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Structure

English title, author names and institutions.
Abstract (average 200-400 word)
Introduction
Methods
Results
Discussion and conclusion
References (most 30)
Whole text should not exceed 4500 words except for refences and abstract.

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Conclusion
References (most 15)

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300 words of text and original images about the subject

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MIDDLE BLACK SEA JOURNAL OF HEALTH SCIENCE

APRİL 2018 **VOLUME 4** **ISSUE 1**

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EDITORIAL

Three full years ...

In thid process we start with small steps but with big goals, we are happy to be an international scanned journal.

Thank you very much to the referees, authors and the editorial board members from Turkey and different countries in our publishing family.

Again, in this issue, you can also access original articles on topics ranging from psychology, nursing to basic medical sciences and surgeon sciences.

Our aim is to continue to contribute to the science with new formations in more beautiful publications with the wish to meat in the next issue

See you soon…

PhD. Asst. Prof. Ülkü KARAMAN

Editor

Middle Black Sea Journal of Health Science April 2018; 4(1):1-6

RESEARCH ARTICLE

Treatment of Distal Radius Fractures by Intramedullar Nailing with Micronail®

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Abstract
Objective: Distal radius fractures are common fractures in the adult population. For treatment, intramedullary nailing has the advantage of providing effective internal fixation with minimum soft tissue damage. We aimed to present our experience with the use of intramedullary nailing device Micronail® (Wright Medical Technologies, Arlington, TN, USA) in the treatment of unstable extra-articular and simple intra-articular distal radius fractures.
Methods: Forty-three patients (mean age 54.7±10.8 years; 54.7% women) with unstable extra-articular and simple intra-articular distal radius fractures suitable for closed reduction (A21, A2.2, A23, A3, C2.1) were included in this retrospective study. Intramedullary distal radius fixation procedures were performed using Micronail® intramedullary nails in our clinic between February 2011 and January 2017. Clinical outcome measures were range of motion (ROM); visual analog scale (VAS); patient-reported Disabilities of the Arm, Shoulder and Hand [DASH] score; clinician-based Gartland–Werley score; radiographic Stewart score; radiographic parameters (radial inclination, volar tilt, radial height, radio-ulnar variance), and complications.
Results: The surgery lasted an average of 32.5±2.42 min. The mean postoperative follow-up duration was 31.4±5.8 weeks. Complete fracture union was obtained at 5.24±0.7 weeks. The postoperative VAS pain score was 2.4±1.2, which was remarkably low. The DASH score was 20±3.7, the Gartland–Werley score was 5.2±4.53, and the Stewart score was 1.7±1.4 on postoperative evaluation. ROM values were over 70° for all motions. Compared with the healthy side, the median loss in ROM was less than 17° for flexion, extension, pronation, and supination. In the postoperative radiological evaluations, there were significant increases in radial inclination (p=0.005), volar tilt (p<0.001), and radial height (p<0.001), and a decrease in radio-ulnar variance (p=0.001) compared to the preoperative values. Thirty patients (69.8%) had no postoperative complications, remaining 13 patients experienced minor complications that were treated effectively.
Conclusion: Intramedullar nailing with Micronail® is a minimally invasive technique, which provides effective and safe fixation of unstable extra-articular and simple intra-articular distal radius fractures.
Key words: Distal radius fractures, Intramedullar nail, Minimally invazive

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Introduction

Distal radius fractures are common fractures in the adult population (Liporace, 2009). Depending on the severity of the fracture and the needs of the patient, several operative and nonoperative treatment options have been used for the management of distal radius fractures. Operative management methods include closed reduction, external fixation, and open reduction with internal fixation, (Liporace et al., 2009, Bales and Stern, 2012). Intramedullary nailing has recently gained popularity in the treatment of extra-articular or

simple intra-articular distal radial fractures (Nishiwaki et al., 2011). This technique has the advantage of providing effective internal fixation with minimum soft tissue damage.

Micronail® (Wright Medical Technologies, Arlington, TN, USA) is a minimally invasive titanium locking screw fixation for two-part dislocated extra-articular fractures and average displaced intra-articular distal radius fractures. Since its introduction to the market in 2006, clinical studies have shown that use of Micronail® reduces soft tissue complications and provides fixed-angle support (Ilyas and Thoder, 2008; Geerts et al., 2011, van Vugt et al., 2010). However, these studies have been mostly preliminary reports with limited sample sizes. Therefore, a greater number of experiences should be published in order to reach a more precise consensus on the advantages and disadvantages of the Micronail® in the treatment of distal radius fractures.

In this study, we aimed to present our experience with the use of Micronail® in the treatment of unstable extra-articular and simple intra-articular distal radius fractures in a series of 43 patients.

Methods

Twenty-nine patients with unstable extra-articular and simple intra-articular distal radius fractures suitable for closed reduction (AO/OTA classification A21, A2.2, A23, A3, C2.1) were included in this retrospective study. Following closed reduction and circular casting, cases with volar tilt >20°, articular incongruity >2 mm, radial inclination >15°, and radial shortening >5 mm on radiographs were treated surgically. Intramedullary distal radius fixation procedures were performed using Micronail® intramedullary nails in our clinic between February 2011 and January 2017. The exclusion criteria were open or contaminated wounds; open physes; displaced intra-articular fragments; irreducible articular or extra-articular fractures; partial articular fractures involving the volar or dorsal rim (AO type 23); small and comminuted articular fragments that could not be reduced adequately by closed or percutaneous means; and fractures that extended proximally into the metaphyseal-diaphyseal bone.

The study was conducted in compliance with the Helsinki Declaration. The informed consent requirement was waived due to the retrospective design of the study.

Study parameters

The following data were retrieved from patients' files and recorded: demographics (age, gender), handedness, type of injury, type of distal radius fracture, concomitant fractures, duration of follow-up, length of hospital stay, total surgery and scopy time, and time to fracture healing. Clinical outcome measures were range of motion (ROM); visual analog scale (VAS); patient-reported Disabilities of the Arm, Shoulder and Hand [DASH] score; clinician-based Gartland–Werley score (Graham 1997); radiographic Stewart score (Stewart et al. 1984); radiographic parameters (radial inclination, volar tilt, radial height, radio-ulnar variance), and complications. The radiographic criteria of acceptable healing defined by Graham (Gartland and Werley 1951) were used for evaluation.

Operative techniques and postoperative follow-up

Micronail®-based intramedullary nailing was performed under local or general anesthesia with fluoroscopic control, with the patient in the supine position. First, closed reduction and temporary fixation were performed using a K-wire introduced from the ulnar side of the radius. Then, a 2-cm incision was made over the radial styloid process to create a cortical window between the first and second compartments, through which an appropriately sized implant was placed following the scraping process. Fixation was performed via three distal subchondral (locking) screws. A new incision 2 cm in length was made dorsally for proximal locking and fixated via two screws under fluoroscopy. The incision sites were then sutured.

Finger motion began immediately after surgery. Postoperative treatment consisted of a wrist splint for five days. Approximately one week after surgery, the splint was removed, and radiographs were taken. As long as there were no complications, load-carrying physical therapy was initiated. Clinical results were evaluated during a six-month follow-up consisting of four visits: three weeks, six weeks, 12 weeks, and six months after surgery.

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics for Windows, version 22.0 (IBM Corp., Armonk, NY, USA). Data were evaluated using the Shapiro–Wilk test for normality of distribution. A Chi-square or Fisher's exact test was used for comparing categorical data, while Student's

t test or the Mann–Whitney U test was used to compare continuous data according to the normality of the data. To compare preoperative and postoperative continuous variables, a paired t test or the Wilcoxon signed rank test was used according to the normality of the difference in variables. Data were expressed as mean±standard deviation and frequency (%) where appropriate. The statistical level of significance was set at $p<0.05$.

Results

The mean age of the patients was 54.7±10.8 years, and 54.7% were women. In most of the patients, the distal radius fracture was caused by a fall (65.5%). There was no concomitant fracture in 74.4% of the patients.

The surgery lasted an average of 32.5±2.42 min. The mean postoperative follow-up duration was 31.4±5.8 weeks. Complete fracture union was obtained at 5.24±0.7 weeks (Table 1).

Table 1. Operational characteristics and outcome measures

	Study population (n=43)
Total surgery time (min)	32.5±2.42
Scopy time (min)	22.2±3.9
Duration of follow-up (week)	30.9±5.7
Length of hospital stay (day)	3.7±0.6
Time to fracture union (week)	5.24±0.7
VAS pain score	2.4±1.2
DASH score	20±3.7
Gartland–Werley score	5.2±5.3
Stewart score	1.7±1.4
ROM (°)	
Flexion	75.2±15.2
Extension	70.1±4.45
Pronation	78.7±15.1
Supination	80.3±5.2
Compliance to the radiographic healing criteria of Graham (1997)	
Radial inclination <15°	37 (86.04)
Volar tilt <20°	39 (90.7)
Articular incongruity (<5 mm)	43 (100.0)

Data are given as mean±SD.

VAS, visual analog scale; DASH, Disabilities of the Arm, Shoulder and Hand

The postoperative VAS pain score was 2.4±1.2, which was remarkably low. The DASH score was 20±3.7, the Gartland–Werley score was 5.2±4.53, and the Stewart score was 1.7±1.4 on postoperative evaluation (Table 1).

ROM values were over 70° for all motions (Table 1). Compared with the healthy side, the median loss in ROM was less than 17° for flexion, extension, pronation, and supination (Figure 1).

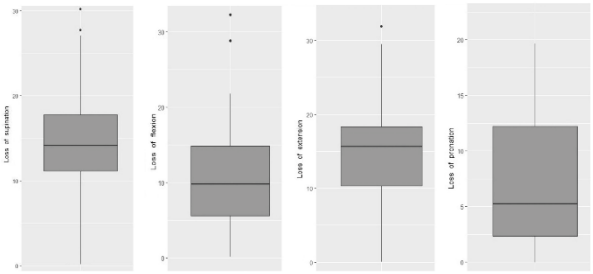

Figure 1. Loss of range of motion (ROM) compared to the healthy side for flexion, extension, pronation, and supination. The horizontal line within the box indicates the median; the boundaries of the box indicate the 25th and 75th percentile; and the whiskers indicate the highest and lowest values of the results. The mild outliers are indicated by dots.

In the postoperative radiological evaluations, there were significant increases in radial inclination ($p=0.005$), volar tilt ($p<0.001$), and radial height ($p<0.001$), and a decrease in radio-ulnar variance ($p=0.001$) compared to the preoperative values (Table 2).

Table 2. Radiographic outcome (n=29)

	Preoperative	Postoperative	p value
Radial inclination (°)	16.5±3.9	19.6±5.75	0.005
Volar tilt (°)	-12.1±11.3	6.7±6.1	<0.001
Radial height (mm)	3.1±2.8	9.6±1.7	<0.001
Radio-ulnar variance (mm)	2.7±1.8	1.08±0.86	0.001

The compliance rate to the radiographic criteria of Graham (1997) was over 80% for radial inclination, volar tilt, and articular incongruity (Table 1).

Thirty patients (69.8%) had no postoperative complications. Three patients experienced radial nerve paresthesia, and three other patients had infections. Tendon rupture and tenosynovitis were recorded in two patients, and Sudeck's atrophy was observed in one patient. All postoperative complications were treated effectively.

Discussion

Distal radius fractures are common upper extremity fractures of adulthood with increasing prevalence, particularly in pediatric and elderly populations (Nellans et al. 2012). In most cases, distal radius fractures can be treated conservatively by non-operative methods such as closed reduction, splint, and circular casting. However, in conservative treatment by using non-operative methods, time to fracture union is long, and the risk of non-alignment and fracture displacement is high (Miller et al. 2005). For patients treated with non-

operative methods, full load-carrying capacity can be obtained very late. There are no well-defined criteria for the decision between operative and non-operative treatment, it depends on various factors such as severity and type of fracture, patient's needs, experience of surgeon, and surgical facilities of the clinic (Laino and Tejwani 2012, Obert et al. 2013). Currently, many surgical fixation methods, each achieving stable reduction with advantages and disadvantages, are present, but there is not enough evidence recommending one type of fixation over other (Obert et al. 2013,Diaz-Garcia and Chung 2012).

The surgical treatment options for distal radius fractures include open reduction and internal fixation with plates, and percutaneous or external fixation techniques (Obert et al. 2013, Diaz-Garcia and Chung 2012, Othman 2009). Among these options, the Micronail® is an intramedullary titanium pin used for internal fixation of unstable extra-articular and simple intra-articular distal radius fractures. It has the advantages of providing support by locking screws and minimally invasive intramedullary surgical technique sparing surrounding soft tissues (Geerts et al.2011). Although the Micronail® is advantageous, studies documenting the results of this techniquer are limited. In our clinic, we have been applying intramedullary fixation with the Micronail® since 2011. We usually treat distal radius fractures conservatively by closed reduction and circular casting. However, we apply surgical treatment for cases that show high volar tilt, articular incongruity, radial inclination, and radial shortening on radiographs following conservative treatment. In these cases, if the distal radius fracture is unstable extra-articular or simple intra-articular, we perform open reduction and intramedullary fixation with the Micronail®. In this article, we presented our experience with the Micronail® in a retrospective series of 29 patients.

Fixation of distal radius fractures by intramedullary nailing has been introduced in the last decade (Ilyas and Thoder 2008). Initial reports indicated good functional and radiological outcome, but high rate of postoperative complications (Ilyas and Thoder 2008, Dremstrup et al. 2013). The improved technology of Micronail® allowed minimally invasive surgery, and decreased soft tissue injury and related complications. The limited number of previous studies evaluated the efficacy and safety of internal fixation of distal radius fractures with the Micronail® (Geerts et al.2011, van Vugt et al. 2010, Tajima et al. 2012). In a series of 18 patients with 20 two-part dislocated extra-articular and average displaced intra-articular distal radius fractures, van Vugt et al. (van Vugt et al. 2010) showed that all fractures healed without major loss of alignment without major complication. Geerts et al. (Geerts et al.2011) applied the Micronail® in 10 patients with A2 or A3 distal radius fractures, and obtained union in all patients without loss of alignment. Short immobilization period of 5 days was reported to be sufficient, after which full load-carrying exercises should be initiated (Geerts et al.2011). The Micronail® allows early mobilization and return to daily life. Dremstrup et al., (Dremstrup et al.2013) performed fixation of 60 A2 and A3 distal radius fractures by using the Micronail®, and reported that all fractures healed, with an average radial volar tilt of 2°, radial length of 11 mm, and a radial inclination of 22. They concluded that the Micronail® provides a stable fixation of selected distal radius fractures, and good functional and radiological outcome with minimum complications. In a randomized study, Schønnemann et al. (Schønnemann et al.2011) compared the clinical and radiological outcomes of external fixation with Hoffmann II compact non-bridging in 30 patients and internal fixation with the Micronail® in 31 patients. They found that the Micronail® provided significantly better grip strength, but longer operation time compared to external fixation. Radiological outcome was similar between two fixation methods (Schønnemann et al.2011). Nishiwaki et al. (Nishiwaki et al.2011) also applied the Micronail® in 31 patients with dorsally displaced unstable distal radial fracture, and reported that on the radiographs obtained at one year after the surgery, radial inclination was 25°, volar tilt 11°, radial length 10 mm, and ulnar variance 1 mm. They concluded that this technique is an effective treatment for extra-articular or simple intra-articular distal radial fracture causing minimal complications. Similar to previous reports, in the present study, our patient population consisted of unstable extra-articular and simple intra-articular distal radius fractures suitable for closed reduction. The operation duration was 32.5±2.42 min on average, which is shorter than around 1 hour reported in literature (van Vugt et al. 2010). We followed patients for 30.9±5.7 weeks after the surgery, and obtained complete fracture union in all patients at 5.24±0.7 weeks. The postoperative VAS pain score was 2.4±1.2, which was remarkably low. In the study by Geerts et al. (Geerts et al.2011), the postoperative pain was also

reported to be low with a VAS score of 1.3. The DASH, Gartland-Werley, and Stewart scores indicated that the Micronail® provided good clinical and radiological outcome as reported in literature. In comparison to healthy side, the median loss in ROM was less than 17° in all directions, which was slightly higher than the previously reported 10 difference between two wrists (Geerts et al.2011, van Vugt et al. 2010). Similar to the previous studies, we obtained good radiological outcome on radiographs obtained in the last assessment. Accordingly, radial inclination was 19.6°, volar tilt was 6.7°, radial height was 9.6 mm, and ulnar variance was 1.08 mm. In our series, most patients did not experience any postoperative complications, while the remaining patients had minor and treatable complications. Our results supported the present knowledge that intramedullar nailing with the Micronail® provides safe and effective fixation of selected distal radius fractures with the advantage of minimum soft tissue damage.

The main limitation of our study was its non-comparative retrospective design and small sample size. Nevertheless, given the limited number of studies in literature on the Micronail®, we think that our present experience on this device would contribute to the literature and clinical management of distal radius fractures.

Conclusion

In conclusion, arthroscopic reduction and internal in conclusion, intramedullar nailing with Micronail® is a minimally invasive technique, which provides effective and safe fixation of unstable extra-articular and simple intra-articular distal radius fractures.

Ethics Committee Approval: The requirement for the ethics committee approval was waived for the retrospective design and valid legal regulations at the time of the study.
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RESEARCH ARTICLE

Mode of Delivery and Number of Children Effect on Sexual Function

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Abstract
Objective: To reveal the effect of the delivery mode (vaginal delivery, cesarean delivery) and the number of children on sexual function.
Methods: Eightywomen who applied to our clinic for routine gynecological control between July 2017 and January 2018 were included in the study. Age of women's, parity, demographic analysis andArizona Sexual Experiences Scale (ASEX) were done. The patients were divided into four groups: group I only had one vaginal delivery, group II only one cesarean delivery, group III two/three vaginal deliveries, group IV two/three cesarean deliveries.
Results: We found significantly lower ASEX scores in the cesarean delivery andone child group (p=0,000). When the groups were examined; ASEX scores were respectively; I 14,45 - II 11,65 - III 17,35 - IV 14,15 (p=0,000). Finally vaginal delivery and having more than one child has created a tendency to have female sexual dysfunction.
Conclusion: Even though we found in our study there is no clear evidence in the literature that cesarean delivery might be protective for the development of female sexual dysfunction. There is need of randomized, well-controlled, long-term studies. Sexual dysfunction is a relatively common health problem and efforts to recognize and treat this problem should not focus only on delivery mode.
Key words: Female sexual dysfunction, Mode of delivery, Number of children, ASEX.

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Introduction

Sexual health is an important part of the quality of life of women. World Health Organization has defined it as "a state of physical, emotional, mental and social well-being related to sexuality; it is not only the absence of disease, dysfunction or infirmity" (World Health Organization, 2012).

Pregnancy process, delivery, lactation period affects multiple physiological and mental functions that hinder sexuality. But the healthcare professionals tend to focus on topics related to vaginal trauma, operative vaginal delivery, episiotomy, cesarean delivery instead of physiological variations (Brtnicka et al., 2009).

Female sexual dysfunction (FSD) is one of themost common health problem. Although some clinicians say that FSD is seen up to 90%, it seems to affect practically half of the women population (Fugl-Meyer, 2000; Kadri et al., 2002; Oberg et al.,

2004; Derogatis et al., 2008; Ghorat et al., 2017). Multifactorial situations in woman's life cycle such as aging, hormonal status, pregnancy releated status (delivery, puerperium, breastfeeding, perineal trauma), physiological and medical disorders determine the ratio of FSD (Von Sydow, 1999; West et al., 2008).

The literature researching the effects of pregnancy and delivery on postpartum sexual function is heterogeneous and inconclusive. But it's clear that FSD is seen more likely in postpartum period (Brown et al., 1998; Barrett et al., 2000; Signorello et al., 2001; DeJudicibus et al., 2002; Thompson et al., 2002; Ejegard et al., 2008; Klein et al., 2009; Boroumandfar et al., 2010).

Considering the World Health Organization recommendation that cesarean delivery rates should not be higher than 10 to 15% (World Health Organization, 1985), the cesarean rate is continuously and worryingly increasing in Turkey since the 1990's (Turkey Demographic and Health Survey, 2008). As the half of turkish obstetricans think that preference tendency might be related fewer effects of cesereanon sexual functions (Arikan et al., 2011). Notwithstanding unconvincing data on the relationship between mode of delivery and postpartum sexual dysfunction, in our study we aimed to reveal the effect of the delivery mode (vaginal delivery, cesarean delivery) and the number of children on sexual function

Methods

This prospective study received approval from the human research ethics commitee at the Ordu University Medical Faculty Research and Training Hospital. Participants were recruited from the gynecology clinic between July 2017 and January 2018. Eighty healthy women who applied to our clinic for routine gynecological control were included in the study. The exclusion criteria were as follows: chronic disease, poor obstetric history (macrosomic birth, stillbirth, shoulder dystocia, advanced genital tract injury), comorbid conditions in pregnancy (gestational diabetes, gestational hypertension/preclampsia, thyroid dysfunction), gynecologic pathology that may have an impact on sexual function (such as vaginitis, pelvic inflammatory disease, chronic pelvic pain, myoma, adnexal mass). More than three children women were exculded too.

Age of women's, parity, demographic analysis was done. There are severel index and scale for evaluating sexual function. We administered Arizona Sexual Experiences Scale (ASEX). The ASEX was selected for use in this study as a well validated 5-item questionnaire that is psychometrically sound and easy to self-adminester. The ASEX scores are between 5 and 30. High scores are associated with sexual dysfunction (McGahuney et al., 2000).

The patients were divided into four groups: group I only had one vaginal delivery, group II only one cesarean delivery, group III two / three vaginal deliveries, group IV two / three cesarean deliveries.

Statistical analyses were performed with the SPSS 20 programme. Compairing the four groups One Way Anova analysis was used.

Results

Eighty women were recruited for this study. All of them completed the demografic analysis and ASEX. The mean age of the women was 36,66±6,35 (18–45).

The average ASEX score was 14,4.We found significantly lower ASEX scores in the cesarean delivery group (p=0,000). The mean ASEX score was 12,9 in the casarean delivery group whereas 15,9 in the vaginal delivery group.

In the group with one child, ASEX scores were significantly lower too (p=0,000). The mean ASEX score was 13,05 in the one child group while it was 15,75 in the more than one child group.

When four groups were compared we also found a significant difference between the ASEX scores. The mean ASEX scores were respectively; I 14,45 - II 11,65 - III 17,35 - IV 14,15 (p=0,000).
Mode of delivery, number of children, and four group results are shown figure 1, 2 and 3

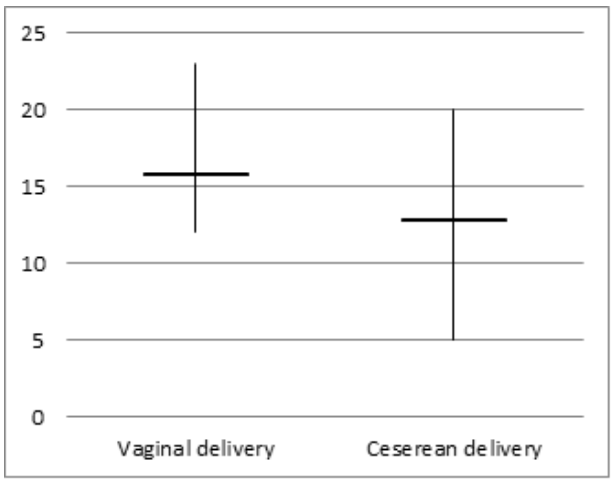

Figure 1. ASEX Skorları

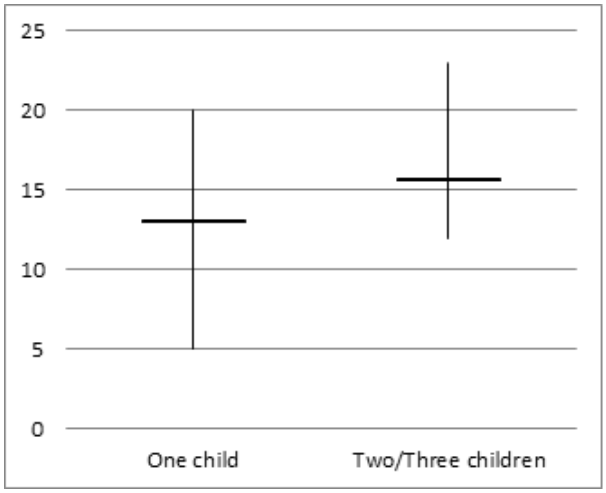

Figure 2. ASEX Skorları

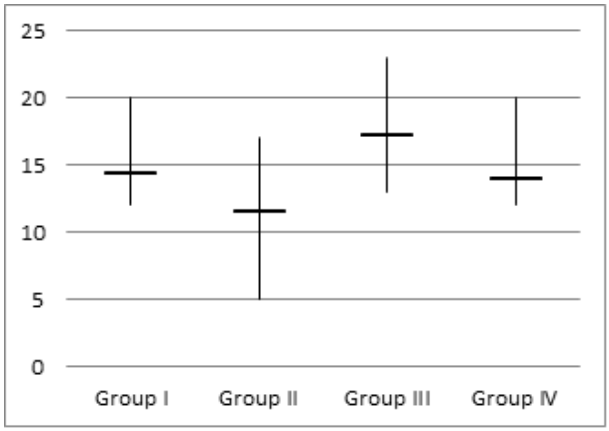

Figure 3. ASEX Skorları

Abstractly vaginal delivery and having more than one child has created a tendency to have FSD. This might be releated with neuromuscular vaginal trauma and longer breastfeeding period. And also fatigue, postpartum depression, body image is prominent.

Discussion

Female sexual dysfunction is an ignored tabu yet it is also very common and reducing the quality of life. Although many women reported problems with sexual intercourse, only approximately 10 % felt the need to seek help or advice (Glazener, 1997).

There is conflicting evidence about the role of delivery mode and number of children on sexual health outcomes. The literature is very heterogeneous and debateble. A good many of studies reported no significant relationship between delivery mode and sexual dysfunction (Barrett et al., 2000; Klein et al., 2009; Hannah et al., 2004; Woranitat et al., 2007; Connolly et al., 2005; Pauls et al., 2008; Gungor et al., 2007; Shirvani et al., 2010; Hannah et al., 2002; Hosseini et al., 2012; Fan et al., 2017; Saydam et al., 2017; Gun et al., 2016; Ghorat et al., 2017; Rezaci et al., 2017). Despite that some studies like our study found significant relation between them (Griffiths et al., 2006; Chang et al., 2010).

Klein et al. found that women with an intact perineum or perineal tears had less sexual dysfunction comparison with perineal trauma. Dean et al. reported that cesarean delivery was associated with better vaginal tone yet not releated to good sexual function. Kahramanoglu et al. revealed that caesarean section was not superior to vaginal birth and irrespective of their type of delivery, sexual function 6 months after childbirth was similar to pre-pregnancy scores.

Rathfisch et al. and Baksu at al. focused on episiotomy and found relation beetween episiotomy and sexual dysfunction. In another episiotomy study Gun et al. reported the relationship between the degree of perineal laceration and postpartum dyspareunia and observed that there was still not a clear evidence to say episiotomy is an etiologic factor on sexual dysfunction in the long term.

Brown at al. and Thompson et al. had studies about relation between pain and sexual dysfunction. They reported that noncomplicated vaginal delivery was not associated with sexual dysfunction but operative vaginal delivery which had higher pain was related with sexual dysfunction.

Conclusion

Delivery mode and number of children have a significant impact on the quality of sexual life and should be paid more attention. On the other hand, there is need of randomized, well-controlled, long-term studies. Yet it is hard for ethical reasons and less patient acceptance. But well-designed, large simple sized studies will contribute the literature.

When we look the literature there is no clear evidence that cesarean delivery might be protective for the development of female sexual dysfunction. Even though we found in our study; having vaginal delivery and more than one children group of women has worse sexual function than cesarean delivery and single children group. Forwhy there are lots of variables in the etiology of sexual dysfunction, not only delivery mode and number of children. Because of this reason sexual dysfunction is a relatively common health problem and efforts to recognize and treat this problem should not focus only on delivery mode.

Ethics Committee Approval: The requirement for the ethics committee approval was waived for the retrospective design and valid legal regulations at the time of the study.

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RESEARCH ARTICLE

A Retrospective Assessment of Specific Learning Disorders

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Abstract

Objective: Specific learning disorders (SLD) are delays or deviations observed in an individual's ability to speak, read, write, understand and do arithmetic. Diagnosis and the educational process is very difficult. Abnormalities of the central nervous system are shown as the cause of SLD, in addition to hereditary and environmental interactions. SLD has four subareas of reading disorder (dyslexia), written comprehension disorder (dysgraphia), mathematic disorder (dyscalculia) and other types. SLD may be accompanied by attention deficit and hyperactivity disorder, depression, anxiety, emotional and social problems. Epidemiological research has found rates of 1-33%. The lack of clarity in SLD criteria with very different rates of diagnosis may be linked to the difficulties of diagnosis and method deficiencies. Studies have shown it is observed more often in males in terms of gender, with no significant correlation between females and males. This study aimed to retrospectively assess SLD diagnoses from 2009 to 2017.

Methods: The study accessed data for all SLD children from 2009-2017 and included 846 child diagnoses in total.

Results: The study found the percentage of a population of 201,347 people aged from 0-18 years containing 197 SLD cases was 0.09%. Single sample chi-square test observed a significant level of increase as the years passed. Additionally, in terms of gender, the incidence in males (69.14%) was higher than in females (30.85%). The increase in SLD according to year was identified to be significantly rapid.

Conclusion: According to the data obtained in the study, it was concluded that there is a need for in-depth research into topics from SLD diagnosis to methods on a country basis.

Key words: Specific learning disorder, retrospective assessment, increase rate of specific learning disorder

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Introduction

Diagnosis of learning difficulties includes a range of difficulties in terms of education and life adaptation, because learning processes are a complicated construct and as a result it is not easy to find a solution (Saenz et al., 2005). Additionally, the inclusion of factors like individual differences and intelligence points or visual acuity within the process may be listed as other difficulties (Özyürek, 2003). As a result, there are problems experienced in the diagnosis and education of those with learning difficulties both globally and in Turkey.

Specific learning disorders (SLD) encompass disorders determined as delays or deviations in speaking, reading, writing, comprehension and arithmetic gains and in using them fluently in life.

Central nervous system anomalies are shown as the cause of SLD (Asfuroğlu and Fıdan, 2016). However, hereditary qualities and environmental interaction are also stated as causes (Karaman et al., 2012).

Reading disorder (dyslexia), written comprehension disorder (dysgraphia) and mathematic disorder (dyscalculia) within SLD may be observed alone or together (Gorker et al., 2017). As a result, there are difficulties experienced with diagnosis. However, early diagnosis and rehabilitation is necessary in terms of academic gains and increased quality of life (Tore, Balazs, 2015).

SLD is most commonly accompanied by attention deficit and hyperactivity disorder (ADHD) (Beitchman and Young, 1997). Additionally, emotional problems, socialization problems, behavior including crime, anxiety and depression are commonly observed (Beitchman et al., 2001; Kempe et al. 2011). A study identified high anxiety and depression among students with SLD (Deniz et al, 2009)

The number with SLD is great; however, sufficient studies have not been reported (Yao and Wu, 2003). Epidemiological studies related to SLD have found different results. As there are no definite criteria defined in epidemiological studies, academic performance and other assessments are completed (Gorker et al., 2017). As a result, due to relative evaluations, results of 1-33% are encountered in the literature (Asfuroglu and Fidan, 2016).

This study performed a retrospective assessment of the prevalence of SLD. Thus, the proportional increase rate was assessed between the years and additionally proportions related to prevalence are presented. This study will contribute to the very few epidemiological studies in the literature. Additionally, there are no studies about the increase rate of SLD through the years found in the literature. This situation is the subjective construct in this study.

Methods

The Ministry of National Education definitions related to special education for those with disabilities, placement in an educational organization and monitoring processes were laid out in the framework of the special education services regulations in the Official Gazette number 26184 published in 2006 (OEHY, 2006). In line with this, all disabled individuals were determined, with educational placement processes organized by special education service boards in each province and large counties. The technical infrastructure services (diagnosis, placement, monitoring and support reports and recommendations) for processes organized by the boards are provided by counseling and research center directorates. As a result, documentation and archives are held in these centers. This research, run as a retrospective cohort study, assessed the statistical data related to SLD held by Altınordu Counseling and Research Center Directorate Special Education Department Chair in Ordu province from 2009 to 2017 after receiving necessary permissions. The study accessed data for all children with SLD for the years from 2009 to 2017 and included a total of 846 pediatric diagnoses.

Statistical Analysis

Relationships between variables were explored using the one-sample chi-square test and two-sample chi-square test. Data were analyzed using SPSS 25 software (SPSS, Inc., Chicago, IL, USA). An alpha level of 5% was used for all statistical tests.

Results

The study found the 197 SLD individuals in a total population aged from 0-18 years of 201,347 individuals was equivalent to 0.09%.

According to the single sample chi-square test, there was a significant level of increase observed through the years (df=8, p=0.000). However, there was no significant correlation with gender through the years (chi-square test; p=0.745).

Table-1. Distribution of specific learning disorder levels according to year and

Years	Male	Female	Total
2009	9	7	16
2010	13	7	20
2011	17	10	27
2012	46	24	70
2013	70	30	100
2014	75	31	106
2015	101	37	138
2016	124	48	172
2017	130	67	197
Total	585	261	846
P-Value[1]	0.000*** (χ^2=271.262 ; DF=8)	0.000*** (χ^2=111.310 ; DF=8)	0,000*** (χ^2=376,957;DF=8)
P-Value2	0.745[NS] (χ^2=5.119 ; DF=8)		

1, One-sample Chi-Square Test; 2, Two-sample Chi-Square Test

***, Statistically significant (p<0.001); NS, Statistically insignificant (p>0.05) bnh

When the table is investigated, the percentage of males with special learning difficulties (69.14%) was higher than for females (30.85%). However, no significant difference was identified with the chi-square test (p>0.005).

Table 2. Incidence of Special Learning disorder in Ordu Province from 2009-2018

Years	Total	Population	Incidence Rate (100,000 person-year)
2009	16	234,999	6.81
2010	20	229,142	8.73
2011	27	221,907	12.17
2012	70	225,676	31.02
2013	100	215,663	46.37
2014	106	208,580	50.82
2015	138	206,298	66.89
2016	172	208,452	82.51
2017	197	201,347	97.84
P-Value		0.000*** (χ^2=434.497 ; DF=8)	

***, Statistically significant according to two-sample chi-square test (p<0.001)

When the table is investigated, though the total pediatric population fell from 234,999 to 201,347 through the years, the number of children with SLD increased from 16 to 197. A significant difference was identified according to the chi-square test (p<0.05).

Discussion

According to the data obtained in the study the proportion of the total population aged from 0-18 years of SLD individuals was very low at 0.09%. Studies in similar age groups have reached results showing the prevalence varies from 1-30% (Karaman et al., 2012). Differently, research by Rutter and Yule (1975) investigated 2300 children aged 9 years and identified a prevalence of 5% (cited in Karaman et al., 2012). Polancyzk et al. (2007) identified a rate of 5% in a society-indexed study. The study by Gorker et al. (2017) found a rate of 13.6%. DuPaul and Stoner assessed different studies and identified a rate of 8.9% (cited in Gorker et al. 2016). A study in Turkey reported SLD rates of 37-38% (Gorker et al. 2016). However, Lerner stated that the proportion of SLD individuals in the USA was 15-25% (Balci, 2017). Contrary to the different rates for prevalence, the incidence of SLD is accepted as 5-10% (Karaman et al. 2012). Accordingly, the low rate obtained in the study is significant. SLD is high in reality; however, difficulties are experienced with diagnosis (Yao and Wu, 2003). Torgesen and Dice (1980) linked problems related to diagnosis to inability to clarify sampling variables in studies, differences in SLD definition and problems related to method. In line with this, the low percentage of the number of individuals with SLD obtained in this study may be linked to the lack of clarity of diagnostic criteria, difficulties with diagnosis and method deficiencies.

The incidence rate of SLD according to gender is higher in males, with uncertainties created by the different rates found (Rutter et al., 2004; Moll et al., 2014). Epidemiological studies have identified SLD incidence rates of 1.39-3.19 for males compared to females (Rutter et al., 2004). The incidence rate in males (69.14%) was higher compared to females (30.85%); however, there was no significant difference found. Similarly, research in the USA found rates of 67% in males and 33% in females in the 6-12 year-age group, with rates of 66% for males and 34% for females in the 13-17 year-age group (Asfuroglu and Fidan, 2016).

The research investigated the SLD increase rates according to year. Accordingly, in the center of the study though there was a fall in the 0-19 year-old population rate, there was a significant increase in SLD diagnosis numbers through the years. There is no study encountered in the literature assessing according to year. Though the increase in SLD diagnosis according to year may be linked to the increase in parental educational levels and awareness studies about special education in recent years, significant factors may include causes such as nutritional habits, lack of smart medication use and bad living conditions.

In conclusion, due to the difficulties in diagnosing SLD, there is a need for a higher quality construct with objective quantitative data for diagnosis. Additionally, screening should be performed with a systematic plan within the framework of this construct. Later, in addition to quality education related to SLD, original studies related to causes should be performed. Studies will contribute to the universal dimension; however, there is a need for special studies on a regional or country basis, because studies in different countries have produced highly variable results. In Finland the SLD rate for 7-8 years' age group was 19.9%; however, in Brazil rates of 7.6% were identified in children and adolescents (Taanila et al. 2014; Fortes et al. 2017). Among primary school children in Italy, this rate was 6.06% (Gorker et al., 2017). Different results may be obtained due to the language structure related to reading disorders included within the specific learning disorders. For example, English was determined to be a language with greater tendency to have higher reading disorder rates compared to Italian (Demonet et al.,

2004). Similarly, the incidence of reading disorder is greater for English compared to Japanese and Chinese (Stevenson et al. 1982).

Conclusion

According to the data obtained in the study, it was concluded that there is a need for in-depth research about topics from diagnosis to methods related to SLD.

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RESEARCH ARTICLE

The Current Use and the Evolution of Erythrocyte Sedimentation Rate Measurement

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Abstract

Objective: The golden standard for measuring erythrocyte sedimentation rate (ESR) is the Westergren method. Some other methods for measuring ESR have become available in the recent decades. They differ from a modest modification of the Westergren method to very different methodologies. Even though the methodologies of these tests are different the results of them are assessed as the same test by clinicians. Therefore the bias reasoned by different methodology has caused misinterpretation of the patients by clinicians. The comparison and harmonization of this method will provide a standardization and same interpretation for ESR.

Methods: The golden standard method for measuring ESR which is called Westergren Method and two prototypes of the remaining methods were chosen for comparison. Three different group of patients were were assessed with three different methods in this study.

Results: The monitorization of three samples were observed for 60 minutes. There was no correlation detected depending on the time after the monitorization had started. Hence the adjustment of the results were collected after 20 or 30 minutes for simulating 60 minutes were found significantly different than the classical Westergren method. The detected bias between the adjustment of the earlier result to one hour and the classical method is not always different than the classical method. The sample results were found significantly different in comparison to two methods for all selected patient groups.

Conclusion: There is no sedimentation algorithm detected in ESR monitorization process. Therefore the observed bias is thought to be caused by the adjustment of the earlier results to one hour. The adjusted results of 30 minutes were found to be significantly similar compared to the adjusted results of 20 minutes. The results of the capillary photometric kinetic method were found unbiased with the classical Westergren method and compatible with the clinical observations.

Key words: erythrocyte, sedimentation rate, laboratory hematology, laboratory standards, recommendations, westergren

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Introduction

When well mixed venous blood is placed in a vertical tube, erythrocytes tend to fall down. The meaning of Erythrocyte Sedimentation Rate is measuring the rate of erythrocyte fall or settle in the plasma of a drawn anticoagulated blood specimen over 60 minutes in millimeters/hour (Batlivala 2009; Janson and Tischler, 2012). However it may be measured more quickly in the recently defined ESR methods with centrifugation or other the accelerated sedimentation methods (Janson and Tischler, 2012; Kratz1et al., 2017). ESR is useful but it isn't a specific marker for underlying inflammation. Most recently CRP or other inflammatory markers have

been used to detect or monitor disease particularly cardiovascular disease and metabolic syndrome (Xia and Samols 1997; Colombet et al., 2010; Litao and Kamat, 2014). The theory of erythrocyte sedimentation was first observed and defined in 1897 by Dr. Edmund Faustyn Biernacki, who found that ESR is varied among individuals and that red blood cells (RBCs) fall more quickly in the presence of increased levels of fibrinogen (Grzybowski and Sak, 2011).

In 1918, Dr. Robert Fahraeus observed that ESR differed in pregnant in comparison to non-pregnant women and recommended the test as a candidate marker for detection of pregnancy. In 1921, Dr. Alf Vilhelm Albertsson Westergren used ESR as a marker in the prognosis of patients with pulmonary tuberculosis. Dr. Westergren described the measurement standards for the ESR test that are still used widely today in which sodium citrate is used as an anticoagulant (Westergren, 1926).

There are lots of factors which cause erythrocyte to be settled faster. Some of these factors are sourced plasma protein and erythrocyte mass is also an important factor which affects ESR.

The ESR can be influenced by a wide variety of factors, including alterations of the quality and quantity of the RBCs, as well as the changes in the normal patterns and the amount of various plasma proteins. Therefore this widely used test is vulnerable to misinterpretation in clinical practice (Olshaker and Jerrard 1997; Jurado, 2001).

Aggregation of erythrocytes causes falling and increases the ESR. RBCs are negatively charged and tend to repel one another in a healthy individuals' whole blood sample. In the presence of positively charged, large and asymmetric acute phase proteins such as fibrinogen and immunoglobulins increases the ESR. An accelerated ESR is accompanied mostly with increase Fibrinogen concentration and a less extent in alpha 2, beta and gamma globulins. These asymmetric protein molecules have a greater effect than the other proteins in decreasing the negative charge of erythrocytes which is called zeta potential. Zeta potential causes to keep the erythrocytes apart. The decreased zeta potential causes erythrocyte rouleaux formation which causes a faster sedimentation. Removal of fibrinogen by defibrination or any other reason causes a lower ESR. There was no absolute correlation between ESR and any plasma protein fractions detected. Red cell is also one of the most important factor which affects ESR. Anemia independently increases the ESR because of increasing rouleaux formation of changes in the concentration of plasma proteins. ESR is proportional to the weight of cell aggregate and inversely proportional to the total surface area of erythrocyte. Microcyte sediment is slower than macrocyte because of smaller total erythrocyte surface area (Olshaker and Jerrard, 1997).

Anemia and polycythemia (primary and secondary) represent quantitative changes in erythrocytes in various clinical conditions and will increase and decrease the ESR, respectively. Similarly, hemoglobinopathies and conditions associated with altered erythrocytes such as sickle cell disease have a low sedimentation rate during sickle crises that increases in the presence of moderate to severe infections (Miller et al, 1983; Ahmed et al, 2000).

ESR is a very simple and may be one of the most used laboratory test over 100 years. Although it is a non-specific marker for inflammation it's still assessed oftenly by clinicians in diagnosis and monitorization of many diseases. Recently there are many new measurement methods developed for measuring ESR. Even though these methods are very similar to the original Westergren method there are some differences in the process of measurement. Some of these methods use centrifugation for getting a faster test result and some use micro sedimentation (Table 1). In some methods ESR is measured in 20th or 30th minutes and adjusted to 60th minute by using a formula (Kratz1 et al, 2017).

Table 1. Partial listing of ESR instruments and their methodologies

Method	Instrument	Manufacturer	Methodology
CLASSIC METHOD OR RESULT ADJUSMENT TO 60 TH MIN.	ESR STAT PLUS	HemaTechnologies	Multiple optical readings of the erythrocyte- plasma interface are used to determine the ESR.
	Excyte M	Vital Diagnostics	Measurement of sedimentation at 30 min, mathematically adjusted to a 1- h Westergren ESR
	iSED	Alcor Scientific Inc.	Photometric rheology is used to measure the aggregation of red blood cells. Results are correlated with the Westergren method.
	Sedisystem	B.D.	Seditainer ESR tubes are put into a system rack; samples are homogenized. A camera records the initial cell layer height and the final sedimentation level reading after 20 min. Results are converted by polynomial extrapolation to correlate with conventional Westergren method.
	Starrsed	MECHATRONICS	Measures ESR in dedicated tubes using whole blood diluted with citrate. Fully closed, automated system. Sedimentation is measured after 30 min and extrapolated to 60 min values.
	Streck ESR Auto Plus	STRECK	Measurement of sedimentation at 30 min, mathematically adjusted to a result that is comparable to a 1- h Westergren ESR
	Vesmatic Cube 200	DIESSE	Samples are allowed to settle for 20 min, and results are converted to Westergren units.
CAPILLARY PHOTOMETRIC KINETIC TECHNOLOGY	Test 1	ALIFAX	Utilizes capillary photometric- kinetic technology. Sample is delivered into a capillary tube where it is accelerated via a "stopped- flow" circuit, which causes sedimentation of erythrocytes. Results are transformed to Westergren values and are available within 20 s.
	Microtest 1	ALIFAX	
	Roller 20 LC	ALIFAX	

In this study we are aiming to investigate the difference of new methods and compare the results of these methods with the classical Westergren's method. The methods in use for ESR test differ by their methodology of measurement. The methods may be divided into two main groups simply. One of these two groups is the measurement method and it is based on the detection of the sedimentation level in an earlier stage (20 or 30 min.) and reflection to the 60th minute by a formula. The other is more sophisticated which is based on the acceleration and the monitorization of the sedimentation. Two instruments were chosen for the study each representing the group given above. And the correlation of the results with the Westergren method were investigated.

Methods

Blood samples anticoagulated with K2EDTA (Becton Dickinson, Franklin Lakes, NJ) were routinely obtained from hospitalized patients at the Florence Nightingale Caglayan Hospital İstanbul / Turkey processed for analysis. 2 mL tubes were used in the study including K2EDTA for anticoagulant.

All samples were obtained under standardized conditions (in the morning after a night of fasting) and tested within 4 hours of venipuncture, according to ICSH recommendations. Between October 2017 and December 2017, we selected 74 blood samples from patients with malignancy (n = 22), autoimmune disease (n = 20), or infection (n = 32); all patients had TEST 1 ESR values of 20 mm/h or more and hematocrit values between 33% and 40% (0.33-0.40) Table 2.

WESTERGREN Method: The Westergren method was performed according to ICSH specifications on undiluted blood samples anticoagulated with K3EDTA using glass pipettes (Greiner Bio-One, Kremsmuenster, Austria). During sedimentation, the pipettes were mounted vertically on appropriate supporting racks and kept at room temperature, which never exceeded 25°C.

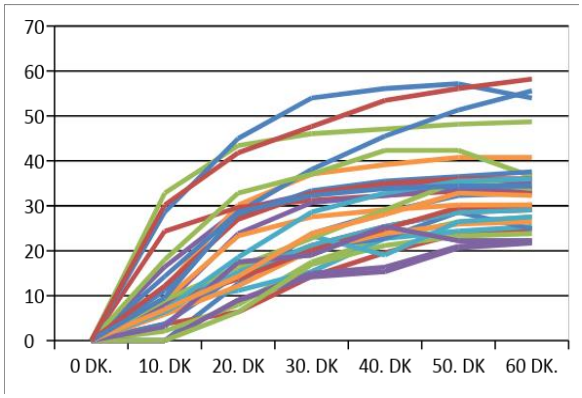
VES MATIC CUBE 200 Method: Samples are initially rotated slowly for 2 minutes and screened for start up volume detection than allowed to settle for 20 minutes, and results are adjusted for 60 minutes to Westergren units.

TEST 1 Method: The TEST 1 analyzer, a closed automated analyzer, determines the duration of sedimentation reaction in blood in a standard-sized primary tube with a perforating stopper. The principle of measurement is the study of the aggregation capacity of RBCs by capillary photometric technology. The tubes are placed in the racks of the instrument, and their contents are rotated slowly for about 2 minutes. By using a closed aspiration needle, the blood is directly drawn from the collection tube, distributed in a capillary, and centrifuged at about 20g. The system uses an infrared ray microphotometer with a light wavelength of 950 nm and performs 1,000 readings in 20 seconds. The electrical impulses, collected using a photodiode detector, are directly correlated to the aggregation of RBCs present at each capillary level. For each sample, an aggregation and sedimentation curve is obtained. A mathematical algorithm converts the raw data obtained from evaluation of optical density signals into ESR results, which are transformed to comparable Westergren values. The system operates at a rate of 180 specimens per hour in continuous loading, providing a result every 20 seconds, and requires 150 µL of blood for each sample (Plebani et al., 1998; Plebani and Piva, 2002; Romero et al., 2003; Piva et al., 2007).

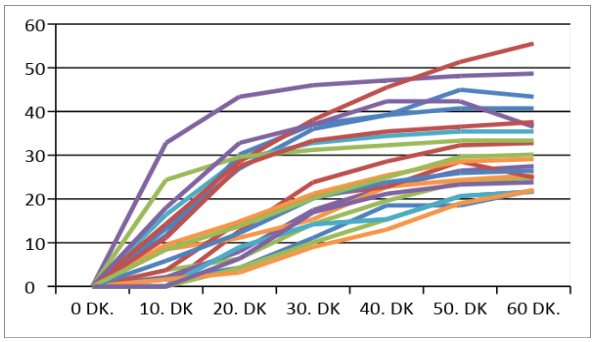
Statistical Analysis We compared the correlations of Westergren with TEST 1 ESR and Westergren with VES MATIC CUBE 200 Method results. All statistical analyses were performed using SPSS 13.0 software (SPSS, Chicago, IL).

Results

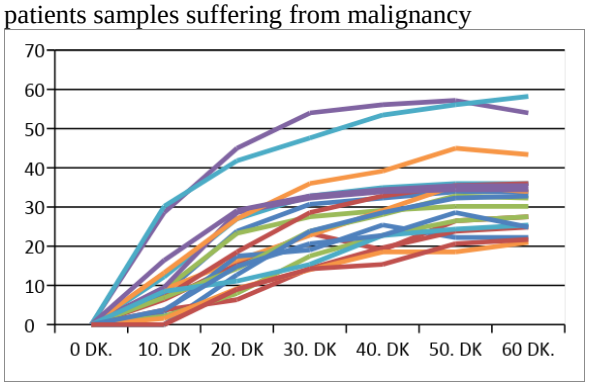
The patients test results with Westergren method for 60 minutes who are suffering from infection, malignancy and autoimmunity are seen in the graphic 1-2 and 3 respectively.



Graphic 1. One hour sedimentation monitorization of the patients samples suffering from infection

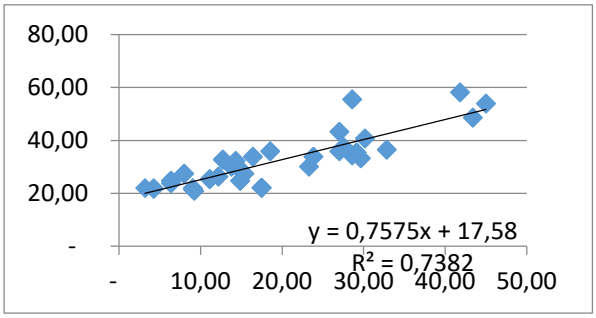


Graphic 2. One hour sedimentation monitorization of the patients samples suffering from malignancy

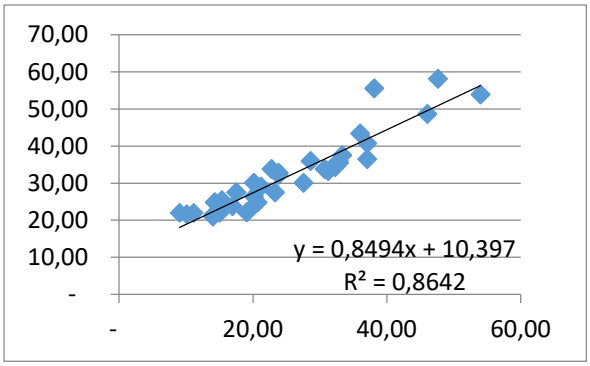


Graphic 3. One hour sedimentation monitorization of the patients samples suffering from autoimmune diseases

It can be seen that in graphic 1-2 and 3 there are similar curves measured in 60 minutes for all patient groups. The results of 20th minute and 30th minute are compared with the results of 60th minute in graphic 4 and 5 respectively. The results of 30th minute was found in more correlation with the 60th minutes results rather than the results of 20th minute.

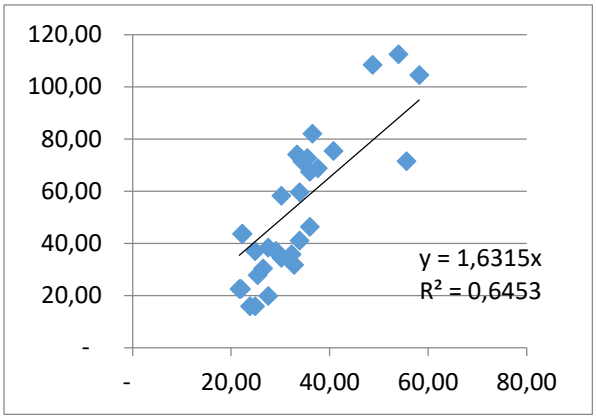


Graphic 4. The results in 20 minutes comparing with the results for 60th minutes

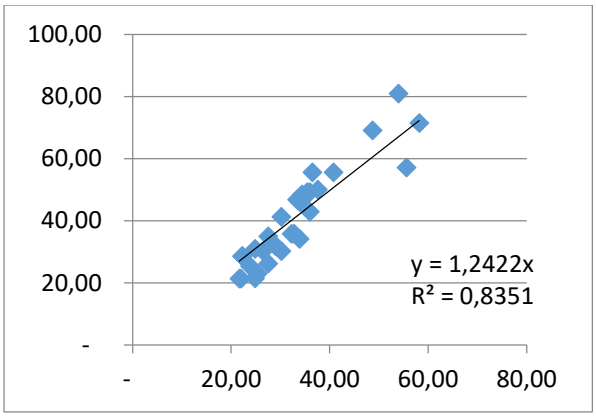


Graphic 5. The results in 30 minutes comparing with the results for 60th minutes

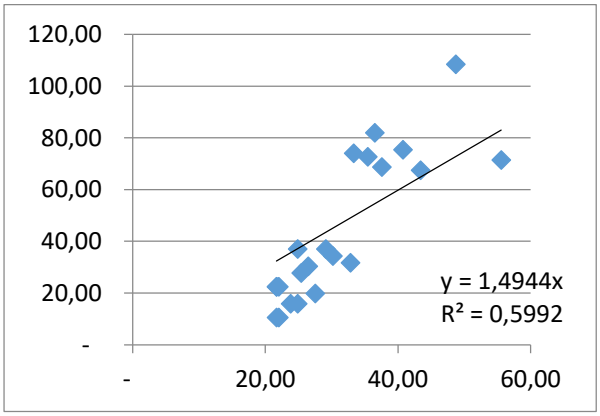
Method comparison of VESMATIC CUBE 200 method with classic Westergren method in the patient group suffering from infection, malignancy and autoimmunity are seen in the graphic 6-8 and 10 respectively. And comparison of TEST 1 method with classic Westergren method in the patient group suffering from infection, malignancy and autoimmunity are seen in the graphic 7-9 and 11 respectively. In all patient groups TEST 1 method was found significantly in correlation with the Westergren method.



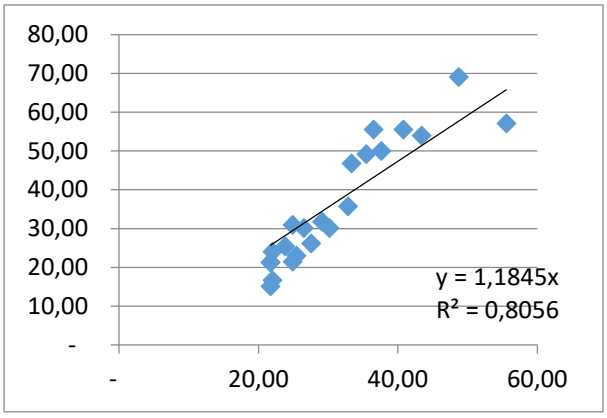
Graphic 6. Regression analysis of Westergren method vs. VESMATIC Cube 200 for patients suffering from infection



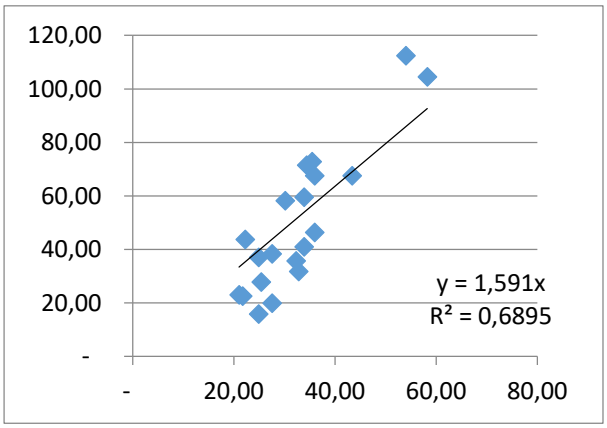
Graphic 7. Regression analysis of Westergren method vs. TEST 1 for patients suffering from infection



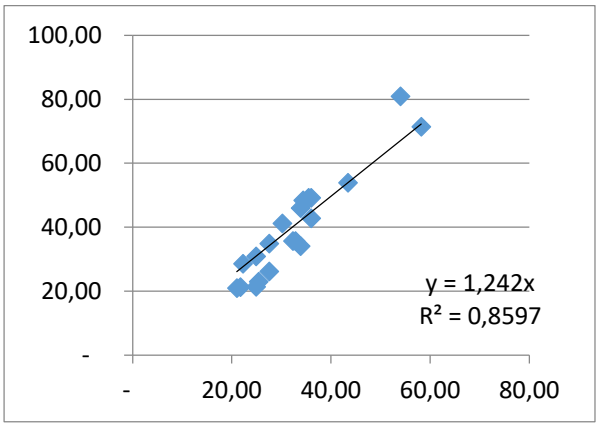
Graphic 8. Regression analysis of Westergren method vs. VESMATIC Cube 200 for patients suffering fr malignancy



Graphic 9. Regression analysis of Westergren method vs. TEST 1 for patients suffering from malignancy



Graphic 10. Regression analysis of Westergren method vs. VESMATIC Cube 200 for patients suffering from autoimmunity



Graphic 11. Regression analysis of Westergren method vs. TEST 1 for patients suffering from autoimmunity

Discussion

The Westergren method is used as the golden standard method for ESR measurement. Because of the methodology of this measurement, plasma proteins, morphology and quantity of erythrocyte affect the results. This is the most important weakness of the method for reliability and the accuracy of the test result (Batlivala 2009). Therefore clinicians should know the morphology and quantity of erythrocyte mass of a patient while they are assessing the result of ESR test. By the way the results of the instruments which are produced to give faster results are examined by the clinicians. As it is understood from the Graphic 1-2 and 3 the adjusted results from 20th and 30th minutes are not well correlated with the results of the Westergren method. The results adjusted from 30th minute has a better correlation with the Westergren method rather than the results adjusted by using the 20th minutes results. Either Westergren or the other methods in which adjustment of the earlier result is being used are sensitive from the quantity of the erythrocytes in the whole blood. (A. Kratz1, M. Plebani, M. Peng, Y.K. Lee, R. McCafferty, S.J. Machin, 2017) Therefore the patients results are not well reflecting their statement in anemia or policytemia. Eventhough the patient is suffering from infection or malignity their ESR measurements may be lower than expected because of polycythemia or over than expected in the cases accompanying severe anemia. This interaction can be assessed for the weakness of these methods even for the golden standard Westergren method. The instruments in which the Capillary Photometric Kinetic Method are used like TEST 1 measurements of the instrument is performed by an accelerated sedimentation process. In this method the most possible sedimentation level is aimed to be detected by an accelerated sedimentation process and the rate of each samples are measured and converted to the Westergren method. Therefore the result of this method is unaffected from the interference of the quantity and the morphology of erythrocytes like anemia or polycythemia. This specificity is the most important strength of the Capillary Photometric Kinetic Method. Extremely fast result evaluation is also one of the most important strengths of this method. This method provide clinicians a clear results which are not affected by erythrocyte mass or structure.

Even though the measurement of ESR is still a non-specific laboratory test with the new Capillary Photometric Kinetic Method will be kept to be used

as the most commonly used test without prior weakness of sensitivity which is based on the erythrocyte morphology and quantity.

Conclusion

Conclusion In this study, westergren method is accepted the golden standart method for E.S.R. measurement since it's first found by Dr. Westergren in the early 20th century with many of the weaknesses in assessment of the patient results during clinical examination. The new Capillary Photometric Kinetic Method is seemed to cover some of the most important weaknesses of the original method. Therefore with the clear explanation of this new method to the clinicians it is believed to be preffered in the diagnosis of inflammation and infection instead of the other similar measurement methods.

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RESEARCH ARTICLE

Ocular Hypertension and Glaucoma after Intravitreal Injection of Triamcinolone Acetonide

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Abstract

Objective: The use of intravitreal triamcinolone acetonide (IVTA) for intraocular neovascular, proliferative and edematous diseases has led to an increased incidence of corticosteroid-induced ocular hypertension. Even though largely replaced with anti-vascular endothelial growth factor (anti-VEGF) agents and slow-release dexamethasone implants, boosters are still required in nonresponsive or minimally responsive patients, in cases of tachyplaxis to these agents, or in combination therapies with anti-VEGFs.

Metods: The records of 136 eyes of 124 patients who underwent 4 mg/ml IVTA treatment for macular edema of variable etiologies of diabetic macular edema, retinal vein occlusions, subretinal choroidal neovascularization, Irvine-Gass Syndrome, retinitis pigmentosa and idiopathic juxtafoveal telengiectasia in the period 2001–2006 were reviewed. Seventy-six eyes of 71 patients of which were followed for at least 3 months were included in the study. The patients were examined at the first day, second week, first month and every month after the injection. Mean intraocular pressure (IOP), IOP exceeding 21 mmHg and percentage of patients exhibiting IOP increase of 5 mmHg after IVTA injection, during the follow-up period were evaluated and compared statistically.

Results: Mean age was 56.64±12.65 years and male to female ratio was 35/36. Mean follow-up time was 12.13±10.30 months. The mean IOP increased statistically (p= <0.001) during follow-up from 14.95±3.15 mmHg pre-injection level reaching to a maximum of 21.66±6.48 mmHg and decreased statistically (p= <0.001) to 15.58±4.16 mmHg at the end of the follow-up. There was no statistical difference between pre-injection and post-injection IOP levels (p=0.406). The IOP levels exceeded 21 mmHg in 46.05% of the eyes. There was an increase of 5 mmHg and more above the pre-injection level in the 53.94% of the eyes. Maximum IOP levels were reached at the 2.77±3.72 month. In 24 (31.58%) eyes, topical antiglaucomatous therapy was needed and later 1 eye (4.6%) required surgical intervention and 1 eye (4.6%) required argon laser trabeculoplasty to lower the IOP.

Conclusion: The most common complication following İVTA injections is rise in IOP. Most of these ocular hypertension cases are controllable by medical therapy. However, the risk of glaucoma requiring surgery or long term antiglaucomatous use validate the necessity of a meticulous patient selection and close monitorization of IOP.

Key words: intravitreal triamcinolone acetonide, macular edema, steroid-induced glaucoma

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Introduction

Triamcinolone acetonide, when injected intravitreally, is an effective agent in the treatment of macular edema secondary to variety of intraocular neovascular, proliferative and edematous diseases such as diabetic retinopathy, central retinal vein occlusion, branch retinal vein occlusion, uveitis, post cataract surgery macular edema, age related macular degeneration (Jonas, 2005). As far as we know no long-term toxic effect of intravitreal triamcinolone injections has been demonstrated. However, the most common side effect following intravitreal triamcinolone acetonide (IVTA) injections is the elevation of intraocular pressure (IOP), occuring up to 52% of eyes, leading to a secondary chronic open angle glaucoma (Jonas et al., 2003)

Increased IOP can occur as a consequence of oral, intravenous, inhaled, topical, periocular, or intravitreal corticosteroid therapy. The intraocular potency and mode of administration have been shown to be important in initiating an ocular hypertensive response (Gillies et al., 2004; Singh et al., 2004; Smithen et al., 2004). The prolonged effect of triamcinolone is mainly due to its low water-solubility. Triamcinolone can be measured for at least 3 or 18 months after intravitreal injection of 4 mg or 20–25 mg, respectively (Beer et al., 2003).

The exact pathophysiology of steroid induced glaucoma is not entirely understood. The elevation in intra-ocular pressure is thought to be due to increased resistance to aqueous outflow. A rise in IOP following intravitreal steroid injection does occur, and this has been demonstrated by many studies (Beer et al., 2003; Jonas et al., 2003; Smithen et al., 2004). Dynamics of this elevation, especially its extent, onset and interval, is crucial for early detection of IOP rise early and for initiation of immediate and proper treatment to prevent permanent damage to the optic nerve head. In this regard, evaluation of IOP elevation following injection of IVTA for various causes of macular edema is aimed in this study.

Methods

The records of 136 eyes of 124 patients who underwent 4 mg/ml IVTA treatment for macular edema of variable etiologies in the period 2001–2006 at Ankara Numune Training and Research Hospital were reviewed. All patients were fully informed about the potential side effects of the therapy and signed an informed consent.

Eyes with known primary or secondary glaucoma, patients with narrow or closed angles and loss of follow-up before 3 months were excluded from the study. A total of 76 eyes of 71 patients which were followed for at least 3 months, were included in the study. Follow-up time was 12.13±10.30 months. A detailed medical history was obtained from each patient and concomitant systemic diseases, previous ocular surgeries, previous laser treatments, if present, were recorded. All of the patients underwent a complete ophthalmologic examination, including uncorrected visual acuity, best-corrected visual acuity, corrective spherical equivalent, IOP, pachymetry, biomicroscopic examination, fundus examination, determination of C/D ratio, and fundus fluorecein angiography, perimetry when needed. The IOP measurements were done routinely using a Goldmann applanation tonometer. Gonioscopic examination was performed regularly in all patients before and after the IVTA injection.

The IVTA injections were carried out at the operating room in 53 eyes and at the retina section in 23 eyes, all under aseptic conditions. All patients received topical anesthesia consisted of 0.5% proparacaine hydrochloride (Alcaine 0.5%, Alcon Pharmaceuticals, Puurs, Belgium) drops applied to the ocular surface 2 times 5 minutes apart before the injection. The periocular skin, eyelid margins and eye lashes were cleaned with 10% povidone iodine. Following placement of a single-use sterile adhesive surgical ocular drape, disposable lid speculum was inserted. Povidone iodine 5% was instilled in the conjunctival cul-de-sacs 3 min before the injection. Triamcinolone acetonide (Kenalog, Bristol-Myers Squibb, New York, NY) in dosage of 4 mg/0.1 mL was injected with a 27 gauge needle perpendicularly in the inferior temporal quadrant, 3.5 mm from the limbus in aphakic/pseudophakic patients and 4.0 mm in phakic patients with the guidance of a sterile caliper. After removing the needle, a sterile cotton-tipped applicator was used for a gentle pressure to prevent reflux. Following optic disc and central retinal artery control by indirect ophthalmoscope and hand motion control of the patient, an antibiotic drop was instilled. Slow free-flow anterior chamber paracentesis with a 1ml insulin syringe needle (26-gauge) was executed when required. Patients were instructed to self-administer antibiotic drop 4 times a day during the following 5 days. The patients were examined at the first day, second week, first month and monthly after the injection. Neither angle

closure nor angle neovascularization developed in any eye during the follow-up period. The preoperative IOP was statistically compared with the postinjection IOPs at different time points. The evaluation was made according to the magnitude of the IOP elevation and the rate at which the IOP dropped to below 21 mm Hg in eyes treated with topical medications. The elevation of IOP above 21 mmHg and the elevation of IOP 5 mmHg above the baseline, the need and the type of surgery performed to lower the IOP in the intractable cases (>25 mm Hg) were noted. In case of IOP elevation a topical medication to lower the IOP was considered. Betaxolol, dorzolamide, brinzolamide, and the combination of dorzolamide–timolol were the first choices for the topical treatment. The type of surgery undertaken was decided based on the severity of the IOP elevation and the comorbidity of the eye. Statistical analyses were done using SPSS software. Paired t test and Wilcoxon signed rank test were used to compare the mean IOP values at different time intervals. A p value of <0.05 was considered statistically significant.

Results

Seventy-six eyes of 71 patients, consisting of 36 women and 35 men, which could be followed regularly for at least 3 months, were included in the study. 60 eyes were followed at least 6 months. The mean age of the patients was 56.64±12.65. The indications for IVTA injection was macular edema caused by diabetic retinopathy (DRP) in 45 eyes (59.21%), retinal venous occlusion (RVO) in 14 eyes (18.42%), subretinal choroidal neovascularization in 13 eyes (17.1%), 9 of which was related to age related macular degeneration (ARMD), Irvine-Gass Syndrome in 2 eyes (2.63%), retinitis pigmentosa in 1 eye(1.31%), idiopathic juxtafoveal telengiectasia in 1 eye (1.31%). One eye without a previous important increase in IOP received a second IVTA injection for recurrent diabetic macular edema at postinjection 3 months without any subsequent IOP increase. Besides the IOP elevation, other complications observed following IVTA injection were secondary cataract development in 35.38% and sterile endophthalmitis in 1.31%.

The mean±sd age of the patients in the DRP group was 58.32±10.53 with 21 female and 19 male. At least 3 months prior to inclusion in the study 8 eyes had been treated with focal, 5 eyes had been treated with grid and 9 eyes had been treated with both focal and grid laser photocoagulation. Four (10.0%) of the patients had type 1 DM and 36 (90.0%) had type 2 DM. Thirteen (32.5%) of the patients also had hypertension. Ten eyes (22.22%) were pseudophakic. Mean±sd follow-up time was 14.04±11.73 months. In the DRP group, preinjection mean visual acuity(VA) was 0.1±0.11 and reached to a maximum of 0.30±0.26 during follow-up. An increase of ≥1 and ≥2 lines of Snellen VA is observed in 82.23% and 64.45% of eyes, respectively. The improvement of visual acuity was statistically significant until 12 months (p=<0.0001). The time to reach maximum VA was 3.18±2.80 months. Macular edema recurred in 19 (44.18%) of 43 eyes. The time that recurrence was first detected after resolution of macular edema was median 6 months. In 1 eye IVTA injection was repeated once. The IOP levels exceeded 21 mmHg in 51.11% of the eyes in the DRP group. There was an increase of 5 mmHg and more above the preinjection level in the 57.77% of the eyes. For the 35 phakic eyes the degree of lens opacification was increased in 16 eyes (45.71%). Sterile endophthalmitis was observed in 1 patient.

The mean±sd age of the patients in the RVO group was 54.71±11.72 with 5 female and 9 male. Three of the patients had CRVO and 11 had BRVO. All of the eyes were phakic. Mean±sd follow-up time was 10.42±7.65 months. In the RVO group, preinjection mean visual acuity was 0.09±0.12 and reached to a maximum of 0.24±0.25 during follow-up. An increase of ≥1 and ≥2 lines of Snellen is observed in 64.28% and 50.0% of eyes, respectively. The increase in VA after IVTA injection was statistically significant only in the 6-8 months interval. The time to reach maximum VA was 3.84±2.95 months. Macular edema recurred in 4 (27.57%) of 14 eyes. The time that recurrence was first detected after resolution of macular edema was median 3.5 months. The IOP levels exceeded 21 mmHg in 35.71% of the eyes in the RVO group. There was an increase of 5 mmHg and more above the preinjection level in the 35.71% of the eyes. For the 14 phakic eyes the degree of lens opacification was increased in 4 eyes (25.57%). In none of the eyes endophthalmitis did occur.

The mean±sd age of the patients in the ARMD group was 66.89±7.56 with 4 female and 5 male. All of the eyes were phakic, except one. Mean±sd follow-up time was 8.39±6.90 months. In the ARMD group, preinjection mean visual acuity was 0.05±0.06 and reached to a maximum of 0.11±0.12 during follow-up. An increase of ≥1 and ≥2 lines of

Snellen is observed in 66.67% and 22.23% of eyes, respectively. The increase in VA after IVTA injection was statistically significant only in postoperative 1 month (p=<0.031). The time to reach maximal VA was 3.21±3.31 months. Macular edema recurred in 71.43% of the eyes. The mean time that recurrence was first detected after resolution of macular edema was 2.90±0.54 months. The IOP levels exceeded 21 mmHg in 33.3% of the eyes in the ARMD group. There was an increase of 5 mmHg and more above the preinjection level in the 66.6% of the eyes. For the 9 phakic eyes the degree of lens opacification was increased in 1 eyes (12.5%). In none of the eyes endophthalmitis did occur.

The mean IOPs at different follow-up intervals are shown in *Table 1*. All the eyes including those under topical treatment are included in the analyses.

Table 1. Mean IOPs at follow-up intervals

Baseline IOP	0.5-1 mo	2-4 mo	6-8 mo	10-12 mo	≥14 mo
14.95±3.15	14.36±6.72	19.05±4.94	18.28±6.0	15.04±3.52	12.67±3.82

Overall, the mean IOPs increased significantly (p= <0.001) during follow-up from 14.95±3.15 mmHg pre-injection level reaching to a maximum of 21.66±6.48 mmHg and decreased significantly (p= <0.001) to 15.58±4.16 mmHg at the end of the follow-up. There was no statistically significant difference between pre-injection and post-injection IOP levels (p=0.406). Maximum IOP levels were reached at the 2.77±3.72 month.

In 35 eyes (46.05%) IOP was measured to be equal or above 21mmHg. A total of 41 eyes (53.94%) experienced an IOP rise of 5 mmHg or more compared to baseline preinjection levels. In 24 eyes (31.58%), topical treatment was initiated to reduce the IOP when persistent elevation was observed. Subsequent trabeculectomy was needed in 1 of the 24 eyes (4.16%) and argon laser treatment in 1 of the 24 eyes (4.16%), both of whom were diabetic, to reduce high IOP levels that were refractory to maximal medical therapy with 2 or 3 antiglaucomatous drugs. In both eyes, the IOP returned to below 21 mm Hg during the follow-up period after surgery. In the remaining 22 eyes (91.66%), IOP elevation was responsive to topical medical treatment.

When the levels of IOP increases were compared, no statistically significant difference was found between etiologic subgroups.

Discussion

Intravitreal injection of long-acting steroids is indicated for the treatment of edematous, inflammatory, and neovascular intraocular diseases (Jonas, 2005). The benefit of intravitreal TA has been addressed in several papers concerned with the treatment of macular edema, however, the exact mechanism remains unclear. There has been a major hypothesis for the mechanism of intravitreal corticosteroid action in inhibiting leukocyte recruitment, thereby, reducing the retinal capillary permeability from blood-retinal barrier (BRB) breakdown and inhibiting the metabolic pathway of vascular endothelial growth factor (VEGF) (Tamura et al., 2005). From the present study, an IVTA injection for macular edema secondary to DRP and RVO provides significant benefits with the onset of a ophthalmoscopic response in macular thickness and VA improvement as soon as 15 days and 2 months for the DRP group, respecctively, and median 1.25 months and 3 months for the RVO group, respectively. This implies that a functional response after the treatment of the edematous retina occurs at a slower rate than does the anatomical response. In the previous studies the clinical effect of IVTA injection for diabetic macular edema over VA were determined according to different acuity charts. Therefore it may not be possible to compare the VA results between studies. The insignificant difference between the baseline VA and the VA seen after 12 months in this study can be explained from a rebound phenomenon of macular edema after a cessation of TA effect. The effect of resolution of macular edema over VA was suggested to be limited if the retinal cellular destruction has occured or if the intercellular structures are damaged by cystoid macular edema. The response to IVTA may be variable among patients according to the extent of macular ischemia, amount of retinal hemorrhages and extent of irreversible photoreceptor loss. Therefore it is difficult to estimate the visual response after resolution of macular edema. This may explain our results of lower and temporary increase in VA despite complete resolution of macular edema in all cases in RVO group. This is consistent with other studies (Cekic et al., 2005). Visual functions may be preserved if IVTA injection can be executed before this irreversible damage develops, in other words as soon as possible. Functional recovery is found lower in this present study in RVO group possibly due to inclusion of cases with CRVO, with much worse prognosis.

The clinical response of DRP patients to IVTA may be observed faster than RVO patients. IVTA may be an optional pretreatment or adjuvant treatment in cases with diabetic macular edema requiring urgent procedures such as panretinal photocoagulation or cataract extraction that are known to increase macular edema.

One of the major side effects related to intravitreal injection of triamcinolone acetonide, is a steroid induced elevation of IOP. Although the proposed mechanism of corticosteroid-induced IOP elevation is increased resistance to aqueous flow via trabecular meshwork, the precise mechanism is still unknown (Clark and Wordinger, 2009).There are a number of observations that can be simplified into three broad categories: corticosteroids can induce microstructural changes in the trabecular meshwork; cause excess deposition of substances in the trabecular meshwork, decreasing outflow facility; and inhibit proteases and trabecular meshwork endothelial cell phagocytosis causing a decrease in the breakdown of substances in the trabecular meshwork (Jones and Rhee, 2006).

In this study preinjection median IOP was 14 mmHg, the maximum median IOP was 20 mmHg during follow-up. Maximum IOP levels were reached at the 2.77±3.72 month. This is consistent with the Mason's study in which triamcinolone was detected 2.75 to 5 months after intravitreal injection of 4 mg (Mason et al., 2004). The median IOP was measured as 15.5 mmHg at the end of the follow-up. IOP increased significantly after İVTA injection compared to pre-injection levels and decreased significantly at the final follow-up interval compared to maximum IOP levels. The statistically significant increase in IOP observed up to 8 months after IVTA injection in this study. There was no statistically significant difference between pre-injection and final post-injection IOP levels.

IVTA injection leads to a significant increase in IOP and magnitude of IOP elevation may vary (Holekamp et al., 2005). In this present study IOP was measured to be equal or above 21 mmHg in 46.05% of the eyes and 53.94% of the eyes experienced an IOP rise of 5 mmHg or more compared to pre-injection levels. This mandates close monitorization of IOP following IVTA injection. In several clinical trials IOP after IVTA injection was found to be 21 mmHg or more in 20-70% of patients (Jonas et al., 2003; Ciardella et al.,2004; Jonas et al, 2004a; Massin et al., 2004; Cekic et al., 2005; Jonas et al., 2005a; Jonas et al, 2005b; Ozkıriş and Erkılıç, 2005.). This wide range of values might be explained by the IVTA dose, variation between definitions of IOP elevation, length of follow-up, sample size, and whether patients have previously received IVTA injections or not. Several reports have suggested the higher frequency of IOP elevation in younger patients, higher baseline IOP, preexisting glaucoma, steroid responsiveness and the type of concurrent eye disease (Jones and Rhee, 2006; Massin et al.,2004; Roth, et al., 2009.). In a meta-analysis, it was shown that there was a tendency toward a higher increase in IOP in patients with uveitis and patients with central retinal vein occlusion (Jonas et al., 2005c). Elevation of IOP commonly occurs as early as 1 day to as late as 12 weeks after the initial treatment. Duration of IOP elevation peaks early, then may normalize. Increase in IOP reaches to maksimum in 1-140 days after IVTA injection (Holekamp et al., 2005).

The role of the dosage of the triamcinolone in IOP increase is controversial (Holekamp et al., 2005, Jonas et al., 2004b, Spandau et al., 2005.). It may be possible to avoid IOP elevations necessitating surgery by screening with topical drops to find out the steroid responders (Breusegem et al.,2009).

Most patients with elevated IOP after IVTA can be successfully managed with topical glaucoma medications (Razeghinejad and Katz, 2012). In this study IOP was controlled by topical medications in 91.66% of the 24 eyes. Subsequent trabeculectomy was needed in 1 of the 24 eyes (4.16%) and argon laser treatment in 1 of the 24 eyes (4.16%), to reduce high IOP levels that were refractory to maximal medical therapy with 2 or 3 antiglaucomatous drugs. In both eyes the IOP returned below 21 mm Hg values during the follow-up period after surgery. These intractable cases may be explained by the presence of diabetes mellitus (Becker et al., 1966). Traditional glaucoma surgical techniques can successfully control elevated IOP and are generally required in less than 2% of cases. The reported treatment methods for secondary ocular hypertension after IVTA were argon laser trabeculoplasty, selective laser trabeculoplasty, trabeculectomy, cyclodestructive procedures, drainage devices, and pars plana vitrectomy (Agrawal et al.,2004; Kocabora et al., 2008; Razeghinejad and Katz, 2012; Rubin et al, 2008; Viola et al., 2006.).

Conclusion

The intravitreal injection of triamcinolone acetonide in a dosage of 4 mg is effective despite leading to secondary ocular hypertension in approximately 50% of the eyes treated; which is mostly reversible and usually manageable by topical antiglaucomatous medication. However, the risk of glaucoma necessitating permanent antiglaucomatous drug use and of an intractable IOP elevation requiring surgical intervention are points to consider that necessitates a strict control for selection of patient with an IVTA indication and close monitorization of IOP.

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CASE REPORT

Intensive Hydatid Cyst Case in Cattle

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Abstract
Hydatid cyst is a significant helminthic zoonotic that threatens human and animal health all over the world including our country. Hydatid cyst being endemic in a geography that includes our country, still constitutes a significant health problem. It causes pathology, growth failure and loss of meat and milk by disrupting the function of organs. Hydatid disease could not be eradicated though diagnostic threatment systems are developed and sometimes cyst could become colossal. The greatest problems for hydatid diseases are the complications based on anaphylaxis and their frequency increase through diameter. In this study, we aimed to present case with intensive hydatid cyst.
Key words: Cattle, hydatid cyst, case

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Introduction

Hydatid cyst is a significant helminthic zoonotic that threatens human and animal health all over the world including our country (Güralp 1981). *Echinococcus granulosus* (*E. granulosus*) causes cystic echinococcosis. The mature adult *E. granulosus* are 2 to 7 mm long and 0.6 mm diameter and found in small intestines of carnivora (dogs, foxes, wolves and jackals). They have 3 segments and the last one is the gravid segment. They are approximately the half of the entire body (Toparlak and Tüzer, 2002). Infective eggs are taken from contaminated food, fodder and water through oral route by secondary hosts like human, cattle, sheep, goat, buffalo, horse, mules, elephant. The segments are easily disrupted with the help of digestive system enzymes. Oncospheres are located at the organs and tissues like renal, cardia, spleen, cerebrum, bone marrow and particularly at liver and lung (Cadona and Carmena, 2013). The host creates a strong immune response and covers the cyst with a fibrous capsule. This blocks the elimination of the cyst by body. In time, these structures grow and constitute vesicles with full of liquid inside. Thousands of scolex are formed from the germination membrane inside the cyst by asexual reproduction. These cysts

are described in two ways. They are named ‘unilocular’ when they are only one cyst and ‘multivesicular’ when there are cysts ındependent of each other. While unilocular cysts are prevail in sheep and human, multivesicular cysts are prevail in cattle. The cyst which had protoscoleces was considered fertile. Cyst with fluid only and without protoscoleces was considered sterile (Dziri 2001; Bowmayn and Lynn,1999).

In this study, we present an intensive hydatid cyst case of determined in a cattle brought to the abattoir for slaughtering.

Case

Antemortem examination was applied to 5 old female cattles from “holstein” strain brought to the abattoir for slaughtering and anorexia, recession, cachectic condition, knotty hair and feather were determined; however fever was regular. In addition, medical history told by the breeder revealed that insemination with long-term treatment was applied for 4 times; but none of them provided fertilization.

In postmortem examination, hydatid cyst forms with many different sizes at liver along with acidity in abdominal cavity were detected. It was notable that these cysts covered the liver all around and parenchyma standed as a thin line between cyst walls. There were great numbers of multilocular type cyst structures encircled with fibrous capsules at the cross section. Within most of them, there available transparent cyst liquid inside the thick capsule and no purulence or calcification was observed. Our examinations did not indicate any protoscolex in the cyst liquid. The weight of the liver was 40 kilograms. Live animal had 300 kilograms live weight; therefore weight of the infected organ was 40/300 (1/7.5) (Figure 1,2).

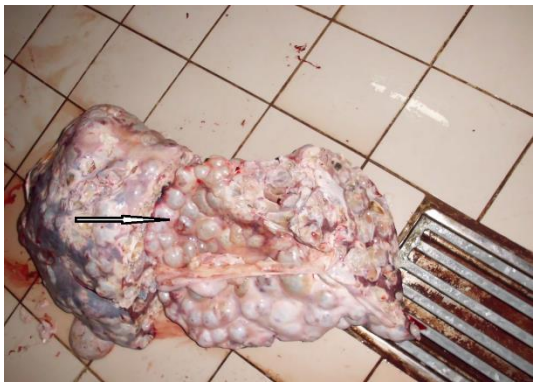

Figure1. Macroscopic appearance of hydatid cyst liver

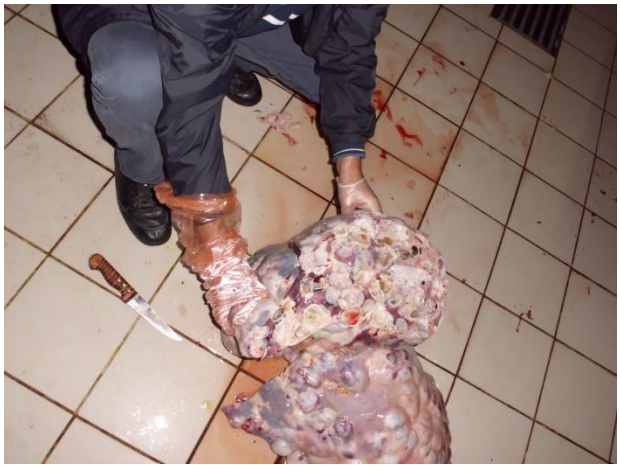

Figure 2. Hydatid cyst of the cut section of the liver

Discussion

Hydatid cyst is a prevalent and important zoonotic disease for the public health. The disease can be fatal without medical treatment. A heavily infested organ may fail or a cyst may rupture and cause a life-threatening allergic reaction. As the disease is frequent in animals is not accepted as ordinary measures encountered. Therefore, though the disease is eradicated in most of European countries, it intensively goes on threatening the public and animal health in our country (Apt et al., 2000; Aciöz et all., 2008). The disease may also cause loss of output and weight in animals thus it constitutes economic importance (Sarıözkan 2009; Karaman et al., 2015). In this study, in consideration of medical history data told by the owner, we detected that the animal was sent for slaughtering by the reasons of weight loss and infertility.

Hydatid cyst usually forms lesions by clinging the organs like lung and liver which have abundant capillar structures and busy bloodstream. However; it was also determined at the organs like kardia, cerebrum and spleen (Gökçen et all., 2006; Avcıoğlu et all., 2010). This case we present describes an intensive hydatidosis that entirely covers the liver as well.

Although hydatid cysts are quite frequent in animals as secondary hosts, the reason why the cases reported in human are further is that, diagnosis and treatment facilities are more common than the veterinary field. The cases that are usually detected in animals, are revealed in postmortem examination of the slaughtered animals in abattoir and diagnosis and treatment in intravital period are quite difficult. This case we present in this study includes a cow slaughtered in Canbolat Kirazlı Meat Integrated Plant in Yalvaç county of Isparta province and we

report that there is an intensive cystic hydatidosis that could rarely be seen.

In hydatid cyst phenomena, we may come across with some different situations like laceration of cyst wall, abscessed or calcific cyst. Moreover, gall retention based on the advanced ligament proliferation and icteric colour change in liver and near tissues, could also be observed. In this case we present, we did not face with any findings except a slight increase of the periton liquid at the abdominal cavity (Balkaya and Şimşek, 2010).

In hydatid cyst cases, 2-5 cysts are often formed in effected organs. These are one of the few cases that the cysts are increased and cover the entire organs in such big amounts. In this case we present, we have come across with much intensive hydatid cysts with enough amounts to cover the entire liver. According to the medical history data, infertility of the animal was identified with a probable progesterone instability in spite of the fact that hormone analysis is not performed at the abattoir. This is the case, suggesting that the cause profound immune system by inhibiting parasite cysts (Sağlam et all., 2011).

Conclusion

Consequently, hydatid cyst case have an important place for both human and animal health and economic aspect. In veterinary field, utilization from new diagnosis and treatment methods, especially dissemination of preventive medicine by using antiparasitic drugs regularly for both secondary and fnal hosts, constitutes urgency for eradication of the cyst hydatid disease for the upcoming years. Antiparasitic drugs regularly for both secondary and final hosts.

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REVIEW

Genomic and Transcriptomic Sequencing and Analysis Approaches

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Abstract
In this review, we explained that genomic and transcriptomic sequences and analysis assays. First of all, we detailed information of genomic and transcriptomic terms and related analyses. Genomics is aimed to elucidate the structural and functional properties of the genomes. Transcriptomics are used to express quantities of transcripts in a physiological state and specific developmental stage. The methods of genomic and transcriptomic analyses imply highly productive sequence analysis or microarray hybridization analysis as well as bioinformatics analyses. The sequencing technologies include set of methods such as preparing template, sequencing, imaging and data analysis. Firstly, the nucleotide information peculiar to DNA and RNA is obtained by means of the chosen technology in accordance with the goal and scope of the study. The obtained sequences are aligned with respect to a familiar reference sequence, or are combined as *de novo*. Subsequently, it is determined whether the distinct genomic sets are connected with the other genomic sets by overlapping distinct genomic sets, such as aligned sequence readings, gene annotation, EST, genetic polymorphism, and mobile elements. So, the structural variant to which the obtained sequence data are peculiar is determined. Within the scope of the study, giving information about sequencing technologies and the methods of analyses of the obtained sequences is aimed for researchers work on this subject.
Key words: Genomics, Transcriptomics, Bioinformatics, Next Generation Sequencing Technology

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Introduction

Genomics and Transcriptomics

Genome is all DNA sequence information which are possessed by an organism. Each genome contains all the information necessary to create and maintain the organism. Genomic analysis is the identification, measurement, or comparison of genomic features such as DNA sequence, structural variation, expression at the gene expression or genomic position, and disclosure of functional element status. Transcriptomics is used to express quantities of transcripts in a physiological state and specific developmental stages. It is possible to sort out the main purposes of transcriptomics work as follows; cataloging of all transcriptomic species including mRNA, noncoding RNAs and small RNAs, identification of 5' and 3' ends, detection of the transcriptional structure of the gene, such as the presentation of spliced patterns, the discovery of the

transcript level of each tissues in different processes. Transcriptomic sequencing is performed using the latest technologies of RNA-sequencing (RNA-Seq) technology. The RNA-seq technique is a very powerful and efficient new method that quantifies the state and organization of an RNA in a sample (Wang et al., 2009). Genomic and transcriptomic analysis methods generally require high-throughput sequencing or microarray hybridization and bioinformatic analysis.

What is bioinformatic?

Bioinformatics covers the fields of biological data collection and storage, data mining, database research, analysis and interpretation, modeling and product design, as well as an interdisciplinary field emerging in science and technology. Briefly, database creation is the process of creating and storing biological information. More specifically, we can define bioinformatics as a computational branch of molecular biology. Bioinformatics, an interface between modern biology and information technology, involves the discovery, development and implementation of computational algorithms and software tools that facilitate the understanding of biological processes. These software tools are intended primarily to serve the health and agriculture sectors. With these high-throughput data analysis methods, biological data can be analyzed and the organization of biological information is ensured. Most of the databases created in this area generate analyzes based on nucleic acids. Later, databases for the storage and organization of millions of nucleotide information obtained with these technologies are being created, and studies on the entry of new data into these databases are still continuing today (Luscombe et al., 2001).

Theoretical Bases

Generating the Nucleotide Information

Genetic information flow is transmitted by DNA molecules between generations except RNA viruses. The structure of DNA was elucidated by James Watson and Francis Crick in 1953. The DNA molecule is a polymeric nucleic acid macromolecule consisting of a five-carbon sugar (deoxyribose), a phosphate group and a nitrogen-rich purine (A: Adenine, G: Guanine) or pyrimidine (T: Thymine, C: Cytosine) bases (Watson and Crick, 1953). The characteristics of living organisms create with the genes which are found in DNA that are first formed by RNA and then protein transformation, which is called central dogma. In the RNA molecule, unlike the DNA molecule, there is a Uracil base instead of the Thymine, and the DNA molecule is double-stranded while the RNA molecule is the single-stranded (Shinkai et al., 2000).

The knowledge of nucleotides in DNA or RNA is obtained by sequencing. For this purpose, hierarchical approach and shotgun approach are used.

Hierarchical Approach

In this approach, firstly, DNA is cleaved into small fragments and then these fragments are cloned into BAC and YAC vectors. Fluorescence in situ hybridization (FISH) is usually used to determine which region of the genome is sequenced. For this purpose, colchicine is applied chemically on the cell in the cleavage stage and the cell is bursed, and then the cells captured at metaphase phase spread on a lamella. Fluorescently labeled probes are added to the clone that is cloned into the BAC and YAC vectors and incubated on the cell on this lamella for a certain period of time. If the part of the genome is sequenced, the fluorescent probe is expected to hybridize to that region, and then the fragments found in the BAC and YAC vectors are taken into smaller plasmid vectors. After sequencing operation, the small parts are read firstly then the contigs are combined and the contigs are combined to obtain the scaffolds. Then the scaffolds are overlapped on each other to determine the entire genome sequence information (Taylor and William, 1990).

Shotgun Approach

At this stage, DNA is first split into small fragments, then sequencing is performed for all the parts, and the resulting arrays are combined by overlapping each other. First, small contigs are obtained and scaffolds are then obtained by overlapping the contigs. And the integration of the scaffolds allows the complete genome (Myers et al., 1997).

Sequencing Technologies

First Generation Sequencing Technology

With this technology, also known as Sanger technology, target DNA is prepared with two approaches; the first is the transfer and replication of target DNA into plasmids, and the second is the amplification of the target DNA by the PCR reaction. The 'cycle sequencing' reaction is then performed. At this stage, denaturation of the template, primer binding, and elongation reactions are performed. The primers cover the target DNA

starting from the immediate vicinity of the region of interest. At each step of primer extension, the chain is terminated by combining fluorescently labeled dideoxynucleotides (ddNTPs) and fragments generated by a nucleotide difference are amplified. The sequence gives the nucleotide identity of the ddNTP DNA sequence at the chain terminating point and thus the sequence is detected by high resolution electrophoretic separation of single-stranded and tagged dNTP extension products in a capillary-based polymer gel. The laser stimulation of fluorescent labels in nucleotides, as particles of apparent length, are extracted from the capillary and combined with the four-color detection of emission spectra to provide a reading represented as a 'trace'. While specific software for this area is converting these traces into DNA sequences, error probabilities are also generated for each basic search (Shendure and Ji, 2008).

Next Generation Sequencing Technology (NGS)

Template preparation, sequencing and imaging and data analysis are the main steps of a new generation of sequencing technology. The combination of these protocols distinguishes one technology from the other and identifies the type of data generated from each platform. The quality and accuracy estimations of the scores as a result of the sequencing obtained by the producers are provided. However, the quality of readings obtained from a platform is not equivalent to that obtained from another platform (Metzker, 2010).

Template Preparation

Today's technologies use randomly fragmented genomic DNA. Common to NGS technologies is the application of the template to a solid surface or support. Millions of sequencing reactions take place at the same spots where the templates to be arrayed are spatially fixed (Metzker, 2010).

Clonally replicated templates

Imaging systems are usually tuned to be determined by a single fluorescence. Therefore, the templates are multiplied. The two most common methods are emulsion PCR (emPCR) and solid phase amplification (Dressman et al., 2003; Fedurco et al., 2006).

EmPCR prevents the random loss of genomic sequences. In this study, sequencing patterns are prepared in a cell-free system. Create a library of trailers and connect adapters containing universal primer fields to the ends of the fragments. This structure allows genomes to be amplified by common PCR primers. The strands of DNA are separated from each other after ligation. Then one DNA molecule is attached to a bead. Once the EmPCR reaction has been successfully accomplished, the beads are immobilized on PicoTiterPlate (PTP) wells (Roche / 454), where NGS chemistry is performed (Shendure et al., 2005; Kim et al., 2007; Leamon et al., 2003).

Solid phase amplification is defined as the clusters cloned on a randomly distributed glass slide. The high-density forward and reverse primers are covalently attached to the plate and ratio of primers to template and support defines the surface density of reinforced clusters. Solid phase amplification to initiate the NGS reaction provides free ends where the universal sequencing primer can hybridize to initiate the reaction in 100-200 million spatially separated templates (Illumina / Solexa) (Metzker, 2010).

Single molecule template

While clonal propagation methods provide some advantages over bacterial cloning, implementing these protocols is very laborious and requires large amounts of genomic DNA material (3-20 μg). Preparation of single molecule templates is easier and requires less starting material (<1 μg). More importantly, these methods do not require a PCR run that generates mutations in clone-amplified templates, masked as PCR variants. At the same time, these methods do not require a PCR run to generate a mutation in clonal amplification templates. In addition, quantitative applications such as RNA-seq, which measure the number of mRNA molecules, provide more accurate results since the number of template is not multiplied (Wang et al., 2009).

With at least three different approaches, the single molecule templates are immobilized on the solid supports prior to the NGS reaction. In the first approach, the primer molecules are spatially distributed and covalently linked to solid support (Harris et al., 2008). Commonly, the bound adapters are hybridized with these primers previously fixed to the surface of template fragments prepared by random splitting of starting material to small sizes (e.g. ~ 200-250 bp). In the second approach, spatially distributed monomolecular patterns are covalently attached to solid support as a primer. A common primer template is then hybridized and sequenced. The DNA polymerase can be attached to the fixed template configuration in both approaches to initiate the NGS reaction. Helicos BioSciences

uses both of these approaches. A third approach is that the spatially distributed single polymerase molecules are attached to the solid support and thus can be sequenced by clinging to the primer-bound template molecules. This approach is used by the Pacific Biosciences firm (Eid et al., 2009). With this technique, larger DNA molecules can be sequenced. Contrary to the first two approaches, this approach can be done by real-time sequencing (Metzker, 2010).

Sequencing and Imaging

There are fundamental differences in the sequencing of single-molecule templates and clonally amplification templates. Clonal amplification resulting in the population of the same templates can be sequenced at the same time. Observed signals are the consensus of nucleotides or probes attached to an identical template within a given cycle (Metzker, 2010).

Cyclic reversible termination (CRT)

Reversible terminators are used in the CRT method in steps involving addition of nucleotides, fluorescence imaging and cleavage. In the first step, the DNA polymerase inserts the nucleotide complementary to the template sequence only in exchange for a fluorophore. When the nucleotide is added, DNA synthesis is stopped by CRT. Once the corresponding nucleotide has been added, the nucleotides that do not participate in the reaction are washed. Then, imaging is performed to determine the identity of the inserted nucleotide. Subsequently, a cleavage step removes the termination / inhibiting group and fluorescein dye. After the addition of a nucleotide a fluorescence signal is released and a new nucleotide insertion is blocked by the CRT method. Illumina / Solexa uses a four-color CRT cycle and Helicos BioSciences performs a monochrome CRT cycle. The initial development of reversible blocking groups attached to the 3' end of the nucleotides has been based on the use of a dideoxynucleotide that acts as a chain terminator in the Sanger sequence. Blocking groups such as 3'-O-allyl-2'deoxyribonucleoside triphosphates (dNTPs) and 3'-O-azidomethyl-dNTPs in CRT have been used successfully (Metzker et al., 1994; Metzker, 2010).

Sequencing by ligation (SBL)

SBL is another cyclic method that uses single-base or two-base encoded probes that are used differently from CRT. In this method, a fluorescently labeled probe hybridizes to the complementary sequence of the primer template. The DNA-ligase then adds the dye-labeled probe primer. The unbound probes are then washed out and removed from the medium, and fluorescence imaging is performed to determine probe identity. In this sequencing cycle, splittable probes are used to remove fluorescent dye and a 5'-PO4 group is reconstituted for subsequent ligation cycles (Orita et al., 1989).

Single nucleotide addition

Roche 454, pyrosequencing

In this sequencing technology, the nucleotide variants are added individually to the sequencing medium. Pyrosequencing is an enzymatic reaction. When nucleotides are added, visible light is produced by the enzymes present in the medium. This method is a non-electrophoretic, bioluminescent method of measuring the release of inorganic pyrophosphate. Unlike other sequencing approaches that use modified nucleotides that terminate DNA synthesis in this method, the DNA polymerase is manipulated by monolithic addition of a dNTP in limiting amounts. The DNA polymerase extends and primes the primer by the addition of complementary dNTPs. DNA synthesis is resumed after the addition of the next complementary dNTP in the distribution cycle. And readings are recorded as light graphics (Ronaghi et al., 1996).

Ion Torrent

Nucleotides are also sent individually in this sorting technology. When a nucleotide is added, instead of using an enzymatic cascade, each dNTP detects released H + ions. The resulting pH change is detected by an ion sensitive field effect transistor (ISFET). The pH change detected by the sensor is proportional to the number of nucleotides detected (Goodwin et al., 2016).

Real time sequencing

It is a technology which influencing the commercial sector. Pacific Biosciences today uses this technology. Real-time nucleotides do not stop the DNA synthesis process, contrary to reversible terminators. During real-time sequencing, the dye-labeled nucleotides are continuously added to the nucleotide. On the Pacific Biosciences platform,

zero-mode waveguide detectors (Zmw) are attached to the lower surface of DNA polymerases. Sequence information includes extended nucleotide primers incorporating phosphorylated nucleotides (Levene et al., 2003).

RNA-seq Technology

The recently developed RNA-seq technique uses a new generation of sequencing technologies. First, the RNAs are cleaved and translated into complementary DNA (cDNA) by adapters that attach to both ends of the fragments. In the next step those parts with or without amplification are sorted in a highly efficient manner. In the next step these amplified or unamplified segments are sequenced in a highly efficient manner. Reading lengths are typically in the 30-400 bp range, depending on the DNA sequencing technology used. After sequencing, the readings are aligned using both the reference genome and the transcriptome data (Wang et al., 2009). Then gene ontology analyzes of the readings are made. Classification and differences of genes expressed at least two folds are revealed on a tissue or cell basis.

Genome Alignment and Assembly

Once the NGS readings are complete, they are aligned to a known reference sequence or combined de novo. Identifying which strategy to use depends on factors such as the intended biological application, cost, labor and time. Sequence information of an organism detected by phylogenetic analysis closest to the material we use is used as the reference genome (Salzberg and Steven, 2009; Chaisson et al., 2009). Genomic sequencing studies of living organisms identified as model organisms such as Arabidopsis thaliana, C. elegans, Drosophila melanogaster and Saccharomyces cerevisiae have been completed. In this alignment approach, the presence of repeating regions in the reference genome, the absence of corresponding regions, the presence of gaps in the reference genome, or the presence of structural variables in the analyzed genome constitute a number of limitations (Frazer et al., 2009). Also, since each NGS platform produces a unique reproducible model for the variable sequence coverage, combining NGS reading types with alignment or aggregation may be incomplete (Aury et al., 2008; Reinhardt et al., 2009).

Sequence Analysis

In genomic research, the basic process is to investigate the association of different genomic clusters (eg, aligned sequence readings, gene annotations, ESTs, genetic polymorphisms, mobile elements, etc.) with other genomic clusters. With this method of comparison, the results of experiments can be characterized, causality and coincidence can be demonstrated and the biological effect of genetic findings can be evaluated (Quinlan and Hall, 2010). Implementing with large data clusters routinely produced with existing sequencing technologies is very complex to search for conflicts between existing web-based methods and features (Quinlan and Hall, 2010). For this reason, fast and flexible tools are needed to efficiently solve complex queries of these data. Genomic assays generally aim to compare features discovered in an experiment with known annotations for the same species. If the genomic features found in the different sequences match at least one base, these bases which are common are called overlapping or intersecting. For example, a typical question might be: 'Which of my new genetic variants coincide with exons?' and other structural variants such as deletions, insertions, duplications, translocations, transversions, multiallele copy numbers, transposon insertions, retrotransposon sites, satellit DNA and mitochondrial DNA variants are presented (Consortium, 2015).

Gen Ontology Analysis

The co-characterization of mutations and phenotypes of genes in genetic research has shown us that genes are common in many organisms. It is therefore clear that the functions of these genes can be understood in all organisms when we can understand the genes and proteins found in living organisms. In other words, when the role of a protein is understood in any organism, it means that it can be understood in other organisms. In other words, the role of a protein, when understood in any organism, means that it can be understood in other organisms. Gene ontology examines gene and protein roles and accumulations in the cell under three headings; these include biological processes, molecular functions and cellular components (Clarke, 2012). The biological purpose to which the gene contributes refers to the biological process. Any process can be performed through one or more regulated associations of molecular functions. Examples of these processes are cell growth, signal transduction. Cell growth, signal transduction is

basically an example of these processes. More specifically, translation, pyrimidine metabolism, cAMP biosynthesis can be given as an example. The biochemical activity of a gene product (including ligands or specific binding to the construct) is defined as the molecular function. It only reveals what needs to be done without actually telling where and when it will happen. By way of example, the term 'enzyme', 'carrier' or 'ligand' may be given as an example. Examples of more narrow functional terms may be given as 'adenylate cyclase' or 'toll receptor ligand'. A cellular component refers to the location of a gene product that is active in the cell. These terms reflect our understanding of eukaryotic cell structure. Terms like "ribosome" or "proteasome" give the cellular component which indicates where the gene product is (Ashburner et al., 2000).

Conclusion

New generation sequencing technologies are used to classify genomes and discover genes with all genomic sequencing, transcriptomic sequencing, extraction of sequence-based profiles of epigenetic markers and chromatin structure, and metagenomic studies (Wang, 2009; Wold and Myers, 2008). Which technology to use for which approach depends on the characteristics of the platforms. Because of the large volumes of high quality bases are produced for each work. In addition, in the case of RNA-seq or direct RNA sequencing, the Helicos BioSciences platform is suitable for applications requiring quantitative information; because it is sequenced without having to convert RNA templates directly into cDNAs (Özsolak et al., 2009).

Compared with automatic Sanger sequencing, the new generation of sequencing technologies is cheaper, but still the cost of sequencing work is high. As a temporary solution to this problem, NGS platforms can be used to target only specific areas in the genome to reduce costs. With this workaround, genomic regions that cause disease or pharmacogenetic effects can be examined through all exons in the genome, specific gene families that constitute the drug targets, or genome-wide association studies (Altshuler et al., 2008; Wang and Weinshilboum, 2008). In addition, custom designed oligonucleotide microarrays are also used to determine the relevant gene regions (Singh-Gasson et al., 1999).

Establishing relationships with biological functions using individual sequences and the associated knowledge of these sequences is an important aspect of genetic data mining. For this, automatic functional annotation is performed. Functional description allows for the characterization of genes by understanding the physiological conception of an excess number of genes and the functional differences between subgroups of sequences. The gene ontology study provides a suitable framework for such analyzes. In this way, interpretations based on similarity can be made by comparing the ones known from the sequences with those unknown. For example, Blast2GO (B2G) is one of the programs used in this context (Conesa et al., 2005). In short, B2G uses the BLAST program to identify genes homologous to fasta formatted sequences and to perform sequence annotations with high efficiency (Conesa et al., 2005). At the same time, genome-wide assays have shown that approximate 40-60% of human genes have alternative splicing additions (Lee, 2002). At the same time, a lot of software has been developed nowadays from read-based alignment software like MAQ, BWA and SOAP to structural variable finding tools like BreakDancer, VarScan and MAQ.

In particular, the analysis has focused on illuminating both protein-coding and protein-encoding regions. However, different analyzes provide us with the understanding that different clusters of predicted genes exist when different additional criteria are used. This suggests that the number of genes that encode proteins are still not fully understood. There are also genes in the genome that belong to RNAs that do not encode proteins. Non-coding RNAs do not transcribe at high rates, but the genome is an important functional output. Non-coding RNAs generally play a greater role in the control processes such as genetic stresses and in the control of genetic networks, in addition to the roles in protein synthesis (ribosomal and transfer RNAs). Thus, transcriptomic readings cover all synthesized RNA, including protein-coding, protein-encoding, sense-antisense and RNA-regulated transcripts (Okazaki et al., 2002).

Today, with 1000 genome project, 2504 individuals from 26 different populations have been sequenced. As a result of this study, 88 million single nucleotide polymorphism (SNP) variants, 3.6 million insertions, 60,000 other structural variants have been identified and shared with the literature (Consortium, 2015). Genomic sequencing have been performed not only for humans but also for microorganisms, plants (rice, grapes, cucumber, corn, soybean, poplar etc.) and animals (chicken, pig, cow, sheep horse etc) (Michael and Jackson,

2013; Bai et al., 2012). Since 1998, 87 animal genomes and 55 plant genomes have been sequenced in non-human living species. Thus, functional elements and other structural variants of other living things will be able to be compared within themselves and have an idea of their evolutionary development (Song and Wang, 2013; Michael and Jackson, 2013). Today, the sequencing studies continue with the latest speed.

There are many ways in which genes measure expression levels comparatively in any developmental process or context. There are many ways in which genes measure expression levels comparatively in tissues that are in any developmental process or condition. For example, in a study conducted in Arabidopsis, it was observed that gene expression profiles were similar as a result of comparative transcriptomic analysis of developmental and dark aged leaf tissues (Buchanan-Wollaston et al., 2005). Today, however, transcriptomic studies are now being carried out by incorporating them into genomic studies together with developing technology. For example, in an effort to determine the alternative splicing status of mouse and human genes, all genomes were sequenced, resulting in similarity in mouse and human conserved alternative splice genes (Sugnet et al., 2003).

As a result, after the sequencing has been carried out, it is completed that genomic readings, read mapping, duplicate filtering, base quality value recalibration, INDEL realignment, Variant Site Discovery, genotype assignments and reporting of variants. Transcriptomic reading continues with alignment of the sequences and subsequent analysis of gene ontology after the assembly process. In this study, classification and differences of genes expressed at least two fold differences are revealed on tissue or cell basis. However, despite the rapid development of this area, there are still gaps in the processing and storage of data (Clarke, 2012).

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