotic arms for use and has more flexibility and could hence be cost-effective.10

**Verb surgicals** – merger of Johnson & Johnson and Verily (Google's concern) is working in the lines of producing another robot in the near future.11

**Components of robots**

The most commonly used Da Vinci robot has 3 main components – the console, the vision cart and the patient-side cart. The surgeon console is the place from where the surgeon performs the surgery using controllers for hand and feet. This controls the camera and the operating robotic arms. It has 3D vision with magnification. The vision cart carries all the instruments that are needed for surgery like the camera processor, light source, pneumo system and diathermy system. The patient side cart has the robotic arms which get attached with camera and instruments in the four arms and perform the actions simulated in the console inside the patient’s body. Docking is the process by which the robotic arms are attached to the ports and arms are aligned for surgery.12,13

**Role of robotic surgery for Partial nephrectomy**

The role of Robotic surgery in partial nephrectomy is well established with many papers. Beyond regular advantages of less bleeding, transfusion, hospital stay and analgesic requirement, the robotic approach provided most importantly less eGFR loss and ability to complete procedures for complex renal tumours.14

A 13 year analysis of Data involving 416 hospitals and 24000 patients, needing renal surgery concluded that the number of robotic surgeries have surpassed the number of laparoscopic procedures in recent times and there was no difference in the outcomes of the two modalities except for longer operative duration and higher cost per patient. For complex tumors, the operative time was similar between laparoscopy and robotic approaches. But the higher cost was due to the use of additional surgical disposables.15 The robotic approach when compared to laparoscopic partial nephrectomy proved better in terms of ability to attempt complex cases with better success, less warm ischemia time, less conversions rate to open, less positive surgical margins, less complications.16

**Emerging role of additional technology**

The Firefly technology introduced in da Vinci Si HD vision system helps in incorporating real-time near infra-red fluorescence imaging with the help of Indocyanine green for providing excellent delineation of vascular anatomy. In partial nephrectomy, it ensures adequate clamping of renal artery prior to tumor dissection and to rule out the presence of additional accessory arteries. Indocyanine green works by binding with plasma proteins which retain it in circulation. Hence, after declamping, uptake is well in normal renal parenchyma and reduced uptake in renal cortical tumors which have reduced expression of the protein. This is better appreciated after the initiation of dissection of tumor from its bed.17,18

The drop down Ultrasound probe provides good radiological imaging. It delineates tumor from normal renal parenchyma. Intra-operatively, helps complete tumor removal, ensuring negative surgical margin and helps preserve normal renal parenchyma. All these techniques helps achieve trifecta- (negative margins, no urologic complications, minimal decrease in renal function) in post operative period. Robotic surgery when selected for appropriate patients, with a technically sound procedure, care guided pathway, peri-operative management, provides good outcomes in most cases achieving goals of pentafecta (long term cancer control and avoidance of all complications). Robotic surgery when available can replicate oncological outcomes of open surgery in complex cases with advantages of minimal access surgery.

**Robot assisted Laparoscopic Radical Prostatectomy (RARP)**

10 year retrospective single centre, single surgeon experience of 902 cases of Radical Prostatectomy surgeries – open Retropubic Radical Prostatectomy(RRP) vs Laparoscopic Radical Prostatectomy (LRP) vs RARP were compared and found to show RARP had lesser blood loss, less transfusion, less hospital stay on comparing the 3 arms and lesser conversion rate to RRP when comparing with LRP. Margin positive rate was same in
3 groups. 1 year continence rate was slightly better in robotic arm when compared to laparoscopic and open surgery. The conversion rate of LRP all over the world are around 2-8%, whereas for RARP is around 0-1%. The complication rate of RARP is lower than LRP or RRP (13% vs 20-28% for LRP and RRP) and minimal Clavien-Dindo grade 4/5 complications. The experience of a surgeon has been proved to be an important factor for trifecta of results in RP surgeries. The learning curve for LRP is steep as compared to RARP. Better vision, dexterity and accessibility of difficult areas in pelvis has made RARP preferable option by surgeons over LRP or RRP.

**Robot assisted laparoscopic Radical Cystectomy with diversion**

Although the use of Robot improves surgeon comfort and less blood loss and need for transfusion and less hospital stay, the oncological outcome of this does not score over open cystectomy and is comparable on the same level. Additional concerning factor in the Indian population is the cost of surgery. The use of Robot in cystectomy increases the cost of procedure by double or triple and may not be suitable for all centres to adapt the same.

The RAZOR trial was a prospective multicentre randomised control trial which evaluated 350 patients with bladder cancer for radical cystectomy under different surgical approaches. The study showed similar oncological outcomes with progression free survival rate being similar. The benefits of minimally invasive surgery of less blood loss, transfusion, hospital stay, analgesic use and scar were better than the open surgery arm.

Literature review comparing open vs robotic cystectomy suggested robotic to have lesser blood loss, need for transfusion, narcotic need, hospital stay and faster GI recovery. However, robot also takes more operative time and is more expensive. No differences in positive surgical margins or lymph nodes, continence rate or recurrence rate were noted. There is still an increased risk of distant metastasis to extra pelvis lymph nodes and peritoneum associated with robot. A single surgeon trial comparing outcomes of radical cystectomy with intra corporeal conduit creation vs. open cystectomy was done over a 2 year period including 39 patients concluded that oncological outcomes and complication rates were similar. iROC is the only randomised control trial comparing complete intra corporeal conduit creation vs. ORC. The study is still midway and will have results close to analyse by 2020. The advantages of this trial being complete intra corporeal anastomosis as a mandate while most other studies compare robotic cystectomy with extracorporeal anastomosis which leads to loss of advantage of minimally invasive approach.

**Robot Assisted Adrenal surgery**

Robotic surgery has shown to be feasible and safe for resection of benign as well as malignant conditions of adrenal gland. When compared to open and laparoscopic adrenalectomy, robotic adrenalectomy is associated with lower blood loss and length of hospital stay but is associated with more cost per surgery. Robotic surgery can provide distinct advantage in case of partial resection in patients with familial syndromes. It may provide advantage over conventional laparoscopy in case of large tumors, pheochromocytomas and in obese patients.

**Role in reconstructive urology**

Robotic pyeloplasty is preferred by surgeons over laparoscopy for the ease of intra-corporeal suturing and in paediatric patients due to smaller surgical scars compared to open incision. The first reported case of Robot assisted vesico-vaginal fistula closure was done in 2004. A single centre retrospective analysis of 4 years data of patients undergoing Robot assisted laparoscopic vesico-vaginal fistula repair was reported. Surgery was successful and all patients had a 2 year symptom-free follow up.

Even post cervical cancer brachytherapy infra-trigonal vesicovaginal fistula was repaired by Robot assisted transpertoneal transvesical approach and is symptom free on follow up. First simple robot assisted simple prostatectomy was performed in 2007. Subsequently a small series of cases were treated by the same technique with less complications and better patient comfort than open procedures. All patients had continence by 3rd month.

Robotic Video Endoscopic Inguinal Lymphadenectomy (VEIL) is a relatively newer surgical procedure to adopt robot assistance and is gaining preference due to its precise movements and visualisation with added advantages of minimally access surgery. Patients have better recovery with lesser complications. Our Indian data on initial VEIL produced successful outcome and good oncological yield.

**Role of robotic surgery in functional urology**

As the ageing population is increasing, the demand for correction of pelvic organ prolapse in expected to grow. Correction of Pelvic Organ Prolapse can be done vaginally or through abdominal approach. Current available data supports superiority of abdominal sacrocolpopexy in correction of apical prolapse. Robotic sacrocolpopexy may become the preferred treatment approach for women with moderate prolapse and an apical component due to avoidance of mesh and related complications with outcomes matching open counterpart and advantages of minimally invasive surgery.

Other procedures performed are the correction of...
female stress urinary incontinence (artificial urinary sphincter) and the treatment of chronic pelvic pain (pudendal nerve neurolysis)\textsuperscript{39}.

**Robot-Assisted Microsurgery in Male Infertility and Andrology**

Role of Robot-Assisted Microsurgery in Male Infertility and Andrology is still evolving. Early data reports some benefits. It has been used for Robot-assisted microsurgical vasectomy reversal, Robot-assisted microsurgical sub-inguinal varicocelectomy, Robot-assisted microsurgical testicular sperm extraction, Robot-assisted microsurgical targeted denervation of the spermatic cord. This area of robotic surgery is still evolving and future looks promising. But, as with any other technology, cost and long term outcome in randomized controlled studies will define further progress in such subspecialties of urology\textsuperscript{40-45}.

**Role of Bed-Side Surgeon in Robotics (patient side surgeon) and learning robotic surgery**

The term patient side surgeon (PSS) plays a vital role in safe conduct of robotic surgery and is the primary interface among the console surgeon, robot and patient. Role of assistant surgeon is more in robotic surgery as compared to open and laparoscopic surgeries. Transition to robotic surgery requires laparoscopically trained assistants. A laparoscopically trained console surgeon cannot obviate the need for a trained bed side surgeon because the bed side surgeon has to assist throughout the procedure. It is not possible for the unscrubbed, remotely located console surgeon to use his or her laparoscopy skills during the surgery. For the same reason, trainees who wish to become robotic surgeons have to learn basic laparoscopy. This training is in addition to training in open surgery that guides all steps performed during robotic surgery. Accurate port placement, robot docking and interchange of instruments are other vital learning steps in robotic training\textsuperscript{46}.

**CONCLUSION**

As robotic system provides three-dimensional, high-definition images with small instruments with endowrist technology, ergonomic position for surgeon and ease of teaching to fellows and residents, the indications of robotic surgery will continue to evolve. Increased cost burden to healthcare provider and patients who bear most cost of surgery due to lack on penetration of insurance, are major problems in adaptation of robotic systems in India.

*“Life can only be understood backwards; but it must be lived forwards.”* Soren Kierkegaard quote defines future of robotic surgery in India.

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Immunization Coverage in a Rural Area of Malappuram District, Kerala: A Cross Sectional Study

Sreelakshmi Mohandas K*, Vivin Vincent**, Teena Mary joy*, Dulari Gupta***

ABSTRACT

BACKGROUND: In India, 5 lakh children under 5 years of age die annually due to vaccine preventable diseases(1). One out of seven deaths among young children can be prevented with 100% immunization and 100% efficacy of vaccines(2). According to CES 2009, immunization coverage for children aged 12-23 months in Kerala was 81.5%(3). However, in the Northern district of Malappuram, the immunization coverage was only 63.9%, the lowest in the state(4).

OBJECTIVES: Hence, this study was carried out to assess the immunization coverage and to study the factors associated with immunization among children between 12-23 months of age in a rural area of Malappuram, Kerala.

MATERIALS & METHODS: A cross sectional study was done in Morayur panchayath in 2014; the minimum calculated sample size was 172(10). Children between 12-23 months of age from Morayur Panchayath were selected by cluster sampling. Data were collected using a pre tested semi structured questionnaire.

RESULTS: 64.7% of children were fully immunized for age and 2.9% were unimmunized in the study. Vaccination delay was found to be 88.5% and the major reasons for delaying were occurrence of minor ailments in the child at the time of vaccination and fear of vaccine side effects like fever and pain. The vaccine coverage for BCG and OPV 0 dose were the highest, 97.5% and 97% respectively.

CONCLUSION: The immunization status of children below 2 years of age in Morayur, A Panchayath of Malappuram district was found to be low. Addressing the fear of vaccine side effects may help to increase the vaccination status of the community.

Keywords: immunization, rural area, vaccine coverage

INTRODUCTION

Immunization is one of the most widely discussed, controversial topics in health care. It is also one of the most successful and effective health interventions ever. It has successfully eradicated small pox, lowered the global incidence of polio and achieved remarkable reductions in disability, illness and death from diphtheria, whooping cough, tetanus and measles.

In the last 10 years, great advances have been made in developing and introducing new vaccines and expanding the reach of immunization programmes. As a result of immunization combined with other health care and development interventions the annual number of deaths among children under five years of age fell from an estimated 9.6 million in 2000 to 7.6 million in 2010, despite an increase in the number of children born each year(5).

According to 2016 WHO reports, immunization averts an estimated 2-3 million deaths every year. With 100% immunization and 100% efficacy of vaccines, 1 out of 7 deaths among young children can be prevented(6). Even then, approximately 19.4 million infants miss out on basic vaccinations globally(6). Vaccine preventable deaths are usually caused by a failure to obtain the vaccines in a timely manner, due to lack of sufficient immunogenicity or due to administration of inactivated vaccine.

Vaccine preventable diseases are responsible for over 5 lakh under five deaths annually in India(7). Our country has the largest pool of unimmunised children in the world, accounting for approximately 4.2 million(7).

In Kerala, the state with the highest epidemiological transition levels, the percentage of fully immunised children in the age group of 12-23 months was 82.5%(9). Looking at it from the other side of the spectrum; nearly 1/5th of children aged 12-23 months in Kerala have not received all the recommended vaccines.

The disparity in immunization coverage comes mainly from the variations among the districts in Kerala, particularly in the northern districts like Malappuram, where the immunisation cover for children aged between 12-23 months is at approximately 63.9%, the lowest in the state(4).

Hence, the objective of this study was to assess the immunization coverage among children aged 12 months-24 months in a rural area of Malappuram district and thereby to study the factors associated with immunization coverage and to look for the reasons for vaccination delay, if any among them.

MATERIALS AND METHODS

A community based cross sectional survey was carried out between June to November 2014 in Morayur Panchayath of Malappuram District Kerala. The panchayath has a total population of 33,960 with 6,900 households and 14.9% of the population being comprised of children less than 6 years of age(11). The study population included children between 12-24 months of age, registered in the anganwadis. However, morbidly sick children and children who are not permanent residents

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A total of 173 children were included in the study with mean age of 17.73±3.6 months. Due to incompleteness of data, 7 children were excluded. The mean age of mother and father were 26.8±4.9 years and 33.4±5.3 years respectively. The mean age of mother at marriage was 18.9±2.3 years. Majority of fathers (74.6%) had an education between 5th and 10th std while 91% of the mothers had a qualification above 10th std. Of the 173 participants, 54.9% were males and 83.8% of the study participants belonged to Muslim religion. Based on order of birth, 35.8% of them were of first and second birth order, each and 28.3% were of third order or above. Only 19.7% of the mothers had a minimum of 4 ANC visits. Approximately, 70% of all participants received their immunizations from the government sector.

RESULTS

A total of 173 children were included in the study with mean age of 17.73±3.6 months. Due to incompleteness of data, 7 children were excluded. The mean age of mother and father were 26.8±4.9 years and 33.4±5.3 years respectively. The mean age of mother at marriage was 18.9±2.3 years. Majority of fathers (74.6%) had an education between 5th and 10th std while 91% of the mothers had a qualification above 10th std. Of the 173 participants, 54.9% were males and 83.8% of the study participants belonged to Muslim religion. Based on order of birth, 35.8% of them were of first and second birth order, each and 28.3% were of third order or above. Only 19.7% of the mothers had a minimum of 4 ANC visits. Approximately, 70% of all participants received their immunizations from the government sector.

The complete vaccine coverage; full immunization; was found to be 64.7%. Approximately, 32.4% of the study participants were partially immunized and 2.9% of them were unimmunized. The immunization coverage for individual vaccines is described in Figure 1. An increasing trend was noticed for vaccine coverage at 6 weeks to the coverage at 14 weeks, from 45.6% to 91.3%.

Around 93.6% of all vaccinations were delayed and the reasons for delay in vaccination are depicted in figure 2. The foremost reason for vaccine delay was non-serious illnesses in the child, 48%.

Univariate analysis is described in Table 1. Multivariate logistic regression is described in Table 2. Low paternal education showed a statistically significant association with full immunization of the child (OR=1.98 (1.06-3.68), (aOR= 0.40 (0.22-0.82))
### Table 1: Univariate analysis for factors associated with immunisation status

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<th>Variable</th>
<th>Fully Immunised</th>
<th>Chi Square (p Value)</th>
<th>Odds Ratio (95%CI)</th>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Muslims</td>
<td>90(62.1)</td>
<td>55(37.9)</td>
<td>2.8 (0.09)</td>
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<td></td>
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<td>6(21.4)</td>
<td>0.45 (0.17-1.16)</td>
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<td></td>
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<tr>
<td></td>
<td>&lt;10th Std</td>
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<td>30 (36.6)</td>
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</tr>
<tr>
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<td>&gt;10th Std</td>
<td>60 (65.9)</td>
<td>31 (34.1)</td>
<td>0.89 (0.48-1.67)</td>
</tr>
<tr>
<td>3</td>
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<td>&lt;10th Std</td>
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<td>4.62 (0.03)</td>
</tr>
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<td>22 (51.2)</td>
<td>21 (48.8)</td>
<td>2.14 (1.06-4.34)</td>
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<td>4</td>
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<td>Skilled/unskilled</td>
<td>7 (46.7)</td>
<td>8 (53.3)</td>
<td>3.65 (0.16)</td>
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<td>33 (73.3)</td>
<td>12 (26.7)</td>
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<td>72 (63.7)</td>
<td>41 (36.3)</td>
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<td>Income (Rs)</td>
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<td>40 (33.6)</td>
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<td>6</td>
<td>No. of ANC Visits</td>
<td></td>
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<td></td>
</tr>
<tr>
<td></td>
<td>1-4 visits</td>
<td>30 (60)</td>
<td>20 (40)</td>
<td>0.69 (0.41)</td>
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<tr>
<td></td>
<td>5-9 visits</td>
<td>82(66.7)</td>
<td>41 (33.3)</td>
<td>0.75 (0.38-1.47)</td>
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<td>7</td>
<td>Sex of the child</td>
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<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>65 (68.4)</td>
<td>30 (31.6)</td>
<td>1.25 (0.26)</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>47 (60.3)</td>
<td>31 (35.3)</td>
<td>1.43 (0.76-2.68)</td>
</tr>
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<td>8</td>
<td>Birth Order</td>
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<td>&lt;2</td>
<td>77 (62.1)</td>
<td>47 (37.9)</td>
<td>1.34 (0.24)</td>
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<tr>
<td></td>
<td>&gt;3</td>
<td>35 (71.4)</td>
<td>14 (28.6)</td>
<td>0.66 (0.32-1.34)</td>
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<td>9</td>
<td>Distance to the nearest vaccination site</td>
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<td>&lt;1.5kms</td>
<td>98(64.1)</td>
<td>55 (35.9)</td>
<td>0.27 (0.60)</td>
</tr>
<tr>
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<td>&gt;1.6kms</td>
<td>14 (70)</td>
<td>6 (30)</td>
<td>0.76 (0.27-2.1)</td>
</tr>
</tbody>
</table>

Fig 2: Reasons for Partial immunization, Unimmunization and Delay in Vaccination

- Non serious illnesses in the child (48%)
- Fear of vaccine side effects (14.5%)
- Ignorance (9.2%)
- Objection from any family members
- Vaccination not delayed (5.8%)
- Multiple reasons (4.6%)
- Access to healthcare difficult (4%)
- Any c/c illness (1.2%)
DISCUSSION

In a developing country like India, despite the fact that immunization services are provided free of cost in public health facilities, immunization coverage remains low in some areas\textsuperscript{13}, especially in rural compared to urban areas.

In our study, full immunization coverage was 64.7% with 32.4% partial and 2.9% unimmunized. The full vaccination coverage is lower than the Kerala DLHS 4\textsuperscript{10} coverage, however higher than the national coverage of 54%\textsuperscript{14}. The immunization coverage in this study is lower than that at a study done in Kangra\textsuperscript{15}, HP (94.2%) and a rural area of Maharashtra\textsuperscript{16} (67.2%). In a cross sectional study carried out by Vasantha et al in a rural area of Trivandrum, 90% of the children were fully immunized, 10% partially\textsuperscript{17}.

The decreasing vaccine coverage from birth dose to 3rd dose at 14 weeks, in our study was from 97.1%-87.9% respectively. Similar findings were noticed in a study done by Gupta et al in Pune\textsuperscript{16}, from 98.5%-84.76%.

The percentage of unimmunized children in rural Morayur was found to be 2.9%, this is higher than the findings from a study done in Bangalore\textsuperscript{18} (1.82%) and in rural area of Trivandrum where there were no unimmunised children\textsuperscript{17}.

As per the analysis of NFHS 2 data by Nilanjan et al for 3 states in India, it was noticed that the chance of being fully immunized was higher among girls as compared to boys, there was an inverse relationship of full vaccination with increasing birth order, a strong positive relation with higher maternal education, full ante natal care and with Hindu religion\textsuperscript{19}. In this study, although not statistically significant, similar findings were observed for gender, increasing birth order and full antenatal care. A study by Ughade et al showed a significant association of timely vaccination with gender, maternal and paternal education\textsuperscript{20}.

In our study, 94% of all vaccines were delayed. This is higher than the findings of 12.8% at Nellimarla\textsuperscript{21} and 31% at rural Goa\textsuperscript{22}. The major reason for delaying was found to be due to the occurrence of non-serious illnesses in the child; like fever, common cold or minor ailments at the prescribed time of vaccination which amounted to 48% followed duly by other reasons like fear of vaccine side effects (14.5%), ignorance (9.2%) and objection from any family member (8.7%). In a study done at Nagpur, negligence (56%) and unawareness (22.7%) of parents were the major causes for delayed immunization\textsuperscript{23}. Ignorance (51.8%) as a cause for delayed immunization was also identified by Ujwala et al in their study at Nellimarla town in Andhra Pradesh\textsuperscript{21}.

CONCLUSION

Although our study was not able to point out statistically significant associations for immunization coverage in the area, various reasons for vaccine delay were identified. Minor illnesses can be addressed during the vaccination sessions. Health workers need to assure parents about taking timely vaccinations to avoid unnecessary delays. Therefore, improving the knowledge about vaccines and increasing awareness about the benefits of vaccination along with addressing the basic fear about vaccinations and vaccine side effects may help to improve the vaccine coverage in the area. Involving the whole family and/ or community, rather than parents alone might help to bring forward better involvement of beneficiaries in the utilisation of vaccinations, both existing and upcoming.

REFERENCES


Hyperosmolar 25% dextrose with 2% lignocaine injection for chronic plantar fasciitis treatment- A prospective observational study from a tertiary care centre, Kerala.


ABSTRACT

Background: Chronic plantar fasciitis is a common cause of foot pain in adults. Real world data with respect to the treatment of the condition using 25% hyperosmolar dextrose with 2% lignocaine is limited from our setting.

Objective: To compare the change in intensity of pain due to plantar fasciitis before and after the injection of 25% dextrose (hyperosmolar) with 2% lignocaine using Visual Analogue Scale (VAS) score.

Materials and methods: A prospective observational study was conducted among patients attending the outpatient clinic of Physical Medicine and Rehabilitation department of a tertiary care centre with confirmed diagnosis of chronic plantar fasciitis. Patients diagnosed with chronic plantar fasciitis during the study period were consecutively enrolled according to the selection criteria. After getting consent they were given injections at 3 time points- immediately after diagnosis, 6 weeks after the 1st injection and 6 weeks after the 2nd injection. The intensity of pain was calculated before and after injection with VAS score. Statistical Analysis was done using IBM SPSS statistics version 20.

Results: A total of 15 participants completed the study. Mean age of the study group was 50 ±9.50 years. Before injection the mean VAS score was 7.67± 1.047, and at 6 months follow up, the mean VAS was 3.4±2.063. Here the reduction of VAS score was 4.27±1.43 with a p value <0.001.

Conclusion: The current study suggests that local injection of 25% dextrose with 2% lignocaine is effective for the treatment of chronic plantar fasciitis as evidenced by the significant reduction in the mean VAS score.

Corresponding Author: Remya Sudevan, Clinical epidemiologist, Dept.of Health Sciences Research,AIMS,Kochi.

INTRODUCTION

Plantar fasciitis is one of the most common causes of foot pain in adults. It is caused by micro-injuries at the proximal attachment of the plantar aponeurosis to the calcaneum. It can be caused by excessive running and other forms of repetitive strain. Its hallmark feature is pain over the proximal plantar surface of the foot, especially when stepping out of bed in the morning1. The pain may be substantial, resulting in the alteration of daily activities. Various terms have been used to describe plantar fasciitis, including jogger’s heel, and tennis heel. There are many differential diagnosis of heel pain. Plantar fasciitis is the most common for which professional care is sought. Approximately 10% of the United States (US) population experiences bouts of heel pain, which results in 1 million visits per year to medical professionals for treatment of plantar fasciitis2. The incidence of heel pain in the Indian population is reported as four times than that of US population. The typical presentation is sharp pain localized at the anterior aspect of the calcaneum. Appropriate nonsurgical treatment usually gives a good outcome even though there are buffet of other treatment options. Phamacotherapy, physiotherapy, or thoses, and local steroid infiltration are some of these. Individually none of the above are beneficial though they are used as such. As a result many patients remain symptomatic and occupationally disabled3,4. 25% dextrose with 2% lignocaine infiltration at the sites of tendon insertions to promote fibroblast proliferation has been found effective in healing tendinopathies at various sites5. There is limited literature regarding this treatment method for plantar fasciitis and the available ones support favourable outcome. The Aim of the study was to assess the change in intensity of pain after the injection of 25% dextrose (hyperosmolar) with 2% lignocaine for chronic plantar fasciitis.

METHODS

The prospective observational study was conducted as per the approval and guidelines of the ethics committee of the study institution (Amrita Institute of Medical Sciences and Research Centre, Kochi). The patients with confirmed diagnosis of chronic plantar fasciitis based on history and clinical examination who were attending the outpatient clinic of Physical Medicine and Rehabilitation department were enrolled for the study after getting the informed, written consent of the participants. Based on the mean and standard deviation of pain with activity in pre and post periods of injection of 25% dextrose with 2% lignocaine in chronic plantar fasciitis, (91.6±9.2) and (38.7 ±33.1) observed in an earlier publication(Br J Sports Med 2009 43: 303-306) and with 80% power and 95% confidence, minimum sample size came as 5. A total of 20 patients were re-
recruited, of whom 15 participants completed the study. Patients with unilateral or bilateral heel pain of more than 6 months duration who have not responded to conservative management were included in the study. Patients with acute plantar fasciitis, associated trauma, significant co-morbidities such as: local skin problems, diabetic neuropathy and previous surgeries in the foot were excluded from the study.

The study was conducted prospectively to assess the change in pain intensity with 25% dextrose (hyperosmolar) and 2% lignocaine injection in chronic plantar fasciitis patients. A 5ml syringe was filled with 1ml of 2% lignocaine and 1ml of 50% dextrose, giving a 25% dextrose solution. The procedure was performed under aseptic precautions using a 26 G needle. The solution was injected into the insertion of plantar fascia on the calcaneum. The procedure was repeated twice more at intervals of six weeks apart. The intensity of pain was measured using Visual Analogue Scale and VAS score was estimated before giving the injection and 6 months after the injection. Visual Analogue Scale is a patient self-reported pain scale, which has demonstrated validity and is useful for documenting incremental improvements from treatment. VAS score range from 0-10. No pain marked as 0 and worst imaginable pain marked as 10. The patient was instructed to refrain from any heavy loading activity during the week following the procedure.

Statistical Analysis was done using IBM SPSS statistics 20 windows (SPSS Inc., Chicago, USA). The summary statistics for categorical variables were reported as frequency and percentage and the continuous variables were expressed as mean (SD). For comparing the pain difference of pre and post injection of 25% dextrose with 2% lignocaine, paired t test was applied. Probability value (p value) less than 0.05 was considered for statistical significance.

RESULT

The mean age of the study population was 50 ±9.50 years. Among the 15 participants 14 were females. Six patients (40%) had pain on left side and nine (60%) had pain on right side. The mean VAS score before injection was 7.67 ± 1.047, and that at 6 months follow up was 3.4±2.063. The reduction of VAS score was 4.27± 1.43 with p value < 0.001(Table 1). Among the patients, mean VAS score difference of the males was 4.50±0.707 and that of the females was 4.23±1.535.

DISCUSSION

Plantar fasciitis is one of the most commonly encountered musculoskeletal problems. The diagnosis of plantar fasciitis is mainly based on history and physical examination. Obesity, occupations requiring prolonged standing and weight-bearing etc, are the main predisposing factors. In our study, we analyzed the effectiveness of injection of 25% dextrose (hyperosmolar) with 2% lignocaine in reducing the pain associated with chronic plantar fasciitis.

Long term overuse cause injury to a tendon which follows a degenerative pathway and results in breakdown of extracellular constituents, namely type I collagen and proteoglycans ultimately leading to tissue disorganization. Injection of 25% dextrose at the site of such tendon injury is supposed to promote fibroblast proliferation and tissue repair, thereby relieving the pain and improving function.

Our study was conducted in patients who were diagnosed with chronic plantar fasciitis. Among the 15 patients that were taken into study, 93% were females. An earlier study by Michael B Ryan et al also reported similar incidence where out of 20 patients, 3 were males and 17 were females.

In our study, the mean age of the patients was 50 ± 9.50 years. This is comparable with other similar studies. The average age in Ryan’s et al study was 51 years. All the patients in that study were of the same ethnicity. Age and VAS score shows positive correlation but it’s not statistically significant. Among the patients, mean VAS score difference of the males was 4.50±0.707 and that of the females was 4.23±1.535.

The VAS score before the first injection and 3 months after the third injection (ie. at 6 months follow up) were assessed and compared in the 15 patients who completed the study. The average initial VAS score was 7.67± 1.047 and that at 6 months follow up was 3.4 ± 2.063. The reduction in the VAS score was 4.27± 1.43 and P value is <0.001. The study by Ryan et al also showed a significant improvement in pain relief.
significant decrease in all mean VAS items from pre-test to post-test (p<0.001)³.

**CONCLUSION**

The current study suggests that local injection of 25% dextrose with 2% lignocaine is effective for the treatment of chronic plantar fasciitis as evidenced by the significant reduction in the mean VAS score for 6 months. The procedure is generally safe as there were no adverse effects noted during the study.

**REFERENCES**

Assessment of 1p19q chromosomal status in gliomas by Fluorescence in situ hybridization at a tertiary care hospital

Priya Roys*, Vidya Jha*, M V Thampi*

ABSTRACT

BACKGROUND: Malignant gliomas are the most common type of primary brain tumors. These are astrocytomas, oligodendrogliomas, ependymomas and oligoastrocytomas. Deletions or absence of chromosomes 1p and 19q are frequently seen in oligodendroglioma and oligoastrocytoma tumors. Combined deletion of 1p and 19q is a predictor of prognosis and may predict response to treatment. A comprehensive evaluation and follow-up program is necessary for patients with 1p/19q deletion.

AIM: To study the molecular characterization of 1p36/19q13 chromosome from patients in Amrita Institute of Medical Sciences, Kochi.

MATERIALS AND METHODS: A retrospective study was conducted over a period of one year which included 50 patients. Fluorescent In situ hybridization was used for testing 1p19q deletion. The clinical details and demographic data were collected and analysed.

RESULT: In a study of 50 patients, the average age that shows a deletion in 1p or 19q arm is 44.65 years. The 1p/19q deletion is seen predominantly in females and in Hindu religion. Frontal and temporal lobes are the most common locations for these tumors. The most common symptoms included seizures, headaches and personality changes. Other symptoms vary by location and size of the tumor. Out of all glioma types, astrocytomas (40%) predominate in this study.

CONCLUSION: The study reveals that most of the patients of gliomas with 1p/19q deletion are females with a median age of 44.65 years and from Hindu religion. The most common symptoms are seizures, headaches and personality changes. Astrocytomas are the most common gliomas in this population. The 1p/19q status in glioma will continue to serve as a useful paradigm for the use of molecular signatures to supplement clinicopathologic data in the diagnosis and management of human gliomas.

Corresponding Author: Vidya Jha, Assistant Professor & Consultant, Dept.of Human Cytogenetics, Amrita Institute of Medical Sciences, Kochi.

INTRODUCTION

Cancer is a genetic disease that could develop either from a predisposing mutation followed by acquired somatic mutations or from an accumulation of somatic mutations that develop into a cancer phenotype1. Malignant gliomas are the most common type of primary brain tumors. The heterogeneity of gliomas regarding clinical presentation, pathology and response to treatment makes this type of tumor a challenging area of research. Primary malignancies that originate in the brain involve mainly glial cells (42%). Types of tumors are astrocytomas, oligodendrogliomas, ependymomas and oligoastrocytomas2. The higher the grade, the more abnormal the cells and the more aggressive the tumor. The World Health Organization (WHO) system classifies gliomas into four grades (I, II, III and IV), depending on the histology of the tumor. Treatment and prognosis vary for different grades of tumors. Malignant or high-grade gliomas are grade III (anaplastic astrocytoma, anaplastic oligodendroglioma, anaplastic oligoastrocytoma, and anaplastic ependymoma) or grade IV (glioblastoma); tumors of grade I and II are designated low-grade gliomas. Grade II tumors may evolve into grade III tumors over time. The current update (2016 CNS WHO) breaks with the century-old principle of diagnosis based entirely on microscopy by incorporating molecular genetic parameters into the classification of CNS tumor3. When the tumor makes its presence known, the most common symptoms are seizures, headaches and personality changes. Other symptoms vary by location and size of the tumor and can include weakness, numbness, or visual symptoms4.

Comparative genomic hybridization (CGH), fluorescence in situ hybridization (FISH), polymerase chain reaction–based microsatellite analysis, and p53 sequencing are the most widely used techniques for detection of loss of heterozygosity5. Testing for 1p/19q status in the clinical setting appears to be most useful in 2 situations. The most common is that of a tumor that appears as classic oligodendroglioma, where 1p/19q status is used as a prognostic marker and a potential guide to patient management. Second is the diagnostic utility for cases where a histologic mimic of oligodendroglioma or a morphologically ambiguous tumor is considered6. The study aims to assess 1p19q chromosomal deletion status in glioma patients by fluorescent in situ hybridization. It also aims to find out association of age, sex and ethnicity with gliomas.

MATERIALS AND METHODS

A retrospective study was done over a period of 2 months. Data from archives of Dept. of Human Cytogenetics was taken for a period of 1 year (2018) which revealed 50 patients of Glioma where FISH test for 1p/19q deletion was done. Ratio of 1p:1q ≤ 0.88 and 19q:19p ≤ 0.74, indicated a 1p and 19q deletion respectively. Statistical test was done using SPSS version 19.
RESULTS
Out of 50 glioma patients assessed, the most common type of glioma based on histopathological examination is Astrocytoma as shown in Table 1. The most common lobe involved is Frontal lobe as shown in Table 2.
Out of 50 patients, 20 patients showed deletion of 1p/19q/both on FISH.
Co-deletion (Fig.1a,b) is shown in 8 patients. The association of sex, age and ethnicity with deletion is shown in table 3.
1p deletion (Fig. 2a,b) is shown in 19 patients with mean age 44.37 ± 12.781 with more females and hindus as shown in table 3.
19q deletion (Fig. 3a,b) is shown in 9 patients with more females and hindus as shown in table 4.
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<thead>
<tr>
<th>Glioma Type</th>
<th>Frequency</th>
<th>Percentage</th>
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<tbody>
<tr>
<td>Anaplastic Glioma</td>
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<td>10</td>
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<tr>
<td>Astrocytoma</td>
<td>20</td>
<td>40.0</td>
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<tr>
<td>Glioblastoma multiforme</td>
<td>16</td>
<td>32.0</td>
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<td>Low grade Glioma</td>
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<td>2.0</td>
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<tr>
<td>Mixed Glioma</td>
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<td>6.0</td>
</tr>
<tr>
<td>Oligodendroglioma</td>
<td>5</td>
<td>10.0</td>
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Table 1: Frequency distribution of different types of glioma

<table>
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<tr>
<th>Lobe type</th>
<th>Frequency</th>
<th>Percentage</th>
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<tr>
<td>Frontal</td>
<td>24</td>
<td>48.0</td>
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<td>Insular</td>
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<td>4.0</td>
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<td>Occipital</td>
<td>3</td>
<td>6.0</td>
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<tr>
<td>Parietal</td>
<td>6</td>
<td>12.0</td>
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<td>Temporal</td>
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<td>30.0</td>
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Table 2: Frequency distribution of glioma in different brain lobes

<table>
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<th>p - value</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>% / Mean age</td>
<td>n</td>
</tr>
<tr>
<td>sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>male</td>
<td>23</td>
<td>74.2</td>
<td>7</td>
</tr>
<tr>
<td>Female</td>
<td>8</td>
<td>25.8</td>
<td>12</td>
</tr>
<tr>
<td>Age (Mean ± S.D)</td>
<td>31</td>
<td>43.03 ± 15.512</td>
<td>19</td>
</tr>
<tr>
<td>Ethnicity</td>
<td>Hindu</td>
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<td>11</td>
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<tr>
<td></td>
<td>Muslim</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Christian</td>
<td>6</td>
<td>2</td>
</tr>
</tbody>
</table>

Table 3: Association of 1p deletion with sex, age and ethnicity
DISCUSSION

According to the brain tumor statistics by American Brain Tumor association, Gliomas represent 24.7 % of all primary brain tumors & 74.6 % of all malignant tumors. Glioblastomas represent 55.4 % of all gliomas. These have the highest number of cases of all malignant tumors. Astrocytomas represent 75 % of all gliomas. Oligodendrogliomas represent 1% of all primary brain tumors. In this study, Astrocytomas (40 %) predominate followed by Glioblastomas (32 %), glioma types (anaplastic & lower grades about 12%), Oligodendrogliomas (10%) and the mixed type of gliomas (6 %).

1p/19q deletion gliomas were mostly in the frontal region, followed by the parietal region, and with lowest frequency in the temporal region. Goze et al. reported a relatively lower incidence of allelic loss of chromosome 1p and 19q in a consecutive series of 12 Grade II gliomas involving the insula. However, Wu et al. reported a high rate of 1p/19q co-deletion in insular oligodendroglial tumors. It was also found that glioblastomas predominantly involved the frontal lobe. In this study assessed in 50 glioma patients, about 48 % of gliomas are of frontal origin, 4 % of insular origin, 6% of occipital origin, 12 % of parietal origin and the rest 30 % of temporal origin.

In the literature, adult oligodendrogliomas have a peak incidence at median age of 41 years. In this study, the average age that shows a deletion in 1p or 19q arm (Fig 1a & 1b) is 44.65 whereas the average age that did not show any deletion in 1p or 19q arm (Fig 3a & 3b) is 33.3.

### Table 4: Association of 19q deletion with sex, age and ethnicity

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<th>Deletion present</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>Male</td>
<td>Female</td>
<td></td>
</tr>
<tr>
<td></td>
<td>n   / % / Mean age</td>
<td>n   / %</td>
<td></td>
</tr>
<tr>
<td></td>
<td>26   / 63.4</td>
<td>4            / 44.4</td>
<td>0.293</td>
</tr>
<tr>
<td>Ethnicity</td>
<td>Hindu</td>
<td>Muslim</td>
<td>Christian</td>
</tr>
<tr>
<td></td>
<td>25   / 61</td>
<td>7        / 17.1</td>
<td>9        / 22</td>
</tr>
</tbody>
</table>

### Table 5: Association of 1p deletion/19q deletion/co-deletion with sex, age and ethnicity

<table>
<thead>
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<th>Parameter</th>
<th>Deletion absent (n = 30)</th>
<th>Deletion present (1p/19q/both) (n = 20)</th>
<th>p-value</th>
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<tr>
<td>Mean age</td>
<td>42.80 ± 15.723</td>
<td>44.65 ± 12.504</td>
<td>0.661</td>
</tr>
<tr>
<td>Sex (n,%)</td>
<td>Male</td>
<td>Female</td>
<td></td>
</tr>
<tr>
<td></td>
<td>22 (73.3)</td>
<td>8(40)</td>
<td>0.018</td>
</tr>
<tr>
<td></td>
<td>8(26.7)</td>
<td>12(60)</td>
<td></td>
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<tr>
<td>Ethnicity (n,%)</td>
<td>Hindu</td>
<td>Muslim</td>
<td>Christian</td>
</tr>
<tr>
<td></td>
<td>18(60)</td>
<td>6(20)</td>
<td>6(20)</td>
</tr>
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</table>
20

Relative few children are diagnosed with oligodendroglioma; it accounts for $\leq 3\%$ of the primary brain tumors found in children ages 0–14, and $\leq 0.5\%$ in children ages 15–19, and $\geq 25\%$ in adults as per the literature. The current study results were concordant with the results reported in literature. There were no pediatric glioma cases found in this study.

Glioma demographics have an excess of male patients as per the literature. But in this study, it was found that more females (60%) had shown a deletion in 1p or 19q arm (Fig 1a & 1b) than males (40%). Its association had also shown a statistically significant correlation (p-value = 0.018) with 1p/19q deletion, which is inconsistent with the findings reported in the world literature. Hence, as per the study results, female group in Kerala population should be paid more attention when they present with symptoms of headache and seizures.

About 30 Hindus, 12 Muslims & 8 Christians were included in the study. Results shows that more Hindus (60%) had shown a deletion in 1p or 19q arm (Fig 1a & 1b) than Muslims (30%) and Christians (10%). The p-value is obtained as 0.535 hence there is no significant difference between ethnicity and deletion in 1p or 19q arm. As per the literature, the most common symptoms are seizures, headaches and personality changes. Other symptoms vary by location and size of the tumor and can include weakness, numbness, or visual symptoms. These results were consistent with the test results obtained from 50 glioma patients in this study.

CONCLUSIONS

Fluorescence in situ hybridization (FISH) is the most widely used technique nowadays for the detection of loss of heterozygosity at 1p and 19q. This helps in detecting the cases of gliomas particularly which may be missed on histopathology. The significance of doing this cytogenetic analysis in patients with brain tumors is that the recent classification of CNS tumors by WHO is based on molecular signatures and the response to therapy is found good in patients with deletion. 1p/19q status in oligodendroglioma will continue to serve as a useful paradigm for the use of molecular signatures to supplement clinicopathologic data in the diagnosis and management of human gliomas.

REFERENCES


Comprehensive phenotypic mapping is essential for the development of an integrated data-driven medical support system for the diagnosis and management of autism spectrum disorders

Sreeja A*, Vinayan K P**

ABSTRACT

Background & objectives: Autism spectrum disorders (ASD) denotes a group of etiologically heterogeneous complex neurodevelopmental disorders marked by impairments in social communication skills, restricted or stereotypic forms of behavior. There are no identifiable biomarkers and the disorder is dimensionally defined with complex genetic and epigenetic factors influencing the clinical phenotype. Extensive evaluation followed by integration of clinical, laboratory and molecular information may be needed to develop and facilitate better treatment plans for individual patients.

Methods: This study was part of a multidisciplinary project to develop an integrated data-driven medical support system for improving the current diagnosis and management paradigm of ASD and also to facilitate research to identify potential endophenotypes and therapeutic targets. A detailed clinical proforma developed with a set of sixty parameters was used to extract all the phenotypic characteristics of a cohort of children with ASD. Childhood autism rating scale- II edition (CARS) was used to categorize the patients based on severity.

Results: 151 autistic children falling within the CARS band of 20-53 were selected based on retrospective chart review. Each of the comorbidities and phenotypic characteristics were mapped and their prevalence estimated across different categories based on the severity of ASD. Significant phenotypic variability was shown for children with same CARS band and also across disease severity spectrum.

Interpretation & conclusions: Our findings show that comprehensive phenotypic mapping is the initial and essential step in the development of an integrated data driven medical support system for ASD. Such a system will also have remarkable translational value in the future directions of ASD research.

INTRODUCTION

Autism spectrum disorders (ASD) denotes a group of complex neurodevelopmental disorders marked by impairments in social communication skills and often restricted or stereotypic forms of behaviour. Other aspects of the disorder may include cognitive deficits, speech delays and difficulties in sensory integration. Autism is highly heterogeneous with variability in clinical features, severity and even in its neurobiology. Etiopathogenesis of ASD is now understood to be highly complex with the involvement of multiple genetic and epigenetic mechanisms along with a plethora of environmental stimuli. The presence of comorbid neurological conditions often necessitates medical attention and may also sometimes lead to early detection of this disorder. In view of this phenotypic and etiological heterogeneity, it becomes difficult to develop tests that can assess each individual in a consistent manner. The phenotypic heterogeneity of this complex disorder is often perceived as a barrier in the study of neurobiological mechanisms. Inadequate understanding of these underlying neurobiological mechanisms is currently the major roadblock in the identification of robust therapeutic targets to improve the short term and long term outcomes.

A "one-size-fits-all" strategy for treatment continues to be a challenging problem for complex disorders. Usually a specialist is expected to derive judgements based on the explicit evaluation of the problem. However, the clinical problem is often ambiguous causing difficulty in making an ultimate conclusion. The traditional perspective of the diagnostic process is scientific thinking, which incorporates the theory of hypothesis and the validation based on patient information through a systematic process. Recent research explores intuitive thinking based on pattern recognition by matching clinical patterns with memory. Experienced doctors follow patterns of symptoms by giving weightage to certain factors based on scientific literature and personal experience to make suitable conclusions. Owing to the challenges described above, clinical diagnosis and management of Autism Spectrum Disorder (ASD) is difficult at this time point. It is possible that integrated knowledge sources and institutionalized instruments will provide better insights into this complex disorder and associated comorbidities. Computational or bioinformatics models are better suited to handle the heterogeneity of these complex medical datasets for
exploring the association between clinical phenotypes and the underlying disease process thereby developing improved diagnostic techniques and enhanced therapeutic possibilities. The clinical experiments and even routine therapeutic check-ups present diverse methodologies, both demanding a solid bioinformatics framework efficient to do (i) the integration of relevant information from multiple knowledge sources like clinical and biological data, (ii) guaranteeing the right handling and investigations of genomic information, and (iii) utilizing well-defined strategies for process flow and decision making.

Several studies have demonstrated the presence of overlays in genes and biological processes among ASD and its comorbid conditions. In children with ASD, the most prevalent comorbidities include attention-deficit hyperactivity disorder, mood and anxiety disorders, epilepsy, and behavioural problems. These varied comorbidities introduce a lot of issues as they diminish the quality of life, complicate the treatment and increment morbidity and mortality. As there is no single biomarker which differentiates people with ASD from normal population, the diagnosis is often made based on a set of clinical criteria. Substantial development has been made in the course of recent decades in the advancement of screening and diagnostic instruments for ASD. Instruments support clinicians to store detailed and organized information with increased precision and consistency of patients for in-depth evaluation and recommendations for assistance. Scores from these instruments have been utilized to quantify the severity of the symptoms of ASD and also to classify people with and without ASD. Based on these, instructional, psychological, and language treatments integrated with adjunct therapies for particular symptoms are prescribed. Extended research is expected to refine these instruments for their efficient use in clinical settings.

A comprehensive and a precise evaluation plan will be more cost efficient and beneficial for the clinical practitioners in treating autism. There is a growing need to design a standard data collection and analysis platform that can examine the full extent of the disorder, not just the behavioural parameters. Unidimensional scoring systems for ASD like CARS and ADI-R, while being able to accurately diagnose and score the severity of disorder, do not have a provision to evaluate the multi dimensional non-behavioural aspects of the disease. Many studies have reiterated that while commonly used screening instruments provide useful information, they alone aren’t sufficient for an in-depth assessment of ASD. Despite meeting the objective of diagnosing the disease, the assessment should also provide information about the patient’s qualities and shortcomings, distinguishes the dysfunctional behaviour and comorbid neurological and medical disorders, elucidate the effect of the patient’s condition on the family, and also benchmark the formative abilities of the child. Hence the evaluation process must determine a guideline for treatment by distinguishing the abilities and difficulties of the patient and giving helpful information for the medical practitioners.

A consistent data framework accelerates the integration of data from multiple knowledge sources and creates computational models that coordinate information and knowledge from clinical and fundamental research to gain a deeper understanding of the disease, in this way encouraging customized treatment choices. It empowers clinicians by giving them reliable user-friendly tools to convert advances in learning into enhanced effective treatments customized to each individual patients. The present study examines the need of employing an integrated analysis of multidimensional clinical symptoms as a necessary adjunct to single scoring tests in ASDs to enable a more methodical mode of data analysis.

**MATERIALS AND METHODS**

The present study was part of a multidisciplinary project to develop an integrated data-driven medical support system for improving the current diagnosis and management paradigm of autism spectrum disorders and also to facilitate research to identify potential endophenotypes and therapeutic targets, as part of the research project under the CSRI program. The study team included a paediatric neurologist well versed in the diagnosis and management of children with ASD, clinical psychologists and an expert in bioinformatics.

**Data**

A cohort of autistic children with valid CARS score were identified by the retrospective medical chart review at the department of Paediatric Neurology of a tertiary care university academic hospital. Code of human research ethics (ICMR 2006) was observed to in all stages of research with utmost priority to maintain the confidentiality of the patient. To prevent discrepancies that may arise out of memory recall bias, medical records were again cross checked with the hospital records. The study was approved by Institutional Ethics Committee (IEC).

The case notes were selected from those children who were previously tested by a trained psychologist at AIMS, Kochi by means of interviews with the parents or guardians who accompanied the children. Childhood Autism Rating Scale (CARS) was used as a standardized global assessment and diagnostic tool that rates children on an autism severity scale ranging from normal to high to diagnose and categorize the children based on the severity of autism. A CARS band of 15-60 within different severity levels were defined as ASD for this study. The detailed clinical proforma developed with a set of sixty parameters divided into four main categories like Baseline demographic characteristics, Behavioural attri-
I Behavioural Attributes

Behavioural assessments were carried out along with the CARS test through parental interviews and direct observation. Social communication issues and speech problems were encountered in 131 (87%) of the children. Hyperactivity was reported by the parents for 101 (67%) cases and 81 (80%) of them confirmed to have co-occurring ADHD after psychological evaluation. Repetitive behaviours were seen in 50 (33%) cases and stereotypic behaviours were seen in 78 (52%) cases. 89 (59%) children had a history of tantrums and 65 (43%) patients were found to be prone to mood swings. Aggression was observed in 47 (31%) cases, Echolalia in 64 (42%) children and 65 (43%) children displayed cognitive issues. Alterations in sleep patterns were also noted for 29 (19%) cases. 65 (43%) children had specific diet preferences including craving for fried and crispy items, chocolates, bakery items, sweets and milk products.

II Medical and Neurological Comorbidities

139 (92%) children reported developmental delay with 50 cases having global delays, 15 language delays, 52 isolated speech delays and 22 delay in motor milestones. 17 (11%) children had delayed birth cry in their past medical records. The average age at which the symptoms were first observed was 1-1½ years. Regression was reported in 64 cases (43%) where regression in eye contact, speech and language delay was specifically noted in 35 cases. Eye contact was seen to be poor or ill-sustained in 119 (79%) cases of which 107 cases have severe/moderate autism. 87 (58%) children were right handed in this cohort. 13 (8%) cases presented with hypotonia as a clinical feature; among them 9 showed severe autism. Motor development abnormalities were observed in 23 (15%) children. Neurocutaneous markers were observed in 53 (35%) children. Hypopigmented macules and café-au-lait-spots were the common patterns observed. 22 (15%) of the children displayed dysmorphic features and 20 (13%) showed microcephaly, while 54 (36%) had other congenital anomalies. Epilepsy/Seizure disorder was observed in 53 cases (36%) and 28 (19%) had Febrile seizures. EEG was reported as abnormal in 54 children (41%), and in 24 (16%) children MRI brain showed abnormalities. Figure 1 graphically depicts the distribution of various neurological comorbidities in different categories of AS based on the CARS scores.

III Family Variables

146 (97%) children were born out of non-consanguineous marriages. 136 (90%) children were conceived naturally with an average birth weight of 2.90 kg; remaining 10% of children were the products of treatment for infertility. 128 (85%) children were from middle class family and 142 (94%) cases were bought up in a nuclear

<table>
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<th></th>
<th></th>
<th></th>
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</thead>
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<td>Mild- Moderate Autistic (CARS Score 30 - 36.5)</td>
<td>Severe Autistic (CARS Score &gt;=37)</td>
<td>Total</td>
<td>Minimal Autistic (CARS Score 15 - 29.5)</td>
<td>Mild- Moderate Autistic (CARS Score 30 - 36.5)</td>
<td>Severe Autistic (CARS Score &gt;=37)</td>
<td>Total</td>
<td>Total</td>
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<td>&lt; 5 yrs</td>
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<td>13(9%)</td>
<td>32(21%)</td>
<td>11(7%)</td>
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<td>15(10%)</td>
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</tr>
<tr>
<td>Total</td>
<td>12(8%)</td>
<td>20(13%)</td>
<td>18(12%)</td>
<td>50(33%)</td>
<td>19(13%)</td>
<td>49(32%)</td>
<td>33(22%)</td>
<td>101(67%) N = 151</td>
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</table>

Table 1: Demographic characteristics of the population under study
family. For children with age < 5 years, the average age of fathers was found calculated at 36.4 and for mothers at 30.3. For 20% of the children, close relatives also shared the autistic symptoms. 35 parents had basic education less than higher secondary grade out of which 21 cases showed severe autism and remaining showed Mild-Moderate autism.

![Fig 1: Subgroup prevalence of neurological comorbidities stratified by the severity of autism based on the CARS scores.](image)

### DISCUSSION

Several neurological disorders have complex hereditary and epigenetic highlights that lead to complex phenotypes without identifiable biomarkers. Autism Spectrum Disorders are associated with several heterogeneous phenotypes, whose pathophysiology is not clear, therefore, the diagnosis depends on clinical patterns observed. The lack of uniformity in the diagnostic categories remains a major challenge for targeted treatments. The capacity to sort out and semantically assimilate phenotypic manifestations together with genetic and environmental risk factors among ASD subjects could yield imperative new learning regarding shared traits and variances that describe subtypes of ASD, and also help elucidate the underlying process of the disorder. Besides, observing the rate of ASD phenotypes, its subtypes, and the associated comorbidities could help in evaluating the therapeutic efficacy and outcomes. Individualized treatment plan is essential for autistic children since their behavioural needs can vary greatly. The objective of this research is to create assessment procedures and analytical tools to guarantee precise clinical decisions and to give cutting edge information to help the physician advise individualized treatment plans for children with autism. Development of such a platform will also be helpful in other complex neurological disorders. The availability of high-throughput techniques coupled with computational approaches and machine learning techniques for integration and analysis of huge multi-dimensional data has the potential to bring precision medicine into real clinical practice. We had earlier proposed an interactive knowledge framework that can help medical practitioners in providing customized medical treatment and better counselling for the patients with autism$^{6,8}$. Such a framework will be able to integrate heterogeneous information collected as part of clinical activities of diagnosis and treatment of ASD and biological insights gained from genomic databases and literature surveys helping the clinician and the researcher in the real world.

The results in this study highlight that even within the same severity groups as evidenced by CARS scoring; there might be much larger phenotypic differences, probably related to the neurobiological spectrum of these disorders. It is clearly observed that neurological comorbidities are more commonly seen with severe autistic traits and the patterns may vary from patient to patient. Even though unidimensional scoring systems makes it simpler to analyse and categorize the disorders for individual physicians, they alone are inadequate when dealing with complex neurological disorders like autism, which requires a highly scrutinized analysis of its various facets. Bioinformatic tools become indispensable in this regard, where large scale medical data can be studied at the same time and real time solutions can be developed.

To conclude, the use of comprehensive phenotype mapping followed by integrated computational anal-
ysis will help the clinicians and clinical researchers in accurately discerning various aspects of the complex disorders like ASD. It will also help in bringing to light the true extent of diversity among patients while scrupulously documenting all relevant aspects of the disease. Such an approach may pave the way forward for more clinic based, personalized management options in the future.

ACKNOWLEDGEMENTS

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Conflicts of interest

The authors state that the present manuscript presents no conflict of interest.

REFERENCES

Evaluation of the association between parenteral Noradrenaline and arterial lactate levels in the critically ill patients with and without sepsis

Sruthi Haridas*, M Gopalakrishna Pillai*, Dhanasekharan B S**, Gireesh Kumar***, Sreekrishnan T P***, Sabarish B***, Manu Sudhi***, Renjitha Balakrishnan**

ABSTRACT

Aim: This study was designed to evaluate the correlation between Noradrenaline injection and arterial lactate levels in the critically ill patients with and without sepsis.

Methods: This is a prospective, observational study including heterogeneous group of patients of age > 18 years with sepsis and alternate diagnosis in a single centre between June 1 to June 30, 2018. In this cohort, we measured arterial lactate concentration at presentation (L0) and at 2 hours after initiation of Noradrenaline. Lactate clearance was calculated and we evaluated the correlation between Noradrenaline and serum lactate clearance in critically ill patients with sepsis and without sepsis.

Results: 50 patients (38 males, 12 females) in the Medical ICU receiving Noradrenaline were enrolled for the study. The mean age was observed to be 62 ± 13 years. The mean lactate level at 2 hours was 3.02 ± 3.36 and the average 2-hour lactate clearance was 2.5 ± 2.1. Among total 50 patients 27 (54%) had sepsis and 23 (46%) had alternate diagnosis. Among the 27 septic patients, 22 (81%) patient’s lactate was cleared at 2 hours when compared to others with alternate diagnosis 12 (52.2%). The results were statistically significant (p value=0.027).

Conclusion: The lactate clearance at 2 hours seems to be a more reliable prognostic indicator than an initial lactate value at the time of presentation, in cases of septic shock with hyperlactatemia, when early Noradrenaline injection has been initiated. In non-septic patients (hypovolemic shock and cardiogenic shock), we observed a ‘delayed’ lactate clearance.

Keywords: Intensive care, Lactate, Lactate clearance, Noradrenaline, Sepsis, Shock.

Corresponding Author: Sruthi Haridas, PG Resident, Dept.of General Medicine, AIMS, Kochi.

INTRODUCTION

Lactate is an organic compound produced by glycolysis and metabolised primarily by liver and to a lesser degree by kidney. In physiological conditions, lactate is produced by muscles (25%), skin (25%), brain (20%), red blood cells (20%) and intestine (10%)1. The concentration of blood lactate is usually 1mmol/L in normal individuals and > 1.5mmol/L in acute circulatory failure2. Normal individuals produce 15-20mmol/kg of lactic acid per day3. Lactate levels greater than 2mmol/L represent hyperlactatemia, whereas lactic acidosis is defined as a serum lactate concentration above 4mmol/L6,8. There should be a balance between lactate production and utilisation to maintain normal serum lactate levels. Any abnormalities in the lactate metabolism as increased production or decreased utilisation can lead to lactate accumulation. Daily production of lactate in critically ill patients is approximately 1300mmol/L7. In general, three main mechanisms causing lactate accumulation are increased pyruvate production, reduced mitochondrial oxidative phosphorylation of pyruvate and shift of the cellular cytoplasmic redox state such that NADH accumulates and drives the pyruvate/lactate ratio towards lactate. Decreased utilisation is seen in case of multi-organ failure. Lactate levels greater than 2mmol/L represent hyperlactatemia, whereas lactic acidosis is generally defined as lactate concentration above 4mmol/L. Lactic acidosis is the most common cause of metabolic acidosis in hospitalised patients. The causes of lactic acidosis can be divided into those with markedly impaired tissue oxygenation (type A) and those in which impairment in oxygenation does not exist or is not readily apparent (type B)6,8. Studies conducted in 1980s demonstrated that the ability to ‘clear lactate’ to normal in patients suffering from both septic and cardiogenic shock was associated with better outcome. In 1993, a research study reported ‘lactate clearance’ as decrease of lactate to < 2mmol/L by 24 hour as a predictor of survival following traumatic injury. Later the concept of lactate clearance was popularized in 2004 as an indicator of resolution of global hypoxia and thus an independent predictor of mortality7. Recent studies extended the concept of targeting resuscitation in sepsis to achieve a lactate ‘clearance’ of at least 10% as a marker of restoration of oxygen delivery to the tissues with resuscitation treatment. A previous study has shown that lactate clearance of more than 10% reflects a tendency to overcome increased lactate production in sepsis6,7,13.

Sepsis is the most common cause of lactic acidosis and the disturbances of lactate metabolism that occur during sepsis are more complex than an isolated defect.
of cellular oxygenation. Serum lactate level is used as a marker of metabolic stress, tissue hypoperfusion, illness severity and is an independent predictor of mortality.

Sepsis is a medical emergency as like acute myocardial infarction or stroke. Severity of sepsis ranges from infection and bacteraemia to sepsis and septic shock, which can lead to multiple organ dysfunction syndrome (MDS) and death. A 2016 SCCM/ ESICM task force define sepsis as life threatening organ dysfunction caused by dysregulated host response to infection. Thus early identification and appropriate immediate management in the initial hours after development of sepsis is warranted. Hemodynamic abnormalities in the form of tachypnea and hypotension and mild persistent hyperlactatemia will be evident in early sepsis. Thus lactate metabolism has always been a hot bed for researchers and various studies reported that lactate clearance in the early hospital course may indicate a resolution of global tissue hypoxia and that this is associated with decreased mortality rates.

Most dreaded period during the evolution of sepsis is septic shock, although four types of shock are described in the literature, namely distributive, cardiogenic, hypovolemic and obstructive.

Septic shock is type of distributive shock characterised by peripheral vasodilatation. Septic shock is a subset of sepsis associated with mortality in the 40-50% range that can be identified by the use of vasopressor therapy and the presence of elevated lactate levels (Lactate > 2mmol or > 18 mg/dL) despite adequate fluid resuscitation. The most recent Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016 and revised "hour – 1 bundle of care" recommend 'targeted resuscitation to normalize lactate in patients with elevated lactate levels'.

Mechanisms of various shock includes reduced intravascular volume (Hypovolemic shock), intra cardiac (Cardiogenic shock), extra cardiac (Obstructive shock) causes of cardiac pump failure all resulting in reduced cardiac output. But patients often present with combined forms of shock. Resuscitation should be started at the earliest even while investigating the cause is ongoing. Early resuscitation includes fluid therapy and use of vasoactive agents. Fluid therapy to improve microvascular blood flow and increase cardiac output is essential part of treatment of any type of shock. Recent Surviving sepsis guidelines recommend rapid administration of 30 mL/Kg crystalloid for hypotension. But logical endpoints for fluid resuscitation are difficult to define. If hypotension is severe or if it persists despite fluid administration, the use of vasopressors is indicated. It is an acceptable practice in the clinics to administer a vasopressor temporarily while fluid resuscitation is ongoing, with the aim of discontinuing it, once hypovolemia is corrected. Adrenergic agonists are the first line vasopressors because of their rapid onset of action, high potency, and short half-life, allowing easy dose titration. Norepinephrine is the vasopressor of first choice in almost all types of shock due to its predominant alpha adrenergic property. It also has a modest beta adrenergic effects which helps to maintain cardiac output. Administration of adrenaline results in a clinically significant rise in mean arterial pressure, with little change in heart rate or cardiac output. The usual dose is 0.1 to 2.0 µg per kilogram of body weight per minute.

The primary goal of resuscitation should be urgent restoration of blood pressure and also to provide adequate cellular metabolism. This should not be delayed. Restoring a mean systemic arterial pressure > 65 is the ideal initial goal, but the level should be adjusted to restore tissue perfusion, assessed on the basis of mental status, skin appearance, and urine output. As already mentioned, lactate is considered as the marker of cellular metabolism and tissue hypoxia. In patients with shock and a blood lactate level of more than 3 mmol per litre, Jansen et al. found that targeting a decrease of at least 20% in the blood lactate level over a 2-hour period is associated with reduced in-hospital mortality. An elevated serum lactate (> 2mmol/L, depending upon the institutional laboratory normal) is an early indicator of shock and is particularly useful in normotensive or hypertensive patients in whose shock is less likely suspected.

Thus initial management of shock is problem oriented and the goals are therefore same, regardless of the cause of shock. Once the cause is identified, the cause must be corrected rapidly.

In the light of these data, physicians are paying more attention to serum lactate level guided therapy in hospitalised patients to provide early and adequate hemodynamic support in patients with shock to prevent worsening organ dysfunction and failure.

**MATERIALS & METHODS**

**Ethics**
The data collection was done after the authorisation from the Institutional Research Committee.

**Patient and setting**
This is a prospective, randomised observational study including heterogeneous group of patients of age > 18 years with sepsis and alternate diagnosis in single centre between June 1 and June 30.

The study inclusion criteria were adult patients (> 18 years) with sepsis or alternate diagnosis admitted in the Medical intensive care units with typical clinical features of shock requiring Noradrenaline injection. Patients were excluded if they were younger than 18 years of age; had already received a vasopressor agent (dopamine, norepinephrine, epinephrine, or phenylephrine) for more than 4 hours during the current episode of shock; had a serious arrhythmia, such as rapid
atrial fibrillation (>160 beats per minute) or ventricular tachycardia; or had been declared brain-dead. Children were excluded because lactate metabolism in children is different. The dose of Noradrenaline injection administered is 0.1 to 2.0 µg per kilogram of body weight per minute.

Data extraction
Data collected includes patient’s biodata, underlying comorbidities, current diagnosis, presence or absence of sepsis, reason for administration of noradrenaline infusion, lactate levels during admission (L0) and lactate levels at 2 hours (L2) after noradrenaline injection, baseline renal function and outcome of the patient in terms of mortality and morbidity.

Technique
Arterial blood samples were taken for lactate measurement in 2 cc syringes containing heparin. Arterial lactate levels were used instead of venous lactate because of deviation found in absolute value and clearance rate. Lactate concentration was determined enzymatically (ABL800 Flex blood gas analyzer) by spectrophotometric reflectance. The normal lactate concentration range using this analyser is 0.5 – 2.5mmol/L. We measure lactate levels at the “time of presentation” or “time zero” (L0) and after 2 hours (L2) of noradrenaline injection. “Time zero” is defined as lactate level at the time of triage in emergency department.

Case definitions
The patient was considered to be in shock if the systolic blood pressure was < 90 mmHg or mean arterial pressure < 65 mmHg or a drop in systolic blood pressure > 40 mmHg or if the systolic blood pressure was less than 100 mm Hg despite the fact that an adequate amount of fluids (at least 1000 ml of crystalloids or 500 ml of colloids) had been administered (unless there was an elevation in the central venous pressure to >12 mm Hg ), Tachycardia (> 90 beats/ min); Tachypnea (> 24 breaths/ min); and if there were signs of tissue hypoperfusion (e.g., alteration of mental status in the absence of direct brain injury, urine output of <0.5 ml per kilogram of body weight for 1 hour, or a serum lactate level of >2 mmol per litre), metabolic acidosis (predominantly high anion gap).

Lactate clearance can be defined from 2 aspects: magnitude and time needed for the clearance. A threshold of 10% reduction from baseline or normalisation is employed and 2 hours is used as the time frame for lactate clearance. Lactate clearance was calculated by the equation: [(lactateinitial-lactatefollow-up)/lactateinitial] x 100%.

Statistical analysis
We split the study population into two groups according to the presence and absence of sepsis. Statistical analysis was performed using IBM SPSS version 20.0 software. Categorical variables are expressed as frequency and percentage. Continuous variables are presented using mean and standard deviation. To test the statistical significance of the categorical variables with lactate clearance, chi square test was used. To test the statistical significant difference in the mean of lactate level at admission with mortality Mann Whitney U test was used. Differences were considered significant at P < 0.05.

RESULTS
A total of 50 patients with shock who were supported with noradrenaline infusion were analysed. Of these, 12 (24%) were females and 38 (76%) were males. The mean age of patient was 62 ± 13 years.

Out of 50 Patients 34 (68%) had lactate clearance at the end of 2 hours and 16 (32%) did not clear lactate at 2 hours of noradrenaline injection. The average lactate level at 2 hours was 3.02 ± 3.36 and the average 2-hour lactate clearance was 2.5 ± 2.1.

Table 1: Distribution of sex

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Table 2: Distribution of lactate clearance at 2 hr

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Table 3: Distribution of sepsis

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Among total 50 patients 27 (54%) had sepsis and 23 (46%) had alternative diagnosis (hypovolemic or cardiogenic shock)

Among the 27 patients who had sepsis, 22 (81%) patient’s lactate was cleared compared to 12(52. 2%) non-sepsis patients. The results showing statistical significance (p value=0.027).
Evaluation of the association between parenteral Noradrenaline and arterial lactate levels in the critically ill patients with and without sepsis

<table>
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<th>Sepsis</th>
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<th>Lactate clearance - n(%)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes (27)</td>
<td>22 (81.5)</td>
<td>5 (18.5)</td>
<td>0.027</td>
</tr>
<tr>
<td>No (23)</td>
<td>12 (52.2)</td>
<td>11 (47.85)</td>
<td></td>
</tr>
</tbody>
</table>

Table 4: Association of sepsis and 2-hour lactate clearance

<table>
<thead>
<tr>
<th>Mortality</th>
<th>N</th>
<th>Mean</th>
<th>Standard deviation</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Expired</td>
<td>7</td>
<td>3.89</td>
<td>2.20</td>
<td>0.040</td>
</tr>
<tr>
<td>Alive</td>
<td>43</td>
<td>2.95</td>
<td>3.47</td>
<td>0.040</td>
</tr>
</tbody>
</table>

Table 5: Comparison of initial lactate with mortality

The mean of initial lactate level was 3.89 ± 2.20 in dead patients and in alive patients, 2.95 ±3.47 which was found to be statistically significant difference (p value=0.04).

DISCUSSION

Lactate metabolism in sepsis is a complex mechanism. A mild persistent hyperlactatemia is frequently seen during sepsis in hemodynamically stable state. The study conducted by Levy et al. has demonstrated that aerobic glycolysis in skeletal muscle secondary to epinephrine stimulated N+ K+ ATPase activity and not anaerobic glycolysis is the major source of increased lactate in sepsis⁴. There could be reasons of lactate overproduction during sepsis due to increased glycolysis due to insulin like activity of endotoxin, or enhanced catabolism of muscle alanine. There could be also evidence of impaired lactate utilisation caused by altered liver function during sepsis or due to metabolic abnormality. Lee et al has demonstrated the initial vasopressor use as an independent factor for 7-day mortality after adjusting for disease severity⁴. The classical teaching was to avoid vasopressors in lactic acidosis, as they may worsen tissue perfusion and increase lactate production. Furthermore, no much studies have examined the role of vasopressors in severe sepsis-related lactic acidosis.

In this context, consistent with the findings from previous research studies, we found that, early administration of noradrenaline shortens the duration of hypotension and thereby improve vital organ perfusion and decrease arterial lactate levels. Thus early noradrenaline initiation increases the survival rate in septic patients⁶. In our study, we found that, lactate clearance is a more important predictor of survival than initial or maximum lactate level in critically ill patients on Noradrenaline injection whose high mean initial lactate level was 6.5mmol/L. We also noticed that the patients with initial lactate level >3.89 ± 2.20mmol/L has higher risks of mortality.

Furthermore, we observed the lactate clearance at 2 hour as a better prognostic indicator than initial lactate value, especially in cases of septic shock with hyperlactatemia, when early noradrenaline injection has been initiated. The lactate clearance tends to increase in patients with septic shock on Noradrenaline injection. As already mentioned, lactate clearance should be quantified in terms of magnitude and time required for clearance. A clearance of over 10% lactate was found at the end of 2 hours in septic patients on Noradrenaline injection, when compared to patients in whom no septic focus was identified. Thus the rate of lactate clearance was better in septic shock, compared to non-septic patient (hypovolemic shock and cardiogenic shock). In non septic patients, we observed a delayed lactate clearance.

Our results have thus shown that one of the several approaches to increase lactate clearance and thus to improve survival of severe sepsis patients with lactic acidosis is the early use of Noradrenaline.

This study has some limitations because we heterogeneously selected the cases and the sample size was relatively small. In addition, interventions in this study were not standardized or controlled. Despite these limitations, we found that measuring serial lactate levels, early use of Noradrenaline even in hyperlactatemia can improve the lactate clearance and survival rates.

CONCLUSION

Shock is associated with high morbidity and mortal-
ity. Prompt identification of shock is essential so that aggressive management can be started at the earliest. Most common type of shock in our setting is distributive (septic) shock. The lactate clearance at a discrete time point seems to be a more reliable prognostic index than an initial lactate value, taken alone in cases of septic shock with hyperlactatemia, when early Noradrenaline injection has been initiated. A clearance of more than 10% was found at the end of 2 hours in > 80% septic patients on Noradrenaline injection, when compared to non-septic patients.

In patients with other types of shock, namely hypovolemic or cardiogenic, rate of lactate clearance is very low. In our study, only 50% of patients without sepsis has shown clearance of lactate from the circulation in 2-hour period.

In conclusion, although clearance of lactate in the 2-hour period is seen in both patients with sepsis and without sepsis, patients with septic shock has better lactate clearance with Noradrenaline and thus better survival rates. Thus one of the approaches to increase lactate clearance and thus to improve the survival rates in severe sepsis patients with lactic acidosis is early use of Noradrenaline. But this statement may not be appropriate in the setting of a non septic shock.

ACKNOWLEDGEMENT

I extend my sincere gratitude to Ms Sisira of Amrita Institute of Medical Sciences, Kochi for her sincere support.

REFERENCES


To study the clinical profile of patients presenting with thrombocytopenia in emergency department


ABSTRACT

Background: Thrombocytopenia is defined as a platelet count below the lower limit of normal (<1,50,000/microL). It may be associated with a variety of conditions, with associated risks that may range from life threatening bleeding or thrombosis to no risk at all. Approach to patient with unexpected thrombocytopenia, divided according to clinical presentation. This approach can be used by the primary care physician and the consulting hematologist. Degree of thrombocytopenia can be divided into mild (platelet count 100000 to 150000/microL), moderate (50000 to 99000 microL) and severe (<50000 microL). This is a prospective observational study of 100 patients with thrombocytopenia who came to ED during a period of one year. Parameters like age, sex, heart rate, respiratory rate, blood pressure, temperature, saturation, platelet count, bleeding manifestations and transfusion history were collected.

Objective: To study the clinical profile of patients presenting with thrombocytopenia in the Emergency Department.

Result: Among 100 patients presenting with thrombocytopenia to ER, the percentage of male was 60% and female was 40%. Majority of patients were in the age range of 36 to 65 years. Data analysis showed that CLD is the most common cause among patients who presented to ER with Thrombocytopenia.

Conclusion: Thrombocytopenia remains a symptom complex that carries significant length of hospital stay and mortality. The most common cause of thrombocytopenia was chronic liver disease. This study will provide insight into proper allocation of resources to manage this group of patients, investigations and treatment at ER and inpatient level.

Key words: Thrombocytopenia, Blood transfusion, Emergency department

INTRODUCTION

Thrombocytopenia refers to a disorder in which there is a relative decrease of thrombocytes, commonly known as platelets, present in the blood. A normal human platelet count ranges from 150,000 to 450,000 platelets per microliter of blood. These limits are determined by the 2.5th lower and upper percentile, so values outside this range do not necessarily indicate disease. One common definition of thrombocytopenia that requires emergency treatment is a platelet count below 50,000 per microliter. The major causes of thrombocytopenia are chronic liver disease, coronary artery disease, dengue fever, leukemia, sepsis, idiopathic thrombocytopenic purpura, thrombotic thrombocytopenic purpura.

Severe thrombocytopenia with bleeding and certain causes of heparin induced thrombocytopenia, thrombotic thrombocytopenic purpura, hemolytic uremic syndrome, drug induced thrombotic microangiopathy or bone marrow failure syndrome with severe pancytopenia are medical emergencies that require immediate action. In asymptomatic outpatients with thrombocytopenia, common diagnoses include immune thrombocytopenia, occult liver disease, HIV infection and myelodysplastic syndrome. Congenital thrombocytopenia may also occur. In acutely ill patients, common causes of new onset thrombocytopenia include sepsis, DIC and drug induced thrombocytopenia. Many patients in the ICU with thrombocytopenia have more than one cause. We confirm thrombocytopenia by repeating the CBC and reviewing the peripheral blood smear. Management of thrombocytopenia depends on the underlying diagnosis. General principles that apply to all patients include a review of medications that may interfere with normal hemostasis and a decision regarding whether they should be continued, coordination with anesthesiologists and surgeons before invasive procedures, correction of coagulation abnormalities. Active restrictions are often not needed.

METHODOLOGY

Study type: The study design was a prospective observational study consisting of patients with thrombocytopenia at Amrita Institute of Medical Sciences, Kochi

Study setting: Amrita Institute of Medical Sciences, Kochi

Study size: Study population of 100 patients was selected for this study over a period of one year.

Materials and methods: This is a prospective observational study of 100 patients with thrombocytopenia who came to ED during a period of one year. Parameters like age, sex, heart rate, respiratory rate, blood pressure, temperature, saturation, background diseases, platelet count, bleeding manifestations and transfusion history were collected.
RESULT

This prospective observational study included 100 patients who came with thrombocytopenia to Emergency Room of Amrita Institute of Medical Sciences and Research Centre from July 2016 to December 2016. Among 100 patients included in the study satisfying inclusion criteria, age distribution was as follows: 29 (29%) patients were in age group between 15 to 35 years old, 53 (53%) patients were in age group between 36 to 65 years old and 18 (18%) patients were in age group between 66 to 95 years old.

Vitals signs were recorded for all these 100 patients at the time of primary assessment. Out of 100 patients, 72 (72%) patients had normal heart rate, 2 (2%) patients had bradycardia and 26 (26%) patients had tachycardia. In the case of oxygen saturation, (92%) had saturation >90 % and 8 (8%) patients had saturation < 90 %. On checking blood pressure, 75 (75%) patients had normotension, 19 (19%) had hypertension and remaining 6 (6%) had hypotension.

- **Fig 1**: Pie diagram showing gender distribution
- **Fig 2**: Pie diagram showing distribution of background diseases.
- **Fig 3**: Graph showing distribution of degree of thrombocytopenia
- **Fig 4**: Graph showing distribution of bleeding manifestation
- **Fig 5**: Graph showing distribution of platelet transfusion
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DISCUSSION

In this prospective observational study of 100 patients, thrombocytopenia was evaluated and managed with the standard protocol of our institution. According to this study, males were more prone to develop thrombocytopenia (60%). Most of the patients were in the age group between 36 to 65 years old. 72% patients came to emergency department were hemodynamically stable.

Chronic liver disease is the population that has the predilection to develop thrombocytopenia (43%). Followed by other gastrointestinal disorders (17%), and then followed by sepsis (9%), malignancy (7%), intracranial pathology (4%), myocardial disease (4%), hematological (3%), pulmonological disorders (3%), endocrinological disorders (1%) and HIV (1%).

26% patients had mild thrombocytopenia with platelet count between 150000 to 100000/microL, 42% patients had moderate thrombocytopenia with platelet count between 99000 to 50000/microL and 32% patients had severe thrombocytopenia with platelet count less than 50000/microL.

40 patients required blood transfusion and among them 39 patients had bleeding manifestations. Others were managed medically.

In most of the patients, thrombocytopenia was occurred as a result of complication due to other diseases. Only 2% had low platelet count due to thrombocytopenic purpura.

CONCLUSION

This is a prospective observational study of 100 patients who came to the emergency department with thrombocytopenia. In the study 60 out of the 100 patients who developed thrombocytopenia were males; hence males were identified to be more prone to develop thrombocytopenia than females. Most of patients came under the category of moderate thrombocytopenia, with a platelet count between 50000 to 99000/microL. As per the study 39% (39) of patients had bleeding manifestations; 40% (40) of patients were given platelet transfusion. In our Emergency department, the most common cause of thrombocytopenia is Chronic liver disease which accounts for 43% (43).

REFERENCES


Barriers to Tobacco Cessation Advice among Clinical Dental Students: A cross-sectional study

R. Venkitachalam*, Aishwariya R**, Vinita Sanjeevan***

ABSTRACT

Introduction: Dental professionals are ideally placed in the health care system to identify tobacco use and perform tobacco cessation counselling. Effective tobacco cessation practices warrant an understanding of the barriers faced; particularly by the training dental student.

Aim: To identify barriers among clinical dental students preventing them from performing effective tobacco cessation counselling.

Methods: A cross-sectional questionnaire-based survey was designed and conducted among clinical students (third year, final year and house surgeons) of a dental school in India. Barriers were recorded on a Likert scale rating.

Results: Lack of time to give tobacco cessation advice and inadequate knowledge of quit-lines and Nicotine Replacement Therapies (NRTs) were the most frequently reported barriers. Unavailability of patient materials, inadequate skills and training in providing advice and lack of tracking system to follow up patients were few of system level barriers. Almost 50% of participants opined that there was a resistance from the patient while providing cessation advice.

Conclusion: Tobacco cessation training and provision of adequate resources and infrastructure during early years of dental education could address perceived barriers to cessation advice among clinical dental students.

KEYWORDS: tobacco; dentists; students; cessation.

INTRODUCTION

Tobacco is the most easily available and legally permissible addictive substance which is a major risk factor for various diseases including oral cancer. Alarming-ly, smoking rates are rising and by 2030 up to 10% of deaths in the world may be tobacco related. In India, tobacco is consumed in several forms including smoking as well as smokeless forms. However, tobacco use is now considered a preventable risk factor that causes most deaths in the world and tobacco cessation counselling is by far the most effective approach in tackling this global menace.

Oral health professionals are ideally placed in the health care system to identify tobacco use and its manifestations in a patient and a dental clinic/hospital is an ideal setting for tobacco cessation counselling. Numerous studies show that behavioural counselling by a dental professional increases quit rates among users of tobacco. Cessation rates of up to 18% have been seen when dental professionals counselled their patients to quit. A simple 3-minute chair-side advice has shown to deliver effective outcomes.

Dental professionals acquire and hone a majority of their skills during their training days. Hence it is expected that capacity building for tobacco cessation counselling should also begin during their days in dental school. Smoking cessation counselling is hitherto not part of the routine Indian dental or medical practice; probably because it is not incorporated into the standard medical or dental curricula. Presently, knowledge regarding tobacco cessation counselling is mainly obtained through optional participation in workshops and online courses. In a survey of American dental students who had received formal training in tobacco cessation counselling, there was a general agreement that their educational program adequately prepared them to help smokers' quit.

The perceived barriers that prevent dentists from incorporating tobacco cessation into practice reported in literature include doubting about knowledge and skills in assisting the patients to quit smoking, time and reimbursement issues, unavailability of patient education materials, lack of training and patient’s reluctance to quit. With continued tobacco use expected to endanger millions of lives, it is essential to equip every health professional with basic skill sets to provide cessation advice/counselling. Thus the aim of this study was to identify barriers among clinical dental students preventing them from performing effective tobacco cessation counselling.

METHODOLOGY

Study setting, participants and design:
A cross-sectional questionnaire based survey was designed and conducted among clinical students of a dental school in India. The study was conducted during the period of July to December 2018.

Eligibility criteria:
All clinical students of dentistry (III year, final year and house surgeons) of the dental school were approached for participation for the census-type survey (n = 180).
All students present on the day of data collection were included and those students not consenting to be a part of the study were excluded.

**Survey items and its measurement:**

The study tool included a questionnaire which was developed by the authors. The questionnaire included demographic characteristics like age, gender, year of study, practice of tobacco cessation counselling and 15-items on barriers experienced during counselling. The survey items were developed based on a literature review and was validated by four experts in the field of tobacco control. The content validity score was calculated using the Content Validity Index developed by Martuzaet al. and it was observed to be 88%. The responses on barriers were recorded using a 5-point Likert scale (Strongly Disagree, Disagree, Neutral, Agree and Strongly Agree).

Ethical clearance was obtained from the Institutional Review Board and informed consent was obtained from participants willing to be a part of the study.

**Data Analysis:**

The obtained responses were coded and analysed using Statistical Package for Social Sciences SPSS (Version 17) for Windows. The participants' response to various barriers were expressed as frequencies and percentages. Comparison of individual level barriers among participants stratified by year of study was done using Chi-square test.

**RESULTS**

A total of 151 responses were obtained (Response rate = 83.3%). Among all participants 22% of them belonged to third year, 48.6% final year and 29.3% of them were pursuing internship (house surgeons). Majority of the respondents were females (91%) (Table 1).

It was observed that the third years (94%) and final years (97%) enquired the tobacco use status of the patient during routine case history recording of their clinical cases compared to house surgeons (86%). On identifying their patients as tobacco users, chairside counselling was given by less than 80% of the respondents in all groups. A majority of them (> 75%) in all groups devoted less than 3 minutes towards tobacco cessation counselling (Table 2).

The questions on barriers were broadly classified into three viz. individual-level, system-level and patient-level barriers. The responses obtained through a Likert scale are given in Figure 1-3. Common individual level barriers reported by study participants were lack of time to give tobacco cessation advice and inadequate knowledge of quit-lines and Nicotine Replacement Therapies (NRTs). System level barriers reported were consistently high with deficiency in availability of patient materials, inadequate skills and training in providing advice and lack of tracking system to follow up patients being the major among them. Almost 50% of participants opined that there was a resistance from the patient while providing cessation advice.

Association of individual level barriers with study groups (year of study) was done using a chi-square test. For practical purposes, likert responses of Strongly agree and Agree were recoded as “Agree” while Strongly Disagree, Disagree and Neutral were recoded as “Disagree”. There was a significant difference among the study groups (year of study) with regard to knowledge of NRTs and quit-lines (p<0.001 and p<0.005 respectively) with third year and final year students reporting increased frequency compared to house surgeons. There was no significant difference among the three groups based on the inadequacy of time (p=0.107), lack of incentives (p=0.462), forgetting to give advice (p=0.122) and focusing on other oral problems (p=0.141). It may be noted that the frequencies of final year students reporting lack of time and focusing on other oral problems were comparatively much higher than the other groups (Table 3).

<table>
<thead>
<tr>
<th>Year of study</th>
<th>Gender</th>
<th>Frequency</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>III year (n = 33)</td>
<td>Male</td>
<td>4</td>
<td>12.1</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>29</td>
<td>87.9</td>
</tr>
<tr>
<td>Final year (n = 74)</td>
<td>Male</td>
<td>7</td>
<td>9.5</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>67</td>
<td>90.5</td>
</tr>
<tr>
<td>Internship (n = 44)</td>
<td>Male</td>
<td>2</td>
<td>4.5</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>42</td>
<td>95.5</td>
</tr>
</tbody>
</table>

Table 1. Characteristics of study participants
<table>
<thead>
<tr>
<th>Question</th>
<th>Response</th>
<th>III year</th>
<th>Final year</th>
<th>Internship</th>
</tr>
</thead>
<tbody>
<tr>
<td>Do you enquire tobacco use status of the patient while recording case</td>
<td>Yes</td>
<td>31 (93.9)</td>
<td>72 (97.3)</td>
<td>38 (86.4)</td>
</tr>
<tr>
<td>history or during examination?</td>
<td>No</td>
<td>1 (3)</td>
<td>1 (1.4)</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Sometimes</td>
<td>1 (3)</td>
<td>1 (1.4)</td>
<td>6 (13.6)</td>
</tr>
<tr>
<td>If the patient happens to be a tobacco user, do you give any kind of</td>
<td>Yes</td>
<td>21 (63.6)</td>
<td>51 (68.9)</td>
<td>34 (77.3)</td>
</tr>
<tr>
<td>cessation advice?</td>
<td>No</td>
<td>4 (12.1)</td>
<td>3 (4.1)</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Sometimes</td>
<td>8 (24.2)</td>
<td>20 (27.0)</td>
<td>10 (22.7)</td>
</tr>
<tr>
<td>How much time on an average do you spend giving tobacco cessation</td>
<td>Less than 3</td>
<td>26 (78.8)</td>
<td>58 (78.4)</td>
<td>34 (77.3)</td>
</tr>
<tr>
<td>advice for patient</td>
<td>minutes</td>
<td>6 (18.2)</td>
<td>13 (17.6)</td>
<td>9 (20.5)</td>
</tr>
<tr>
<td></td>
<td>More than 10</td>
<td>1 (3.0)</td>
<td>3 (4.1)</td>
<td>1 (2.3)</td>
</tr>
<tr>
<td></td>
<td>minutes</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 2: Assessment practices of tobacco use among patients

<table>
<thead>
<tr>
<th>Individual level barriers</th>
<th>Response</th>
<th>III year</th>
<th>Final year</th>
<th>Internship</th>
</tr>
</thead>
<tbody>
<tr>
<td>I have inadequate knowledge on NRTs</td>
<td>Disagree</td>
<td>12 (36.4)</td>
<td>58 (78.4)</td>
<td>30 (68.2)</td>
</tr>
<tr>
<td></td>
<td>Agree</td>
<td>21 (63.6)</td>
<td>16 (21.6)</td>
<td>14 (31.8)</td>
</tr>
<tr>
<td>X2 = 18.11 df = 2 p &lt; 0.001</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I have inadequate knowledge on quitlines</td>
<td>Disagree</td>
<td>12 (36.4)</td>
<td>46 (62.2)</td>
<td>32 (72.7)</td>
</tr>
<tr>
<td></td>
<td>Agree</td>
<td>21 (63.6)</td>
<td>28 (37.8)</td>
<td>12 (27.3)</td>
</tr>
<tr>
<td>X2 = 10.75 df = 2 p &lt; 0.005</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I forget to give tobacco cessation advice</td>
<td>Disagree</td>
<td>26 (78.8)</td>
<td>68 (91.9)</td>
<td>40 (90.9)</td>
</tr>
<tr>
<td></td>
<td>Agree</td>
<td>7 (21.2)</td>
<td>6 (8.1)</td>
<td>4 (9.1)</td>
</tr>
<tr>
<td>X2 = 4.21 df = 2 p = 0.122</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I do not undertake tobacco cessation activities due to lack of</td>
<td>Disagree</td>
<td>29 (87.9)</td>
<td>70 (94.6)</td>
<td>41 (93.2)</td>
</tr>
<tr>
<td>incentives</td>
<td>Agree</td>
<td>4 (12.1)</td>
<td>4 (5.4)</td>
<td>3 (6.8)</td>
</tr>
<tr>
<td>X2 = 1.54 df = 2 p = 0.462</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I feel there is inadequate time to give advice</td>
<td>Disagree</td>
<td>21 (63.6)</td>
<td>43 (58.1)</td>
<td>34 (77.3)</td>
</tr>
<tr>
<td></td>
<td>Agree</td>
<td>12 (36.4)</td>
<td>31 (41.9)</td>
<td>10 (22.7)</td>
</tr>
<tr>
<td>X2 = 4.47 df = 2 p = 0.107</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I chose to focus on other problems</td>
<td>Disagree</td>
<td>31 (93.9)</td>
<td>58 (78.4)</td>
<td>36 (81.8)</td>
</tr>
<tr>
<td></td>
<td>Agree</td>
<td>2 (6.1)</td>
<td>16 (21.6)</td>
<td>8 (18.2)</td>
</tr>
<tr>
<td>X2 = 3.91 df = 2 p = 0.141</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 3: Association between individual barriers and study groups (year of study)
Barriers to Tobacco Cessation Advice among Clinical Dental Students: A cross-sectional study

I feel there is inadequate time to give advice
I have inadequate knowledge about quitlines
I choose to focus on other oral problems with more priority than tobacco use
I have inadequate knowledge about nicotine replacement therapy
I forgot to give tobacco cessation advice
I do not undertake tobacco cessation advice due to lack of incentives

Fig: Participant responses to individual level barriers for tobacco cessation advice

I feel there is lack of a formal tracking system in the dental college to follow up the patients
I feel there is inadequate availability of patients education materials
I think there is inadequate space to hold confidential conversation
I lack training to counsel patients who smoke tobacco
I lack training to counsel patients who use smokeless tobacco
I feel there is inadequate faculty support for providing tobacco cessation services at individual level

Fig 2: Participant response to system level barriers for tobacco cessation advice
DISCUSSION

There is evidence that tobacco cessation efforts in the dental setting can have an impact on patients’ tobacco use\(^5\). A dentist/student who recognizes a patient to be a smoker/tobacco user has the duty to help the patient refrain from the habit. But several factors, known and unknown deter the dental students from performing this task. Identifying barriers to tobacco cessation counselling may enhance the effectiveness of a training program and help address the deficient areas. Further, identifying them and recommending appropriate curriculum and training changes could enable more students and future health professional perform this duty. Student attitudes may be greatly influenced by the dental school environment. Dental schools should also consider the environment and factors such as the attitude of the faculty and curriculum while implementing tobacco cessation in clinical practice.

The students though demonstrating favourable attitude toward asking and advising about tobacco use, demonstrated less positive attitude towards specific strategies such as Nicotine Replacement Therapy. To overcome this barrier, perhaps a training approach similar to that used by Seidman et al. could be used. He suggested including pharmacists at the dental school to show students various tobacco cessation medications and provide instructions regarding these medications. This could help the students understand the medicines’ properties better. The students can also be supplied with nicotine gum, patches and lozenges which can be appropriately given to their patients presenting with a positive tobacco usage history.

An important majority of them (> 75%) in all groups devoted less than 3 minutes towards tobacco cessation counselling. The present academic and clinical requirements of dental schools in India places great emphasis on the curative aspects of dental care leaving preventive practices such as eliciting a detailed tobacco history and providing cessation advice to merely a formality. It is also interesting to note that higher percentage of final year students agree that lack of time and focus on other problems as a barriers compared to third year students and internship. This reinforces the aforesaid viewpoint on academic and clinical scenario in Indian dental schools.

The barriers to tobacco cessation advice reported most commonly were lack of specific knowledge and skills. Similar results were reported in other studies\(^{12}\). The lack of knowledge and skills combined with limited clinical time available is oftentimes a concern. This overall gap may be filled by converting patient interactions at clinical departments being transformed into “teachable moments” to not only train future dental undergraduates in brief preventive strategies like tobacco use prevention and cessation but also provides more effective, evidence-based cessation interventions\(^4\). The responsibility of providing training in tobacco cessation counselling should be shouldered by the dental school in order to inculcate interest and build necessary skills in students.

Patient resistance/lack of motivation of patients was a significant barrier reported by students in this study. However, the existing literature is divided on this aspect. While few studies have reported that patients are comfortable with dental professionals providing cessation advice\(^6,13\) there have also been reports of lack of pa-
tient interest as a major deterrent for counselling\(^1,^2\). We suggest tobacco cessation training programs consider including strategies to address patient resistance and enhance motivation, such as motivational interviewing techniques.

Another barrier reported was the lack of patient education material. Any dental school with a tobacco cessation unit must ensure the all the necessary educational material is available for patient use. Similar findings were reported in studies conducted among dental students elsewhere\(^15\). Students could be encouraged to prepare patient education materials and use them for providing cessation advice. This would ensure better involvement of students.

Lack of confidential spaces was also reported as a barrier to effective cessation counselling. Every dental school should have a specific area designated towards tobacco cessation activities. Dental schools should ensure specific designated areas for effective tobacco cessation activities and strive to strengthen existing tobacco cessation curricula or for including the same in the dental course.

The Dental Council of India plans on establishment of Tobacco Cessation Clinic in every dental school in India is a step in the right direction\(^16\). It is hoped that this would inculcate the practice of providing tobacco cessation advice and other cessation methods right from their formative years of dental education. Thus, the dental Institutions across the country would provide an ideal and sustainable foundation which collaborates to strengthen tobacco control measures in the country.

**CONCLUSION**

This study provides evidence that dental students have favourable attitudes toward tobacco cessation, and majority expressed interest in training. However, dental students may need more guidance and information regarding specific tobacco cessation skills and strategies.

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**CONFLICTS OF INTEREST**

None

**REFERENCE**


Pulmonary alveolar hemorrhage: A case report on rare complication of Ruxolitinib therapy in a myelofibrosis patient

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ABSTRACT

Myelofibrosis (MF) is a clonal hematopoietic stem cell disorder characterized by the abnormal accumulation of myeloid cells. Janus kinase (JAK2) inhibitor- Ruxolitinib had been approved for the management of patients with intermediate to high risk MF. In this paper, we report a case of a 61 year old woman who was diagnosed with JAK2 positive chronic myeloproliferative neoplasm with hypereosinophilia on bone marrow biopsy. She was diagnosed to have secondary myelofibrosis which was confirmed on reassessment of bone marrow biopsy, for which she was initiated on Ruxolitinib. Initially, she showed improvement in constitutional symptoms but later on showed worsening of disease with pleural effusion. She also had recurrent fever with frequent episodes of tachypnoea. On further evaluation, she was diagnosed with pulmonary alveolar hemorrhage (PAH). An alarming factor is that a few case studies have been reported with pulmonary adverse effects to Ruxolitinib which raises a concern.

Keywords: Myelofibrosis, ruxolitinib, pulmonary alveolar hemorrhage, extra medullary hematopoiesis.

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INTRODUCTION

Myelofibrosis is a malignant hematological neoplasm arising from precursors of myeloid lineages in the bone marrow1,8. Somatic mutations in the JAK2, MPL, CALR and TET2 genes of blood stem cells have been identified in many patients2,9. Dysregulation of intracellular Janus kinase/signal transducers and activators of transcription (JAK/STAT) signalling pathway and proinflammatory cytokines act as pathogenic mechanisms3,4. The disease develops at any age but typically after 50 years with a preponderance in males2,5. The common symptoms are progressive anemia, constitutional symptoms and splenomegaly. Management of the disease encompass medications, blood transfusion, chemotherapy, radiotherapy, surgery and stem cell transplantation4. The median survival for the affected individuals is 2-11 years7.

Treatment for myelofibrosis is determined by risk stratification. Current pharmacologic treatment in MF is neither curative nor it extents the survival period for a long period6. Allogeneic haemopoietic stem cell transplantation (allo-SCT) is the only curative therapy for MF, but it carries its own risk of death or chronic morbidity from graft-versus-host disease (GVHD)9. Traditionally available therapies are hydroxyurea, thalidomide with/without prednisolone, lenalidomide with/without prednisolone, radiotherapy and splenectomy10. For intermediate 2/high risk myelofibrosis, JAK inhibitor Ruxolitinib has shown promising results (COMFORT 1 and 2 trials) with an increment in overall survival. Ruxolitinib is the first of its kind to gain approval by the FDA on November 16, 2011 for the treatment of MF7. The usual recommended dose is 15mg or 20mg BD which is then adjusted based on the platelet counts. In India, it was approved by the DCGI in the year 2013 and is made available to the patients through the Patient Assistance Program (PAP) scheme. Sudden discontinuation of the drug can cause withdrawal syndrome in the form of fever, biological inflammatory syndrome, acute respiratory disease syndrome, pulmonary hypertension etc. Anemia and Grade 3 thrombocytopenia are the most frequent adverse effects of Ruxolitinib. The other reported adverse effects of Ruxolitinib are increased risk of opportunistic infections (tuberculosis, reactivation of hepatitis B, herpes zoster, or urinary tract infection) delay in hematopoietic recovery and tumor lysis syndrome. Pulmonary symptoms are rarely reported7,11,12.

A rare and life threatening manifestation of myelofibrosis is the pulmonary extramedullary haematopoiesis. Hardly few cases have been reported on myelofibrosis with pulmonary symptom such as pulmonary alveolar hemorrhage(PAH)13. Pulmonary alveolar hemorrhage is confirmed by the presence of hemosiderin macrophages in the alveolar space on biopsy histopathology14.

Case Presentation

A 61 year old woman had presented with complaints of anemia (Hb: 4.3g/dl), thrombocytopenia (Plt: 122.0K/uL) and leukocytosis (WBC: 85.4K/uL). She had numbness of hands and feet, and abdominal pain. Her plasma coagulation tests were normal. She underwent bone marrow evaluation and was diagnosed as JAK2 positive chronic myeloproliferative neoplasm with hypereosinophilia. Initially, she was treated with imatinib, hydroxyurea and steroids. She responded well with the therapy for almost 2 years. Then the disease progressed with worsening of symptoms such as severe abdominal pain, severe fatigue, intermittent fever and splenomegaly. She was diagnosed to have secondary myelofibrosis which was confirmed by reassessment of bone marrow biopsy. She was initiated on Ruxolitinib (15mg twice daily) and continued on the same dose for almost...
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2 months. Initially, she showed improvement in constitutional symptoms but later on showed worsening of disease with pleural effusion. She also had recurrent fever with frequent episodes of tachypnoea. On further evaluation, she was diagnosed with pulmonary Pseudomonas infection and PAH, which was confirmed by the presence of macrophages and hemosiderins in the bronchial washing along with an acute drop in haemoglobin. Despite aggressive supportive treatment with antibiotics, bronchodilators and oxygen support, the disease progressed and she succumbed to death. The possibilities for the development of PAH in this patient could either be due to extramedullary haematopoiesis or due to the documented pulmonary Pseudomonas infection. An alarming factor is that a few case studies have been reported with pulmonary side effects to Ruxolitinib which raises a concern.

Sudden withdrawal of the drug can cause RWS (Rapid withdrawal syndrome) due to rebound of cytokines. The syndrome is very rare according to the publications reported to date and appears with in 24 hrs of drug cessation. Systemic inflammatory response syndrome (SIRS), respiratory distress, progression in splenomegaly, fever, pruritus, shock like syndrome, pericardial effusion, disseminated intravascular coagulation, tumor lysis like syndrome are the reported symptoms of RWS. Instead of drug cessation, tapering the dose and wean off the drug has to be done. Corticosteroid is used to prevent cytokine rebound and if it is not subsiding reintroduction of ruxolitinib is needed13,14,15. On the contrary adverse effect developed in a 58 year old male patient with primary myelofibrosis who had complaints of malaise and dyspnea while on ruxolitinib after 15 days of initiation of treatment. He was diagnosed to have mild ARDS. Even after excluding the potential causes like infection and cardiologic pathologies, it was considered secondary to ruxolitinib. He was then initiated on methyl prednisolone to prevent cytokine rebound syndrome and continuous positive airway pressure therapy16. This case report also gives us awareness about the pulmonary adverse effect of ruxolitinib.

Real world data has shown derangement in cellular immunity, immune suppression and risk of opportunistic infections with the use of Ruxolitinib. Cryptococcus neoformans pneumonia, Pseudomonas infection, asymptomatic/latent tuberculosis, reactivation of pulmonary tuberculosis, herpes zoster, atypical bacterial, mycobacterial, fungal, and viral infections are some of the reported opportunistic infections17,18.

CONCLUSION

We report this case because it is a rare complication not yet reported in patients on Ruxolitinib therapy and requires further attention. This can also helps in creating awareness among the physicians while providing
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Conflicts of Interest

The authors declare that there is no conflict of interest.

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