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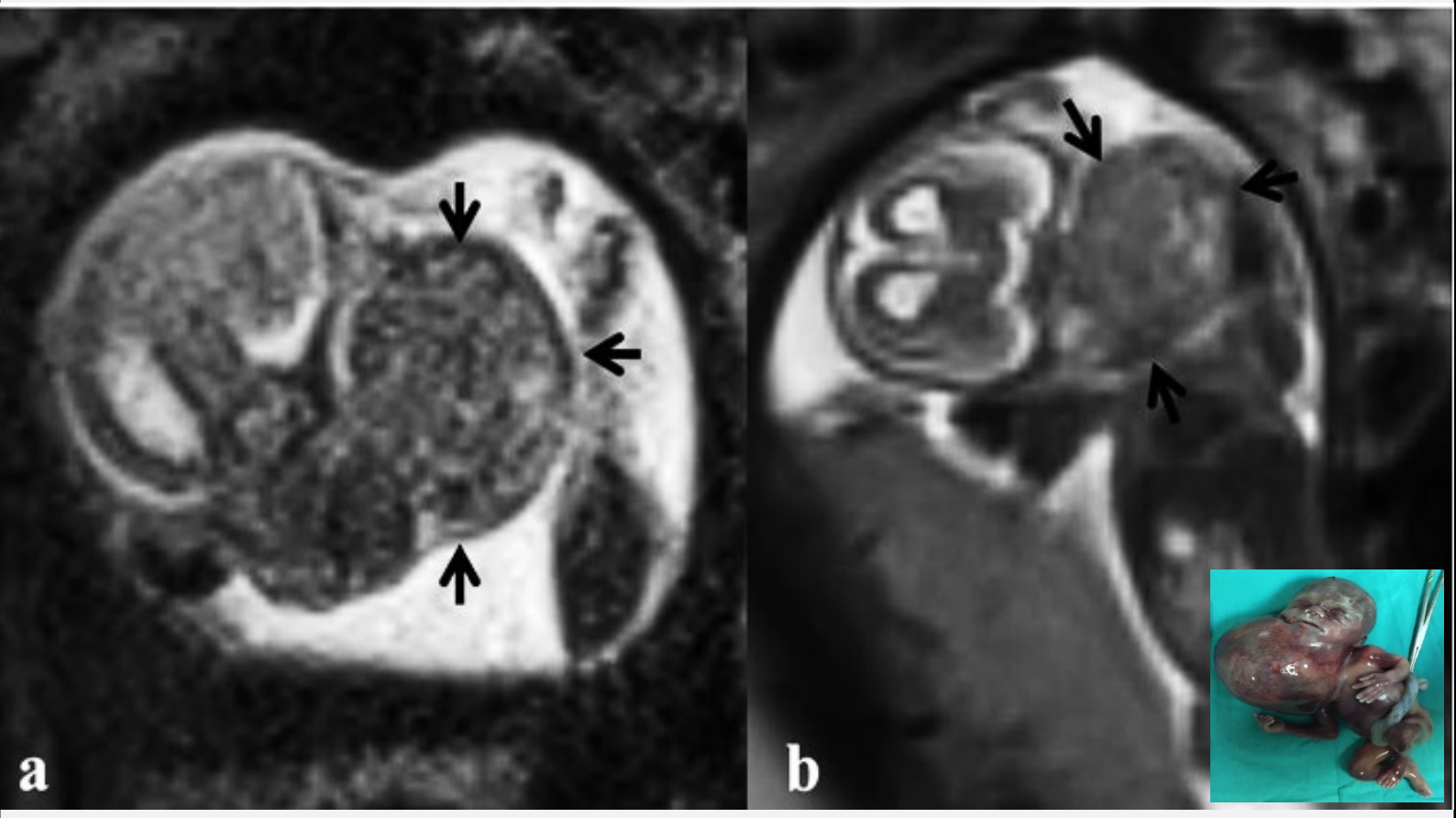

High Lights

- Ovarian Immature Teratoma During Pregnancy
- Evaluation of some tumor markers, acute phase proteins, sialic acid and lipid bound sialic acid before and after chemotherapy in stomach cancer
- Factors triggering epileptic seizures in patients over 50 years
- Prenatal diagnosis of a giant fetal cervical teratoma by magnetic resonance imaging

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Review Article Doi: 10.17546/msd.39076

Ovarian Immature Teratoma Detected During Pregnancy

Pinar Solmaz Hasdemir[1]*, Tevfik Guvenal[1], Serkan Menekse[2], Ulas Solmaz[3], Ali Riza Kandiloglu[4], Faik Mumtaz Koyuncu[1], Ali Ayhan[5]

Abstract

Objective: Malignant ovarian immature teratomas should be considered in differential diagnosis of adnexal masses detected during pregnancy. This paper is reviewing the clinicopathologic and prognostic characteristics and therapeutic options for treatment of immature teratoma during pregnancy in the context of a case of pregnancy complicated with immature teratoma.
Material and Methods: A PubMed and Scopus search was conducted with the key words 'ovarian immature teratoma' and 'pregnancy' and all related published articles assessed. A total of 24 cases, included our case were included in the study. Age at presentation, clinical findings, histological grades and stages, treatment options and the prognosis of both mothers and fetuses was analysed.
Results: The median age of the patients in the published reports was 27.0± 4.2 (range 21-36) years. The main presenting symptom was adnexal mass followed by abdominal or pelvic pain. Chemotherapy was added to the surgical treatment in 68.2% of the patients; a Bleomycin, Etoposide and Cisplatin protocol was the preferred treatment option. Prognosis for both mother and foetus were good.
Conclusion: Immature teratoma during pregnancy should be treated immediately with surgery ± chemotherapy especially in high grade patients.

Key words: chemotherapy, germ cell tumors, immature teratoma, pregnancy

Introduction

Pure immature teratoma of the ovary' term describes the germ cell tumor of the ovary by excluding patterns of endodermal sinus tumor, choriocarcinoma, and dysgerminoma (1). Pregnancy complicated by an immature teratoma is fairly rare, with a reported incidence of 0.07% (2). The consequence of a low incidence is a lack of consensus on management strategies. We described here a woman diagnosed with immature ovarian teratoma during pregnancy and review the clinicopathologic and prognostic characteristics and therapeutic options of immature teratoma cases during pregnancy. To the best of our knowledge, this is the first comprehensive review in literature which collects ovarian immature teratoma during pregnancy cases.

Material and Methods

A PubMed and Scopus search was conducted with the key words 'ovarian immature teratoma' and 'pregnancy' and all related published articles assessed. Totally 19 case reports and 12 review articles about the germ cell tumours of the ovary and ovarian tumours during pregnancy were determined. Cases in articles with a review of prior published cases were included if the clinicopathologic information about the cases was clearly stated. Crossing cases from the articles precluded. Cases who first diagnosed by ovarian pure immature teratoma during or related with their pregnancy were included in the study. Patients were examined by age of the patients, grade and stage of the tumour, gestational week and symptoms at diagnosis, operation type, chemotherapy, birth week-birth way, second look laparotomy, disease free survival and prognosis. Manuscripts with incomplete data (<50% of analysed criteria) and case reports published in local journals with weak data were excluded. Age, clinical findings, histologic grade and stage, treatment options and the prognosis of both mothers and fetuses were analysed by descriptive analysis with SPSS 21.0 statistical programme (SPSS package, version 21.0, SSPS Inc., Chicago, IL, USA).

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Case

A 25-year old primiparous woman at 19 weeks gestation presented to the emergency department with a two week history of abdominal and pelvic pain of increasing severity on the day of admission. Physical examination revealed diffuse abdominal pain with rebound tenderness. Abdomino-pelvic ultrasound showed a normal 19 week pregnancy. The left ovary was in normal appearance. An 80x40x40 mm solid mass with anechoic cystic areas was seen on the right and posterior side of the uterus, with mild right-sided hydronephrosis and free fluid in the recto-uterine pouch. Serum CA125 level was slightly elevated (39.1 U/ml, range: 0-35 U/ml) and serum alpha-fetoprotein level was elevated (38.74 ng/ml, range: 0-9 ng/ml).

An emergency laparotomy was performed. A large, 150 mm diameter right adnexal mass was detected and ruptured during removal revealing white-red, jelly-like material. Frozen section could not be performed but a right salphingo-oopherectomy was done. Pathological examination revealed an immature teratoma (grade 3) of the ovary with benign peritoneal cytology. She didn't agree with chemotherapy during her pregnancy.

She complained of intermittent pelvic pain without cervical shortening or uterine contractions during the rest of the pregnancy. A planned cesarean section birth and second look laparotomy was performed in the 32nd gestational week after antenatal steroid administration for fetal lung maturation. The 1x2 cm tumoral mass from the peritoneum of the recto-uterine pouch was removed and omentectomy, appendectomy and peritoneal biopsies were performed. Pathological examination revealed that, the mass from peritoneum of the recto-uterine pouch was immature teratoma and the rest of the biopsies and excised tissues were benign. She was started on chemotherapy with BEP protocol (bleomycin 30 mg, etoposide 100 mg/m2, cisplatin 20 mg/m2) three weeks after the operation. She completed the 6th treatment regimen with a recurrence at 1st year follow-up and died just after the operation for recurrences. The baby died right after birth because of congenital pneumonia

Results

Clinicopathologic features and therapeutic approaches for the cases are summarized in Table 1 (1- 20). Distribution of age ranged from 21 to 36 years with a median of 27.0± 4.2 years. The main presenting symptom was adnexal mass (eight patients) followed by abdominal or pelvic pain (four cases). Four cases presented with combined abdominal pain and mass, five were diagnosed by routine ultrasonography and three by elevated serum AFP (alpha- fetoprotein) levels (some of the patients were noticed to have more than one symptom). One asymptomatic patient was diagnosed during cesarean section. The median gestational week at diagnosis was 18± 10.3 (range 8-40) weeks and the median gestational length was 38.0± 3.6 (range 28- 40) weeks of pregnancy. The grade and stages of the patients summarized in Table 2. Cesarean section was the preferred mode of delivery in 10 women (52.6%). Termination of pregnancy was administered in one case and and spontaneous miscarriage occurred in another one (10.5%).

The teratoma ruptured during operation in four (17.4%) cases. Chemotherapy was added to the surgical treatment in 15 patients (68.2%); a Bleomycin, Etoposide and Cisplatin (BEP) protocol was the preferred treatment option in eight women. Four women, including our case was died because of the rapid disease progress (16.6%). Of the babies 19 were healthy. One had an intracranial immature teratoma, one had hypospadias and the fetus was died with prematurity complications. Three women had a subsequent normal pregnancy.

Discussion

Pure immature teratomas, first characterized by Norris et al in 1976, are rare germ cell tumors which involve three germ layers with at least one of the components having an immature appearance (1, 21). Survival is determined by the size and stage of teratomas, but the grade of the primary tumor is the most important determinant of the likelihood of extra ovarian spread and for the subsequent course. Grading is based on the amount of immature neural tissue (1).

Some 36 years later to Norris et al., Zhang R. et al reported 5-year survival rate as 92.% for immature teratoma based on 63 (non-pregnant) cases with immature teratoma among 145 malign ovarian germ cell tumor cases and histology, surgical approach, chemotherapy and regimens were not predictive of five-year survival rates. Moreover they concluded that, fertility-sparing treatment should be considered for ovarian germ cell tumors without regard for the FIGO stage (22).

Young et al. showed that prognosis for ovarian malignancies was not complicated by a concurrent gestation if adequate treatment is administered timely (23). Management of ovarian tumors in pregnancy requires a multidisciplinary approach and therapeutic decision should take into account histology, grade and stage of the tumor, and the gestational week of the pregnancy (24). Clinicopathologic features and therapeutic approaches for the pregnant pure immature teratoma cases were summarized in Table 1 (1- 20). Age ranged from 21 to 36 years with a median of 27± 4.2 years. The median gestational week at diagnosis was 18± 10.3 (range 8-40) weeks and the median gestational length was 38± 3.6 (range 28- 40) weeks of pregnancy.

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Table 1. Cases diagnosed as immature teratoma during their pregnancy.

Author, Year	Age	Grade	Stage	Week	Symptom	Operation	Chemotherapy	Birthweek-birthway	Sec.look	DFS (month)	Prognosis, other
Norris et al., 1976					All 3 were found in routine USG						3 patients (2 pregnant, 1 determined in pp USG)
Hassan et al., 1984	28	2	?	28	Anemia, abdominal pain, weekness, dyspnea	Right USO+ partial O+ C	VAC (1 course)+ external RT	28	-	-	Exitus in 3 months, healthy newborn
Matsuyama et al., 1989	27	3	1a	pp20	Lower abd pain	Right USO	VAC (7courses)	term	-	48	Good
Montz et al., 1989	N/A	N/A	1a	18	Elevated msAFP	18 w laparotomy	CVB (3 courses)	31, C	-	65	Liver recurrence 5th month (Cure with +3 courses of BEP), healthy newborn
Christman et al., 1990	N/A	3	1c		Adnexal mass (18-20 cm)	Laparotomy, rupture in operation	PVB (1 course in p+ completed pp)	term, V	Yes	?	Healthy newborn Benign in second look
Frederikse n et al., 1991	34	3	1c	17	Elevated msAFP	19 w lap. Right SOF+ omentectomy, rupture in operation	VAC (4 courses)	Term, V	Recurrence at 13th months pp, treated with surgery+ CT		Healthy newborn.
Poremba et al., 1993	27			Term	None	C+ USO	?	Term, C	?		?, Simultaneous with intracranial immature teratoma in baby
Bakri et al., 2000. Case1	33	2-3?	1a	pa10	abdominal pain, mass (14cm)	USO and staging	4 courses BEP	-	-	48	Spontaneous p after 4 years
Bakri et al., 2000. Case2	21	2	3?	8	abdominal pain, fever, sweating, weight loss	TAH+ BSO+ termination	-	termination	-	-	Rapid progress, Exitus in 2th trimester
Kishimato et al., 2002	28	2	3c	34	Found in routine USG, solid+ cystic mass on MRI, msAFP elevated	TAH+BSO+ PP LND+ Partial O+ C	5 courses	38	-	9	Healthy newborn, good for both
Agarwal et al., 2003	?	?	?	33	?	C+ hysterectomy+ O	yes	33, C	-	?	?, Rapid progress- patient didn't want chemotherapy in pregnancy
Han et al., 2005	27	3	1a	16	Elevated msAFP, adnexal mass (5*6cm)	Right USO	BEP (2courses in p+ 3courses pp)	38, V	L/S PPLND+ O+ LO biopsy after birth	26	Good for both, healthy newborn
Zhao et al., 2006. Case1	24	1	1	8	Pelvic mass	Right USO	-	term, V	-	18	Good for both
Zhao et al., 2006. Case2	24	1	1	17	adnexal mass	Left USO	-	term, V	-	30	Good for both

Daponte et al., 2008	?	1	1a	12	Adnexal mass	Right USO+surgical staging	-	34, C	C+ peritoneal biopsy	24	Healthy newborn, Frozen negative
Poujade et al., 2008	36	2		21	adnexal mass in USG (175mm)	Left oopherectomy	Agent? 3 courses in p, 2 courses pp	39, C	C+ left salpingectomy	After CT	remission in mother, healthy fetüs
Karimi-Zarchi et al., 2008	26	3	3c	28	Abdominal pain	Right oopherectomy+ cytology+ partial O	BEP (in p+ 2 courses pp)	39, C	C+ O+ipsilat. LN sampling	18	Good prognose
Ghaemmaghami et al., 2009	25	?	?	13	adnexal mass in USG (76*45 mm)	21w-right oopherectomy+ bx from left ovary, omentum	BEP (in p)	36, C	C+ partial O+ right salpingectomy+ periton bx+ bilateral LND	12	Hipospadias and IUGR in baby
Mourali et al., 2010. Case1	28	1	?	Term	Determined during C, 5 cm solid+cystic	USO+O+ aortic LND+ A	-	term, C	At 2nd C birth	36 to 2nd birth	Healthy newborn, Radical surgery in 2nd s/c birth
Mourali et al., 2010. Case2	22	2	?	15	Adnexal mass (8 cm solid+cystic)	20w-USO+O+aortic LND+A	-	V	-	?	Good prognose.
Helage et al., 2011.	22	2	1c	37	Adnexal mass	37w C+ right USO+ peri- toneal cytology, bx, rupture in operation	BEP (after surgery)	C	-	?	Remission after chemotherapy
Clinkard et al., 2011	23	?	3c	18w	abd.pain+ hyperemesis, right adn mass	acute bilateral oopherectomy+ O	high dose cisplatine and etoposide	abortus	abortus	72	viable 2. pregnancy (medulloblastoma arising in immature teratoma)
Mendivil et al., 2013	32	3	1a	16w	Pelvic pain+ 10 cm adn mass	Robotic right USO+ inspection	-	37, V	-	?	Good prognose for mother, healthy newborn
This case	25	3	?	19w	Abdominal pain, 8 cm right adnexal mass	Right USO+ peritoneal cytology, rupture in operation	5 courses BEP after p	32, C	C+ O+ A+ excision of the residual mass	12	Fetus died with congenital pneumonia, mother died with recurrences.

C: cesarean sectio; V: vaginal birth; O: omentectomy; A:appendectomy; bx: biopsy; p: pregnancy; pp:postpartum; pa:postabortus; BEP: bleomycin+ etoposide+ cysplatine; VAC: Vincristine, Actinomycin D, Cyclophosphamide; LND: lymph node dissection; PPLND: pelvic- paraaortic LND; R: right; L: left; TAH+BSO: total abdominal hysterectomy+ bilateral salpingooopherectomy; USO: unilateral salpingooopherectomy; USG: ultrasonography; MRI: Magnetic Resonance Imaging; CVB: Cisplatin, Etoposide, Bleomycin; msAFP: maternal serum alpha-fetoprotein;

Table 2. Distribution of the grade and stages of the cases.

Grade	Number of patients	Percent (%)	Stage	Number of patients	Percent(%)
1	4	16	**1**	2	8.7
2	6	24	**1a**	6	26.1
3	8	32	**1c**	3	13
			3	1	4.3
			3c	3	13
Missing	7	28	Missing	8	34.8

Prognosis for immature teratomas has improved due to the routine use of imaging during pregnancy and because of chemotherapy. Most ovarian cancers associated with pregnancy were detected by ultrasonography (USG) (12). For immature ovarian teratomas during pregnancy; the main presenting symptom was adnexal mass (eight cases) followed by abdominal or pelvic pain (four cases). Four cases presented with combined abdominal pain and mass, five were diagnosed by routine ultrasonography and three by elevated serum AFP (alpha- fetoprotein) levels. Some of the patients have more than one symptom and one asymptomatic patient was diagnosed during cesarean section. USG simplified the diagnosis in our case similar with most of the other ones in literature (Table 1).

Malignant ovarian germ cell tumors are usually unilateral except advanced stage cases with metastasis to the contralateral ovary (25). None of the cases reviewed was bilateral except the advanced stage cases with distant metastasis. Thus, unilateral salpingo oopherectomy with preservation of the contralateral ovary and uterus are appropriate for treatment of most cases. If metastatic disease is encountered during surgery, cytoreductive surgery is recommended. Second look laparotomy for germ cell tumors is controversial; if inadequate staging was present at the first operation, second look surgery or CT should be considered (25). Staging could not be performed at the first operation in our case, because of the lack of frozen section results. Thus, second look surgery performed during cesarean section. Cesarean section was the preferred mode of delivery for 10 women (52.6%) and second look surgery was preferred to perform during cesarean in 50% of them.

Germ cell tumors are very chemo sensitive. Patients with stage 1a, grade 1 tumors have excellent prognosis, do not require adjuvant treatment and postoperative observation is recommended. Chemotherapy recommended when extra-ovarian disease exists. The role of adjuvant chemotherapy for patients with stage 1, grade 2 or 3 tumor is controversial. BEP is the most commonly used combination (21), every 3 weeks for 3 or 4 courses (26). Chemotherapy was seen to add to the surgical treatment in 15 patients (68.2%); a Bleomycin, Etoposide and Cisplatin (BEP) protocol was the preferred treatment option in eight women.

Highly immature teratomas detected during pregnancy deserve special attention. Grade 2 or 3 immature teratomas are associated with a greater chance of potentially fatal recurrence predominantly within two years of diagnosis as occurred in our case (27). Therefore, the principle of surgery in both pregnant and non-pregnant patients is resection of as much as tumor as is feasible and safe. There is now a general consensus that a vertical midline incision with unilateral salpingo oophorectomy, peritoneal washing and careful inspection of the abdominal cavity is appropriate, preserving the potential for later fertility (27).

The poor prognosis of malignant germ cell tumors treated by surgery alone indicates a need for adjunctive chemotherapy (2). The risk of major malformation during the first trimester of pregnancy is 10% for single agent chemotherapy and 25% for combination chemotherapy (21). Therefore, the second trimester seems safer for chemotherapy. The BEP protocol has been recommended for the treatment of immature teratomas even though there is limited experience for using this regimen during pregnancy (15, 28). The BEP treatment has been associated with ventriculomegaly, transient neonatal neutropenia and bilateral sensorineural hearing loss in two cases (11). More data are needed to determine the safety of these medications during pregnancy.

Preoperative rupture of the tumour is rare but possible due to the large size of the germ cell tumors. Intraoperative rupture worsens the prognosis and dictates a need for ancillary chemotherapy. Four of the 23 cases (17.4%) ruptured intraoperatively as occurred in our case. The patient was offered chemotherapy during her pregnancy and we discussed the risks and advantages with her, but she did not agree with chemotherapy while she was pregnant.

Conclusion

Malignant ovarian immature teratomas should be considered in differential diagnosis of adnexal masses detected during pregnancy. Fertility-sparing surgery with or without chemotherapy during or after pregnancy are a therapeutic option. Chemotherapy improves prognosis, especially if extra ovarian spread exists. Grade 2-3 cases should be encouraged for chemotherapy during pregnancy. However, gestational age at diagnosis, stage of the disease, patient's willingness to keep the pregnancy, and fetal risks secondary to maternal treatments need to consider on a patient basis.

Conflict of Interest: The authors declare that there is no conflict of interest regarding the publication of this paper.

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Evaluation of patient controlled sedation (PCS) during surgical removal of impacted lower third molars

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Abstract

Objective: The current study was conducted to evaluate the safety of patient-controlled sedation (PCS) and the efficiency of elastomeric infusion device during surgical removal of impacted lower third molars and its impact on patients regarding level of sedation, patients' satisfaction and psycho-motor recovery.
Material and Methods: Twenty patients were equally divided into two groups chosen randomly. In both groups, 0.03 mg/kg Midazolam and 0.5 mg/kg Propofol were administered IV as a bolus dose. Group 1 was then given 0.3 mg/kg/hr Ketamine and 1.2 mg/kg/hr Propofol as a maintenance dose delivered through the PCS pump. Group 2 was then given 0.3 µg/kg/hr Fentanyl and 1.2 mg/kg/hr Propofol as a maintenance dose delivered through the PCS pump. For all patients' surgical procedure were done under local anesthesia. Before going to the operating theatre all patients were instructed about the PCS pump and familiarized with it. Patients in both groups were evaluated for hemodynamic stability, patient's &surgeon's satisfaction, psychomotor recovery and adverse effects.
Results: The results of this study showed no statistical difference between the two groups. The use of different drug combinations in both groups showed hemodynamic stability, patients'& surgeon's satisfaction and rapid psychomotor recovery. None of the patients in both groups suffered from any adverse reactions such as: nausea, vomiting, hallucinations, involuntary movements, or over-sedation.
Conclusion: PCS can be considered as a safe option in minor oral surgeries providing the majority of patients with high satisfaction and relaxation, also providing the surgeons with good operating conditions and the cooperation of the majority of the patients. Fentanyl-Propofol and Ketamine-Propofol combinations were both safe with respect to hemodynamic changes with rapid recovery of psychomotor functions in all patients.

Key words: Analgesia, Patient-Controlled, Impacted, Molar, Third, Tooth, Accufuser, Moderate Sedation

Introduction

Dental treatment often causes fear among patients, and although local anaesthetics make dental treatment easy and painless, dental operations arouse fear and anxiety (1) (2). Dental surgical procedures or even just the idea of having a tooth extracted are usually associated with patient discomfort and apprehension (3). This is in agreement with studies indicating that an extraction is considered to be highly distressing and that it belongs to the top 5 most fear-evoking procedures in dental treatment (4) (5)

Historically, general anaesthesia has been the usual pharmacological approach used in management of apprehensive patients. It is satisfactory and effective in sedation and pain control, but it has serious limitations as well as its technical hazards (6). General anaesthesia might be costly even in a free-standing outpatient surgery centre, and few dentists are familiar with procedures for functioning in the hospital environment (7).

The use of some form of sedation is therefore common during dental operations.

Conscious sedation is medically controlled state of depressed consciousness that allows protective reflexes to be maintained, retains the patients' ability to keep an air-way patent independently and continuously, and permits appropriate responses to physical stimulation or verbal command. The field of patient-controlled sedation (PCS) is relatively young, and few practitioners have experience with this technique. The earliest report of PCS is that of Rudkin *et al.* in 1991 (8) who used a modified Graseby PCA pump to permit administration of propofol to patients undergoing third molar extraction. PCS describes delivery of sedative medications that is controlled by the patient throughout the procedure, including initiation of loading doses. The ability to modify the pain experience by simply pressing a button may be as potent an analgesic as the drug itself (9).

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PCS provides adequate relief for patients, and allows them to vary the degree of sedation according to the amount f stress they feel from the operation and the environment. It is often used for sedation during procedures done under regional or local anaesthesia, and is the preferred technique because the total dose can be titrated according to the patients' needs and regulated according to their anxiety. It also lessens the risk of overdose and inadequate sedation. Many studies have shown that this technique is safe and satisfactory (2) (10).

The *Accufuser* is a reliable, disposable device that has a continuous and accurate pre-fixed flow rate and elastomeric silicone reservoir without need for electrical power or extra equipment. The *Accufuser* is specially designed to deliver medications with continuous and bolus dose in the range of patient controlled analgesia infusion therapy. The *Accufuser* is designed for single-use in hospital, outpatient, and home care settings. The Accufuser was originally designed to be used in patient controlled analgesia (PCA) in many procedures. In our study, using the same concept of patient controlled analgesia, we used the Accufuser as a delivery pump for sedative drugs that is controlled by the patient.

Sedative-hypnotics and opioid analgesics are often used together to improve comfort and provide sedative, anxiolytic, and supplemental analgesia during outpatient operations under local anaesthesia. Propofol sedation is used frequently in local and regional anesthesia for its amnestic and anxiolytic effects (11) (12). Although propofol has the advantages of rapid awakening and minimal nausea and/or vomiting, its analgesic activity is insufficient; moreover, it may cause respiratory and cardiovascular depression (13). In minor surgery, propofol is combined with opioids, such as fentanyl, to achieve better analgesia (14) (15). Avramov *et al.* (16) reported that the propofol-combined opioid provides analgesia and amnesia, as well as reduces incidences of nausea, vomiting, and respiratory depression. Ketamine also causes minimal cardiovascular and respiratory depression, and at sub-anesthetic doses, it induces analgesia (17) (18) (19). Recent studies has been showed that low-dose ketamine in combination with propofol sedation, achieves adequate analgesia and preserves respiration (20) (21).

Patients and Methods

After we had ethics committee approval and informed patients' consent, 6 female and 14 male healthy patients (American Society of Anaesthesiologists grade I and II) aged between 18 and 34 who required surgical removal of impacted lower third molars were included to the study. The patients were selected from the outpatient clinics of the Oral and Maxillofacial Surgery Departments at the Faculties of Oral and Dental Medicine, at Cairo University and October 6 University in Egypt. All operations had the same degree of difficulty. Exclusion criteria included taking sedative, hypnotic, or psychoactive medication and serious musculoskeletal problems that would make the ball-bearing test impossible. Before sedation all patients completed the ball bearing test to evaluate their psychomotor function. They were asked to pick up 40 beads with a tissue forceps from one cup and to carry them to another within 40 s. The numbers of beads carried were recorded as the score. This test was repeated at 15, 30, 45, and 60 min, postoperatively.

Before going to the operating theatre all patients were familiarized with the ACCUFUSER® pump (fig. 1) and were shown how to use it. For all the patients, the surgical procedure was performed under local anesthesia and I.V. sedation. A sterile syringe was filled with the sedatives to be dispensed into the pump reservoir. The filled syringe was then connected to the filling port of the pump and the sedatives were injected into the medication reservoir. The Accufuser module button was then fixed on the patient's wrist and the patient was instructed to press the button whenever he/she felt anxious, or whenever they felt that the level of sedation has decreased.

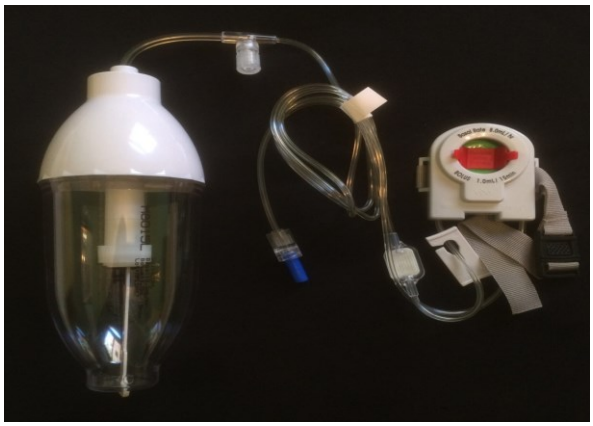

Figure 1: ACCUFUSER Pump

The two groups were chosen randomly. An IV cannula was inserted into a dorsal hand vein and a bolus dose of 0.03 mg/kg Midazolam and 0.5 mg/kg Propofol was administered as an induction dose in both groups of the study. The Accufuser pump was then connected to the IV cannula to deliver the sedative drugs after being prepared by the anaesthesiologist according to each group.

Group 1 was given 0.3 mg/kg/hr Ketamine and 1.2 mg/kg/hr Propofol as a maintenance dose delivered through the PCS pump. The PCS pump was prepared with 40 ml Propofol, 2 ml Ketamine and 3ml Xylocaine. Group 2 was given 0.3 µg/kg/hr Fentanyl and 1.2 mg/kg/hr Propofol as a maintenance dose delivered through the PCS pump. The PCS pump was prepared with 40 ml Propofol, 2 ml Fentanyl and 3 ml Xylocaine.

After the 5th minute of sedation, 4 mL of local anesthetic [4% Articaine with 1/100 000 Adrenaline, 2 mL; Ubistesin™ Forte (**3M Deutschland GmbH** Carl-Schurz-Strasse 1 DE-41453 Neuss Germany)] was given to anesthetize the inferior

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alveolar, lingual and long buccal nerves. The efficacy of the local anesthetic was assessed by verbal questioning and by gently probing the buccal and lingual surfaces of the third molar. After ensuring the profoundness of the local anesthetic, the surgical procedure began. A full thickness mucoperiosteal flap was elevated to gain access to the impacted molar. Buccal and distal bone removal was performed down to the cervical line of impaction using surgical burs mounted on motor driven straight hand piece under copious irrigation. Tooth sectioning or decapitation was done to decrease the resistance, and a point of application was made. A suitable elevator was then applied to the application point to deliver the impacted tooth. The wound was then irrigated using warm saline to remove any debris. Then the wound was closed by interrupted sutures using (000) vicryl. All operations were done by the same surgeon using the same technique.

Throughout the study blood pressure, pulse rate, peripheral oxygen saturation (SaO2) were monitored non-invasively. Monitoring was done and recorded before the procedure, and was repeated every 5 minutes throughout the procedure. Assessment of sedation level was recorded at the 5th minute of sedation using modified five-levelled sedation scale (Table 1) (22).

Table 1: Picture showing sedation level scale.

Sedation Scale	Definition
1	Fully awake and oriented
2	Drowsy, eyes open
3	Drowsy, eyes closed but rousable
4	Drowsy, eyes closed arousable on mild stimulation
5	Unarousable on mild physical stimulation

To evaluate the patient's opinion about the procedure under sedation a modified visual analogue scale from 0 to 10 was applied (0 is totally calm & 10 is worst fear imaginable) (Fig. 2) (23).

Figure 2: Picture showing modified visual analogue scale.

Assessment was repeated every 10 minutes throughout the procedure. The condition of the patient during the surgery under PCS was evaluated by the surgeon on a scale from 1 to 5 (1= patient is calm and cooperative and 5= patient is very nervous and very resistant towards the procedure). Assessment was recorded on the injection of the local anesthetic and during the operation. An object was shown to the patients after 20 minutes of sedation, they were asked to identify it and identify its colour. To evaluate the level of amnesia at 60 minutes and one week post-operatively, the patients were asked whether they remember the injection of the local anaesthetic, the operation and the suturing. They were also asked whether they remember the object that they had been shown during the procedure or not.

The patients were observed for any adverse reactions such as, nausea, vomiting, hallucinations, involuntary movements or drowsiness. The numbers of presses recorded by the digital counter were documented to evaluate the efficiency of sedation.

The collected data were revised, coded, tabulated and introduced to a pc using statistical package for social science (SPSS 22.0 for windows; IBM USA).

Description of quantitative (numerical) variables was performed in the form of mean ± SD. Description of qualitative (categorical) data was performed in the form of number of cases and percent. Error bars represent 95% confidence interval. Analysis of unpaired numerical variable was performed using the unpaired Student t-test, whereas analysis of paired numerical variables was performed.

Results

The study was conducted on 20 patients [14 males (70%) and 6 females (30%)]. The minimum age was 18 years; maximum was 34 years with a mean age of 24.6 ± 4.2 years. Patients were randomly divided into two equal groups, Group 1 (Ketamine – Propofol group): consisted of 10 patients distributed as 10 males and no females. The mean age was 23.4 ± 5.5 years. Group 2 (Fentanyl – Propofol group): consisted of 10 patients distributed as 4 males and 6 females. The mean age was 25.8 ± 3.9 years.

Preoperative heart rate value was recorded for all the patients in each group and considered as the base line value. There was insignificant increase in the intra-operative value when compared with the preoperative heart rate in both groups (Table 2, 3).

Table 2: Showing group 1 Pre-operative and Intra-operative mean heart rate values.

Time / Group	Pre-operative		Intra-operative	
	Mean	± SD	Mean	± SD
Ketamine-Propfol	71.6	11.9	71.9	8.8
Mean differences	Pre-operative – Intra-operative			
P-value	0.9342			

Table 3: Group 2 Pre-operative and Intra-operative mean heart rate values

Time / Group	Pre-operative		Intra-operative	
	Mean	± SD	Mean	± SD
Fentanyl-Propfol	73.9	13.7	75.2	10.19
Mean differences	Pre-operative – Intra-operative			
P-value	0.8061			

On comparing the two groups together by using the t-test, there was no statistically significant difference between the mean heart rate in the two groups (Fig. 3).

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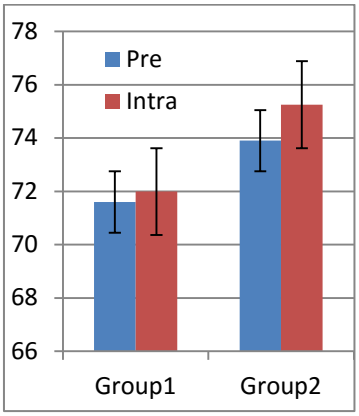

Figure 3: Graph comparing mean preoperative and intra-operative heart rate values between two groups. Bars represent Mean±SD

The preoperative systolic blood pressure was recorded for the patients in each group and was considered as the baseline value. There was insignificant decrease in the intra-operative values when compared with the preoperative SBP in both groups (Table 4, 5).

Table 4: Group 1 Pre-operative and Intra-operative mean systolic blood pressure values

Time / Group	Pre-operative		Intra-operative	
	Mean	± SD	Mean	± SD
Ketamine-Propfol	121.9	11.4	117.8	7.05
Mean differences	Pre-operative – Intra operative			
P-value	0.3497			

Table 5: Showing: group 2 Pre-operative and Intra-operative mean systolic blood pressure values.

Time / Group	Pre-operative		Intra-operative	
	Mean	± SD	Mean	± SD
Fentanyl-Propfol	116.6	14.1	111.6	7.05
Mean differences	Pre-operative – Intra-operative			
P-value	0.3949			

On comparing the two groups together by using the t-test, there was no statistically significant difference in the mean systolic blood pressure between the two groups (Fig 4).

Preoperative diastolic blood pressure was recorded for patients in each group and was considered as the baseline value. There was insignificant decrease in the intra-operative value when compared with the preoperative DBP in both groups (Table 6, 7).

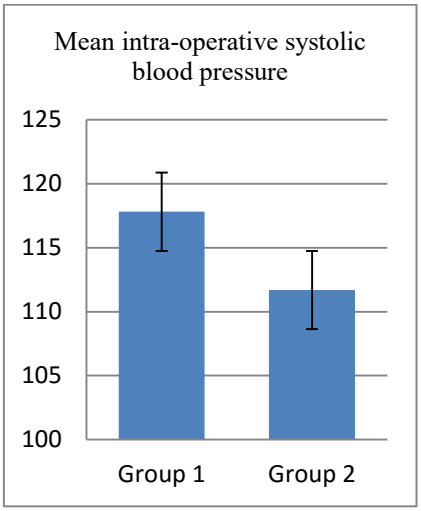

Figure 4: Graph comparing mean intra-operative systolic blood pressure values between the two groups of the study. Bars represent Mean±SD

Table 6: showing: group 1 Pre-operative and Intra-operative mean diastolic blood pressure values.

Time / Group	Pre-operative		Intra-operative	
	Mean	± SD	Mean	± SD
Ketamine-Propfol	72.5	7.7	71.4	5.4
Mean differences	Pre-operative – Intra-operative			
P-value	0.7215			

Table 7: showing: group 2 Pre-operative and Intra-operative mean diastolic blood pressure values

Time / Group	Pre-operative		Intra-operative	
	Mean	± SD	Mean	± SD
Fentanyl-Propfol	73	11	67.2	5.12
Mean differences	Pre-operative – Intra-operative			
P-value	0.1520			

On comparing the two groups together by using the t-test, there was no statistically significant difference in the mean diastolic blood pressure between the two groups (Fig 5).

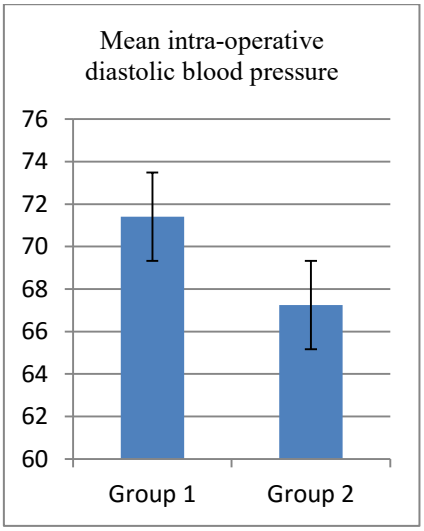

Figure 5: Graph comparing mean intra-operative diastolic blood pressure values between two groups. Bars represent Mean±SD

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There was insignificant increase in the intra-operative oxygen saturation when compared with the preoperative value in group 1, (Table 8) while there was insignificant decrease in the intra-operative oxygen saturation when compared with the preoperative value in group 2 (Table 9).

Table 8: Showing: group 1 Pre-operative and Intra-operative mean oxygen saturation values.

Time / Group	Pre-operative		Intra-operative	
	Mean	± SD	Mean	± SD
Ketamine-Propfol	98.9	0.9	99.2	0.4
Mean differ.	Pre-operative – Intra-operative			
P-value	0.3549			

Table 9: showing: group 2 Pre-operative and Intra-operative mean oxygen saturation values.

Time / Group	Pre-operative		Intra-operative	
	Mean	± SD	Mean	± SD
Fentanyl-Propfol	99	0.6	98.7	0.46
Mean differ.	Pre-operative – Intra-operative			
P-value	0.3711			

On comparing the two groups together by using the t-test, there was statistically significant difference in the mean oxygen saturation between the two groups where [*P* value = 0.0331] (Table 10).

Sedation level was assessed by the anaesthesiologist at the 5th minute of sedation, with all patients in both groups falling in the mild to moderate level of sedation. None of the patients in both groups were under sedated or fell into a level of deep sedation (Table 11).

1, and 2.52 ± 3.1 for Group 2 (Fentanyl – Propofol group). On comparing the two groups together by using the t-test, there was no statistically significant difference in the mean score of the modified visual analogue scale between the two groups where [*P* value = 0.2859] (Table 12).

The mean surgeon's satisfaction value for Group 1 (Ketamine – Propofol group) was 1.4 ± 0.69, and 1.6 ± 1 for Group 2 (Fentanyl – Propofol group). On comparing the two groups together by using the t-test, there was no statistically significant difference in the mean score of the surgeon's satisfaction between the two groups where [*P* value = 0.6278]. About 70% of patients in both groups were calm and cooperative throughout the procedure, while only one patient in the Fentanyl – Propofol group that became very nervous (Fig 6, 7). Evaluation of amnesia was done after 60 minutes and one week post-operatively by asking the patients if they remembered the injection of local anaesthetic, removal of bone and suturing, and if they remembered the object that had been shown to them during the surgical procedure. After 60 minutes 30 to 40 % percent of patients in both groups had some degree of amnesia, with no statistical difference between the two groups. After one week post-operatively, revaluation showed a slight increase in the degree of amnesia in both groups, but this increase was statistically insignificant.

There was no statistical difference between the two groups after one week (Table 13).

Table 10: Comparing mean oxygen saturation values of the two groups together by using the t-test. * Statistically significance

Group / Variable	Ketamine - Propfol		Fentanyl- Propfol		P
	Mean (n =10)	± SD	Mean (n =10)	± SD	
Oxygen Saturation	99.2	0.42	98.7	0.46	0.0331*

Table 11: Number of patients in each group and their sedation score.

Group / Sedation scale	Ketamine-Propofol	Fentanyl-Propofol
	No. of patients in each group	
1.Fully awake and oriented	0	0
2. Drowsy, eyes open	5	4
3. Drowsy, eyes closed but rousable	5	6
4. Drowsy, eyes closed, rousable on mild stimulation	0	0
5. Unrousable on mild physical stimulation	0	0

Table 12: Comparing mean values of the modified visual analogue score for the two groups together by using the t-test.

Group / Variable	Ketamine-Propfol		Fentanyl-Propfol		P-value
	Mean (n =10)	± SD	Mean (n =10)	± SD	
Modified visual analogue scale	1.38	1	2.52	3.1	0.2859

Table 13: Showing the number of the patients who remembered the intra-operative events and the object shown after 60 min and 1 week (n = 10 in each group).

	After 60 minutes		P-value	After 1 week		P-value
	Group 1	Group 2		Group 1	Group 2	
	No. of patients			No. of patients		
Injection of local anaesthetic	6	7	0.3574	4	6	0.2674
Removal of bone and suturing	6	7	0.3574	6	5	0.3606
Object	4	6	0.2674	5	6	0.3606

The mean visual analogue scale (VAS) value for Group 1 (Ketamine – Propofol group) was 1.38 ±

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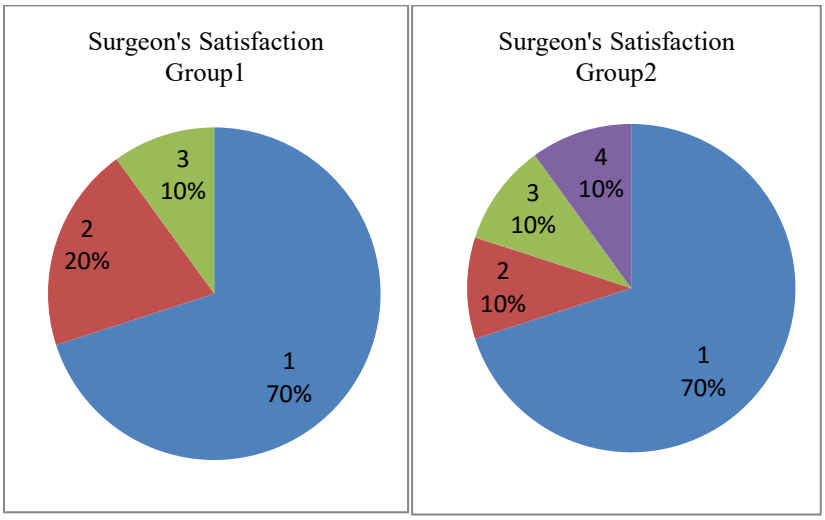

Figure 6 and 7: Pie charts showing percentage of patients in each group and their surgeon's satisfaction score. *(1= patient is calm and cooperative & 5= patient is very nervous and very resistant towards the procedure).

Table 14: Showing comparison between postoperative scores for the ball bearing test with the preoperative score for each group. * Statistically significant

	Ketamine – Propofol group		P-value	Fentanyl – Propofol group		P-value
	Mean (n =10)	± SD		Mean (n =10)	± SD	
Preoperative	18.4	3		19.4	2.1	
After 15 minutes	16.7	2.1	0.1623	17.8	2.8	0.1758
After 30 minutes	17.7	2.4	0.5795	19.5	1.2	0.8995
After 45 minutes	20.1	2	0.1571	19.5	2	0.9161
After 60 minutes	20.5	1	0.0494*	20.2	1.3	0.3239

The mean preoperative score for the ball bearing test for Group 1 (Ketamine – Propofol group) (Table 14) was 18.4 ± 3. There was a statistically insignificant decrease in the 15 minutes postoperative mean score of the ball bearing test 16.7 ± 2.1 when compared to the preoperative score, where [*P* value = 0.1623]. also there was a statistically insignificant decrease in the 30 minutes postoperative mean score of the ball bearing test 17.7 ± 2.4 when compared to the preoperative score, where [*P* value = 0.5795]. There was a statistically insignificant increase in the 45 minutes postoperative mean score of the ball bearing test 20.1 ± 2 when compared to the preoperative score, where [*P* value = 0.1571]. On the other hand there was a statistically significant increase in the 60 minutes postoperative mean score of the ball bearing test 20.5 ± 1 when compared to the preoperative score, where [*P* value = 0.0494].

The mean preoperative score for the ball bearing test for Group 2 (Fentanyl – Propofol group) (Table 14) was 19.4 ± 2.1. There was a statistically insignificant decrease in the 15 minutes postoperative mean score of the ball bearing test 17.8 ± 2.8 when compared to the preoperative score, where [*P* value = 0.1758]. Also there was a statistically insignificant increase in the 30 minutes postoperative mean score of the ball bearing test 19.5 ± 1.2 when compared to the preoperative score, where [*P* value = 0.8995].

There was a statistically insignificant increase in the 45 minutes postoperative mean score of the ball bearing test 19.5 ± 2 when compared to the preoperative score, where [*P* value = 0.9161]. Also there was a statistically insignificant increase in the 60 minutes postoperative mean score of the ball bearing test 20.2 ± 1.3 when compared to the preoperative score, where [*P* value = 0.3239] (table-14).

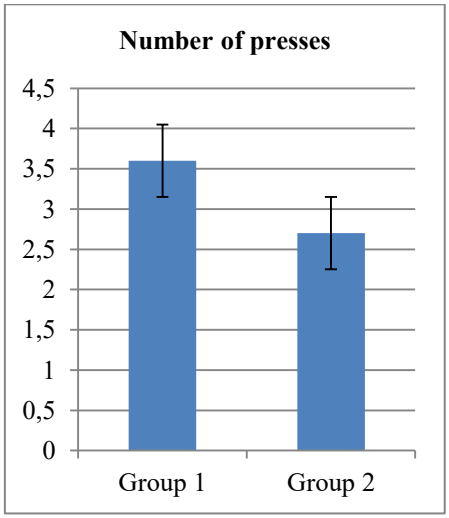

Figure 8: Graph showing the mean number of presses in both groups

The mean number of pump presses for Group 1 (Ketamine – Propofol group) was 3.6 ± 2.6, and 2.7 ± 4.5 for Group 2 (Fentanyl – Propofol group) On comparing the two groups together by using the t-test, there was no statistically significant difference in the mean number of presses between the two groups where [P value = 0.5932] Fig (8).

None of the patients in this study suffered from any adverse reactions such as, nausea, vomiting, hallucinations, involuntary movements, or over-sedation.

Discussion

Procedural sedation and analgesia refers to the technique of administering sedatives or dissociative agents with or without analgesics to induce an altered state of consciousness that allows the patient to tolerate painful or unpleasant procedures while preserving cardio-respiratory function. (24) Sedation depths of "mild," "moderate," and "deep" levels of altered consciousness are frequently cited in the medical literature (25).

Moderate sedation, previously known as conscious sedation, is a pharmacologically induced depression of consciousness during which patients respond purposefully to verbal commands, either alone or accompanied by light tactile stimulation. No interventions are required to maintain a patent airway, and spontaneous ventilation is adequate. Cardiovascular function is usually maintained. (24) (25) (26)Several methods can be used to produce conscious sedation. One of these, patient-controlled sedation (PCS), provides adequate sedation for patients' requirements and enables the patient to vary the degree of sedation depending on the degree of stress caused by the procedure and environment. (27) (28). It provides the opportunity to titrate the drug to individual patients' requirements by setting the dose given as a bolus with "lockout period" between successive bolus doses to avoid the risk of over sedation. Irwin et al (29) stated that as with any bolus-based concept, PCS may produce unwanted peak effects and an unstable sedation profile, which can be avoided using a basal infusion giving the patient the option to have some boluses.

In the present study the surgical removal of impacted lower third molars was chosen to evaluate the efficiency and safety of ACCUFUSER® ELASTOMERIC INFUSION DEVICE in patient-controlled sedation (PCS) as the third molar operations are the most painful , highly distressing and belongs to the top 5 most fear-evoking treatment procedures in dental situations.

Propofol sedation is used frequently in local and regional anaesthesia has the advantages of rapid awakening and minimal nausea and/or vomiting, its analgesic activity is insufficient; moreover, it may cause respiratory and cardiovascular depression (13). to achieve better analgesia propofol is combined with fentanyl (14)and sub-anesthetic dose of Ketamine (17) (19) ketamine-propofol and fentanyl-propofol combinations were evaluated in patients undergoing lower third molar surgery with respect to sedation, hemodynamic stability, side effects, recovery of psychomotor functions, and patient and surgeon satisfaction.

Both groups showed hemodynamic stability throughout the procedure, with insignificant increase in the mean heart rate value and insignificant decrease in the systolic and diastolic blood pressure with respect to the preoperative values. Changes in the heart rate, though not statistically significant, were elevated in each group due, in part, to the use of 1/100 000 Adrenaline local anaesthetic.

It is accepted that induction of anaesthesia with propofol is associated with significant decreases in arterial blood pressure due to its vasodilating effect as well as decrease in cardiac output after induction with propofol. In addition, fentanyl, known for its potential to decrease systemic vascular resistance, probably contributed to the cardiovascular effect of the drugs used in this study. The addition of low dose ketamine has been shown to attenuate the cardiovascular and respiratory depressing effect of propofol (21).

The most common problem encountered during patient-controlled sedation is respiratory depression, observed as decrease in the oxygen saturation. In the present study, both groups showed an insignificant decrease in the mean intra-operative values of oxygen saturation when compared to the preoperative values. The possibility for a decrease in oxygen saturation emphasizes the need for close monitoring during patient-controlled sedation, particularly when opioids are added to the sedative agents. On comparing the two groups together, the mean oxygen saturation of the fentanyl-propofol group was significantly lower than the ketamine-propofol group from a statistical point of view, while there was no clinical significance to this difference as the mean value of both groups was above the normal level of oxygen saturation.

The degree of sedation was monitored in both groups the sedation levels were mild to moderate, with no incidence of deep sedation or under sedation.

The patient satisfaction and surgeon's satisfaction are one of the most important aims of sedation. In this study, the values of the modified visual analogue scale were indicative of high patient satisfaction in both groups. The patients in both groups were cooperative and relaxed during the surgical procedure, with no statistically significant difference between the two groups, except for one patient in the fentanyl-propofol group which became uncooperative and resistant to the procedure due to increased difficulty and duration of the surgical procedure. In studies that compared anaesthetist-controlled sedation with patient-controlled sedation, found that the patients were more comfortable with patient-controlled sedation (30) (31) (32) while in another study, (33) almost an equal number preferred

each technique. In addition, the operators have assessed the operating conditions as good with good cooperation from patients (8) (31) (33) (32).

The anterograde amnesia was greater for the ketamine-propofol group than for the fentanyl-propofol group, but the difference was not statistically significant. Considering total of both groups, 60 to 70 % had some degree of amnesia at different events of the surgery. The level of amnesia may be related to the midazolam induction dose rather than the maintenance drugs used in both groups.

The psychomotor function had improved by the 45th minute postoperatively in the ketamine-propofol group and 30th minute in the fentanyl-propofol group, which allowed for early discharge of all patients from the hospital.. The preoperative scores of the ball bearing test were surprisingly found to be lower than the post-operative scores in both groups. These results were similar to those of Zuhal Küçükyavuz et al, (34) evaluating the effect of low-dose midazolam with propofol in patient-controlled sedation for apicectomy, suggesting that preoperative stress and anxiety possibly reduces the patients' concentration.

The mean number of pump presses in the fentanyl-propofol group was less than that of the ketamine-propofol group, but the difference was of no statistical significance. It has also been observed that when patients require an increment during the procedure, some press the button many times because they are so eager to receive the drug as soon as possible and to get to a deeper level of sedation, thus the number of pump presses may not be the most reliable test to evaluate the sufficiency of the sedative dose.

Conclusion

PCS can be considered as an efficient and safe option in minor oral surgeries providing the majority of patients with high satisfaction and relaxation, also providing the surgeons with good operating conditions and the cooperation of the majority of the patients. Fentanyl-Propofol and Ketamine-Propofol combinations were both safe with respect to hemodynamic changes with rapid recovery of psychomotor functions in all patients

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Clinical and pathological features of isolated pulmonary and liver recurrences in endometrial cancer

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Abstract

Objective: To present the clinic-pathological features of endometrial cancer (EC) patients with isolated liver or lung metastases and to compare the survival differences after diagnosis of recurrent disease.
Material and Methods: The clinical and histopathological data of the patients who were treated with a diagnosis of epithelial EC between January 1993 and May 2013 at Etlik Zubeyde Hanim Teaching and Research Hospital were retrospectively reviewed. Patients with isolated recurrence in liver (ILR) or lung (IPR) were included in the analysis.
Results: The clinical data of 162 patients with recurrent EC were available. Of these, 21 had IPR and 9 had ILR. Patients with ILR presented with more advanced stage, and omental and adnexal involvement was more common compared to patients with IPR. On the other hand, patients with IPR had higher grade disease. Fifty-seven percent of patients with IPR had grade 3 compared to 11% of grade 3 disease in ILR (p=0.02). The median time to recurrence (TTR) was 18 months (range 1-54) in the whole study population. While the median TTR of patients with IPR was 19 months, the median TTR of patients with ILR was 16 months (p=0.204). Both study groups have similar survival. The 1-year post-recurrence survival of IPR and ILR was 66% and 56% (p=0.129), respectively
Conclusion: Although, isolated liver and lung metastases are the result of haematogenous spread in EC, clinic-pathological features of these two recurrence patterns significantly differ. Clinicians should try to categorize these patients separately to better understand the prognostic outcomes.

Key words: Endometrial cancer, Lung metastasis, liver metastasis, haematogenous spread

Introduction

Endometrial cancer (EC) is the sixth most common cancer of women with 320.000 new cases worldwide each year (1). Although patients with EC usually present with early stage disease and have excellent long term survival, 13% of patients recur after initial treatment (2, 3). The failure of primary treatment in patients with poor prognostic factors has been reported as high as 60–70% (4). In high risk EC patients more than 70% of recurrences are complicated with extra-pelvic metastases (5, 6). Recent data suggest that death from EC is mostly due to liver and lung metastases, and this pattern of disease seems similar between low and high-risk histology for patients who died of their disease (7).

Lung is a common host for tumor recurrences and pulmonary metastases result from hematologic spread of EC. Pulmonary involvement is reported in 1.9% to 9% of the first recurrences in EC (8-12). Data on predicting factors for pulmonary recurrences are sparse. Stage IV disease and deep myometrial invasion were found to be associated with pulmonary recurrence(10).

Earlier reports revealed that pulmonary recurrences were related with adverse prognosis which was evident that 75% of patients succumb to disease in the first year of recurrence (9). On the other hand, a recent paper demonstrated that patients with low grade tumors and isolated lung metastases smaller than 2 cm may survive up to 98 months after diagnosis of recurrence (11).

The liver is a common site of metastasis for solid tumors. However the role of liver recurrence from EC is less well defined. Although, most of the previous studies presented liver metastases with other systemic metastatic disease, liver metastasis was also reported to be an independent prognostic factor for diminished survival (13). Both liver and lung metastases were thought to be the result of haematogenous spread; however it is not clear whether the clinical outcomes of these two recurrence sites correspond. In this study, we presented the clinicopathological features of EC patients with isolated liver or lung metastases and compared the survival differences after diagnosis of recurrent disease.

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Material and Methods

The clinical and histopathological data of the patients who were treated with a diagnosis of epithelial EC between January 1993 and May 2013 at Etlik Zubeyde Hanim Teaching and Research Hospital were retrospectively reviewed. Patients with isolated recurrence in liver or lung were included in the analysis. Patients with sarcomatous component in the final pathology were excluded. The revised International Federation of Gynecology and Obstetrics (FIGO) staging system was used to define the surgical stage of the patients (14). The study was approved by the local ethical committee.

Patients with recurrent disease within one month after initial surgery or completion of adjuvant therapy were accepted to have progressive disease. Patients with no evidence of disease at one month follow-up after initial surgery or completion of adjuvant therapy and that recur were included. The period from surgery to recurrence was defined as time to recurrence (TTR) and the period from recurrence to death or last visit was defined as post-recurrence survival (PRS). The period from the surgery to death or last visit defined as follow-up time.

Physical examination and radiological imaging studies were used to diagnose recurrent disease. Recurrent disease limited to liver was defined as isolated liver recurrence (ILR) and the disease limited to lung was defined as isolated pulmonary recurrence (IPR). Response to recurrence treatment was evaluated using WHO criteria (15). According to the assessment made in the first month after treatment, we defined clinical response as following: (a) complete clinical response; disappearance of the macroscopic tumor, (b) partial clinical response; shrinkage over %50 in the macroscopic tumor, (c) stable disease; macroscopic tumor shrinkage less than 50% or not less than 25% growth, (d) progressive disease; more than 25% growth in the macroscopic tumor or macroscopic appearance of new tumor foci.

Patients with complete clinical response were followed every 3 months in the first 2 years, then every 6 months for the following 3 years and then annually. Follow up routine included pelvic examination, abdominopelvic ultrasonography, complete blood count and blood chemistry. Chest X-ray was utilized yearly unless there is a clinical suspicion. Thoracic and/or abdominal computerized tomography was used when needed. Ca-125 level were utilized in the follow-up, even though they weren't used routinely.

Statistical analysis: Statistical analyses were performed using SPSS (SPSS Inc, Chicago IL, USA) version 17.0. The cut-off for statistical significance was set at $p < 0.05$. PRS estimates were determined by using the Kaplan-Meier method. Survival curves were compared using the log-rank test. The factors determining PRS after recurrence couldn't be evaluated in multivariate analysis due to the small population.

Results

The clinical data of 162 patients with recurrent EC were available. Of these, 21 had IPR and 9 had ILR. Median age at diagnosis was 60.5 (range; 40-77) years. The mean preoperative CA-125 level of patients were 80.3 IU/ml and the mean tumor size at first diagnosis was 54.4 (±30.8) mm. The most prominent histology was endometrioid EC in 24 (80%) patients and 17 (56.6%) patients had disease outside the uterus. Clinical and pathological characteristics of the study group were summarized in Table 1.

While 27 patients were left with no residual disease after initial surgery, three patients had suboptimal surgery. Of these, one had residual tumor volume of less than 1 cm and two had residual tumor volume of more than 1 cm. All of the three patients with suboptimal surgery recurred in the liver.

Four patients with IPR and one patient with ILR were treated with salvage surgery. Of these, surgically treated ILR and one of the four patients with IPR were left with no residual disease at the end of the procedures. Other two patients with IPR had suboptimal surgical procedures. Operation note of one the patient with IPR could not be reached. Palliative treatment was offered to five patients with recurrence, and all but one opted for palliation. Rest of the patients was treated with systemic chemotherapy and/or radiotherapy.

Table 2 demonstrates the comparison of surgico-pathological findings between patients with IPR and ILR. Patients with ILR presented with more advanced stage, and omental and adnexal involvement was more common compared to patients with IPR. On the other hand, patients with IPR had higher grade disease. Fifty-seven percent of patients with IPR had grade 3 compared to 11% of grade 3 disease in ILR ($p=0.02$).

Lymph node dissection in the first surgery was more common in patients with IPR than ILR ($p=0.005$). Lymph node metastasis was more prominent in patients with ILR compared to patients with IPR, however this finding was not statistically significant ($p=0.088$).

The mean age of patients with IPR was 62.5 years and the mean age of patients with ILR was 55.7 years (p=0.054) (Table 3). Both patient groups were similar regarding preoperative serum CA-125 levels, mean tumor size, tumor histology, and depth of myometrial invasion, lympho-vascular space invasion, cervical involvement, positive peritoneal cytology, lymph node counts and serum CA-125 levels at recurrence (Table 2 and 3). The median TTR was 18 months (range 1-54) in the whole study population. While the median TTR of patients with IPR was 19 months (range, 1-54), the median TTR of patients with ILR was 16 months (range, 4-36) (p=0.204). Both study groups have similar survival. The 1-year PRS of IPR and ILR was 66% and 56% (p=0.129), respectively (Figure 1).

Table 1. Clinical, surgical and pathological characteristics of patients

Characteristics		n / Mean	% / Median (range)
Age at initial diagnosis		60.4	60.5 (40-77)
Disease free interval (month)		21.3	18 (1-54)
CA 125 level at initial diagnosis (IU/ml)		80.3	29 (1-430)
Tumor size at initial diagnosis (mm)		54.5	50 (15-100)
FIGO 2009 stage	IA	2	6.7
	IB	11	36.7
	II	1	3.3
	IIIA	2	6.7
	IIIC1	3	10
	IIIC2	4	13.3
	IVA	1	3.3
	IVB	6	20
Tumor type	Endometrioid	24	80
	Serous	2	6.7
	Clear Cell	3	10
	Mixed	1	3.3
FIGO grade	1	4	13.3
	2	13	43.3
	3	13	43.3
Depth of myometrial invasion	< ½	4	13.3
	≥ ½ [1]	19	63.3
	Serosal invasion	7	23.3
Lymphovascular space invasion	Negative	11	36.7
	Positive	13	43.3
	Not reported	6	20
Cervical invasion	Negative	21	70
	Stromal	8	26.7
	Not reported	1	3.3
Peritoneal cytology	Negative	24	80
	Positive	4	13.3
	Not reported	2	6.7
Adnexal metastasis	Negative	22	73.3
	Positive	8	26.7
Omental metastasis	Negative	21	70
	Positive	5	16.7
	Not reported	4	13.3
Lymphadenectomy at initial surgery	Not performed	3	10
	Performed	27	90
Number of harvested lymph nodes		45.2	45 (4-93)
Lymph node metastasis	Negative	20	66.7
	Isolated pelvic	5	16.7
	Isolated paraaortic	3	10
	Pelvic & paraaortic	2	6.7
Adjuvant therapy	Not performed	1	3.3
	Performed	29	96.7
Type of adjuvant therapy	Radiotherapy	20	69
	Chemotherapy	7	24.1
	Sandwich therapy [2]	1	3.4
	Concomitant chemoradiotherapy	1	3.4

[1]: Except for uterine serosal invasion,

[2]: Chemotherapy followed by radiotherapy or radiotherapy followed by chemotherapy or sandwich therapy (*3 cycles paclitaxel+carboplatin followed by radiotherapy followed by 3 cycles paclitaxel+carboplatin*)

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Table 2. Comparison of surgical and pathological factors between patients with isolated pulmonary recurrence and isolated liver recurrence.

Surgico-pathological features (%)	Recurrence site		*p value*
	Isolated pulmonary recurrence	Isolated liver recurrence	
FIGO stage III&IV disease	44	89	0.027
Non-endometrioid tumor type	24	11	0.426
Performed lymphadenectomy	100	67	0.005
Metastatic lymph node	29	67	0.088
FIGO grade 3	57	11	0.02
Depth of myometrial invasion ≥ 1/2	81	100	0.16
Positive LVSI	47	71	0.276
Positive cervical invasion	19	50	0.096
Positive peritoneal cytology	10	29	0.212
Adnexal involvement	14	56	0.019
Omental metastasis	10	50	0.029

Table 3. Recurrence site and clinical, surgical and pathological factors

Characteristic	Recurrence site								p
	Isolated pulmonary recurrence				Isolated liver recurrence				
	Mean	Med.	Min.	Max.	Mean	Med.	Min.	Max.	
Age	62.5	61	52	77	55.7	54	40	77	0.054
Removed lymph node number	46.1	48	4	93	41.8	45	8	65	0.759
Tumor size (mm)	53.5	50	15	100	57.5	52.5	25	100	0.832
Preoperative CA125 level (IU/ml)	79.1	28.5	1	430	83.2	29	11	195	0.946
CA125 level at recurrence (IU/ml)	291.4	23	1	3150	220	120	15	650	0.812
Time to recurrence (month)	23.5	19	1	54	16.1	16	4	36	0.204
Follow-up time (month)	39	36	6	108	27.4	23	6	67	0.215

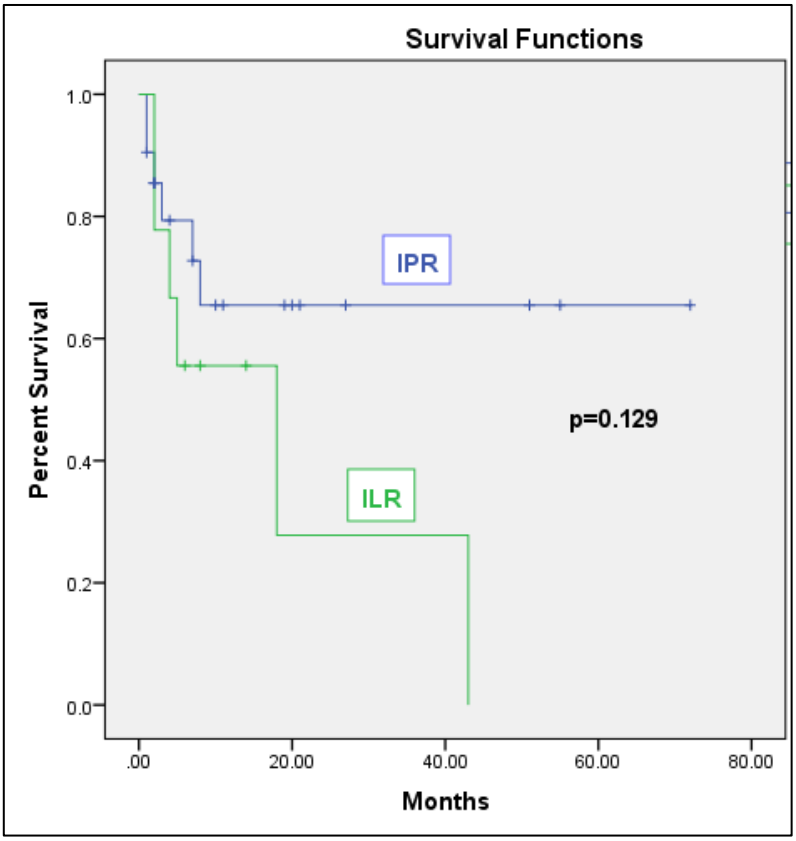

Figure 1. Post-recurrence survival of patients with isolated lung (ILR) and liver (IPR) recurrences.

Discussion

In this retrospective chart review, we presented the outcomes of 30 recurrent EC cases with isolated metastases in liver or lung. Common characteristics of our study group were deep myometrial invasion of the primary tumor (63.3%), advanced disease at first diagnosis (53.3%), and a combination of various high risk features which necessitated an adjuvant treatment modality in 96.7% of the patients. Isolated metastatic disease in lung (IPR) was more common than metastatic liver disease. When we compared the surgicopathological features of IPR and ILR, we found that patients with ILR had statistically significant more advanced disease and omental metastases than patients with IPR. These results show that these two hematogenous spread patterns may be associated with distinct surgicopathological risk factors. Although, survival outcomes of both groups were similarly poor which result into death of more than 40% of the patients at the end of the first year of recurrence, ILR had a statistically non-significant worse prognosis than IPR (p=0.129).

EC usually disseminates with the lymphatic route and hematogenous dissemination is less common. The risk of distant metastases ranges between 4% and 12% and isolated distant failure risk is 4-6% (16). Hematogenous spread in EC include metastases to lungs, liver, bones, brain, spleen, pleura, adrenals and brain (17). Of these, pulmonary metastasis is the most common one which is observed in 2.3% to 8.3% of the cases (18). Previous studies have shown that risk factors for the development of pulmonary metastases in EC were older age, advanced stage disease or higher tumor grade, deep myometrial invasion and involvement of paraaortic lymph nodes or vagina (18). These findings were similar to our results in the current study. Our study group was mainly consisted of patients with stage III or IV and IPR group had higher grade disease than ILR group. The mean time IPR in our study was 23.5 months which represents a figure lying in the lower end of previously reported range 27 to 45.5 months (18). 1-year PRS of IPR group in our study was 66% which was higher than the literature. Although, we could not perform a subgroup analysis to reveal the prognostic factors related with survival, this somewhat favorable survival may be the result of selection of isolated lung recurrences in our study. Most of the studies in the literature which reported poor survival in patients with lung recurrences include patients with multiple distant metastases (9). Optimal management of patients with pulmonary involvement is not clear. While, the fundamental surgical oncology doctrine supports resection of solitary nodules and oligo metastatic disease, patients with multiple, bilateral nodules and/or other systemic disease should be encouraged for participation in clinical trials.

Solid tumors frequently metastasize to the liver. Although, autopsy series have shown that 50% of patients who died of EC will demonstrate hepatic involvement (19), data on the treatment of metastatic disease of EC origin is sparse. In our study group only one patient with ILR were treated with surgery while other patients received systemic chemotherapy. This finding may reflect the effect of historical reports against the surgical treatment of non-colorectal liver metastases which have shown no 5-year survivors after hepatic resection (20). However, recent data revealed favorable outcomes for hepatic resections particularly in the case of isolated liver metastases (21). In the absence of well-structured guidelines, Knowles et al. (21) suggested to use the criteria used for the resection of colorectal metastases and to refer these patients to special hepatobiliary units.

This study has several drawbacks including small sample size and retrospective study design. Long term follow-up in a single tertiary center with major experience is the strong aspect.

Conclusion

In conclusion, both liver and lung metastases were thought to be the result of hematogenous spread, however it is not clear whether the clinical outcomes of these two recurrence sites correspond. Further studies are needed to elucidate the risk factors of IPR and ILR and the prognostic factors related with the treatment. .

Conflict of Interest: The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Evaluation of some tumor markers, acute phase proteins, sialic acid and lipid bound sialic acid before and after chemotherapy in patients with stomach cancer

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Abstract

Objective: It was aimed to compare the some tumor markers, acute phase proteins, sialic acid and lipid bound sialic acid levels in patients with stomach cancer before and after chemotherapy to the healthy controls

Material and Methods: Forthy-eight patients with stomach adenocarcinoma and 20 healthy controls, totally 68 subjects were used. Blood samples were taken from all patients before and after chemotherapy and controls to analyze the levels of tumor markers (CA 125, CA 15-3, CA 19-9, CEA), acute phase proteins (CRP and fibrinogen) and SA (sialic acid), LSA (lipid bound sialic acid).

Results: Before chemotherapy the serum levels of CA 125, CA 15-3, CA 19-9, CEA SA, LSA, CRP and fibrinogen (107.30 U/ml, 65.74 U/ml, 295.86 U/ml, 108.57 ng/ml, 199.60 mg/dl, 41.89 mg/dl, 86.03 mg/l and 469.42 mg/dl) were higher than after chemotherapy group (36.46 U/ml, 34.00 U/ml, 100.18 U/ml, 20.20 ng/ml, 87.67 mg/dl, 31.06 mg/dl, 57.04 mg/l and 379.04 mg/dl) and the controls (8.64 U/ml, 21.65 U/ml, 21.52 U/ml, 2.77 ng/ml, 73.75 mg/dl, 27.47 mg/dl, 2.37 mg/l, 303.5 mg/dl).

Conclusion: The serum levels of SA and LSA may be considered the indicators of poor/good prognosis of stomach cancer. CRP and fibrinogen are suggested as available biomarkers for diagnosis and prognosis in patients with stomach cancer.

Key words: Acute phase proteins, sialic acid, lipid bound sialic acid, stomach cancer, tumor markers

Introduction

The prevalence of stomach cancer has shown differences among the countries. It is still in the second rank at the cancer deaths in the world despite the clear decrease in its prevalence. The stomach cancer is the most commonly case in Van and its vicinity (1). Because the stomach cancer is a insidious disease, it is difficult to understand its etiology, there are many studies on the biomarkers or tumor markers to support the diagnosis. Tumor markers which have different characteristics such as glycoprotein and glycolipid show specific features for many organ cancers. They help to diagnose the cancer and also help to estimate the good and poor prognosis of the cancer patients. The origin of marker can even be the ectopic hormon synthesis, oncofetal antigens and the metabolic products of neoplastic cell or the answer of the patient to the tumor development (2). The qualitative or quantitative chemical, molecular biological or immunologic methods can be used for the diagnosis of cancer.

They are valuable than the other diagnostic tools for determining the early stage of tumor. Today, it was proved that the tumor markers like CEA, CA 15-3, CA 125, CA 19-9 have important places in clinical use for some cancers (3).

The sialic acid, a monosaccharide with negative charge of 9 carbons, has many functions such as protecting the structures of cell membranes and glycoproteins, cell to cell interactions, membrane transport, binding molecule in membrane receptors, effects in the blood glycoprotein structure, regulating the permeability in basal membrane of glomerules (4). The abnormal glycosylation process in tumor cells increases the sialic acid level in the surface of malignant and trasformed cells by contributing to the biosynthesis of carbohydrate structure. Some studies showed that cell form, cell stickness and the growth rate affect the sialic acid content of the cell (5). The ratio of carbohydrate synthesis in the growing cells was found relatively high when compared with the un-grown cell (6).

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Acute phase proteins are mostly synthesized by hepatocytes in response to pro-inflammatory cytokines to tissue injury and infections. CRP, fibrinogen, haptoglobin, complement factors, ceruloplasmin, ferritin and serum amiloid A can be taken into account as acute phase proteins (7). CRP is produced by liver within 6 hours of an acute inflammation by the direct stimulation of IL-6. It is a pentraxin protein which has Ca-dependent ligand binding. The relation between IL-6 and CRP were shown in various types of cancer. CRP was important in poor cancer prognosis and metastasis (8,9). Some researches were found that fibrinogen, blood clotting factor, can be a good tumor marker in pancreas, esophagus and stomach cancers (10-12).

In this study, it was aimed (i) to compare the tumor markers, acute phase proteins, sialic acid and lipid bound sialic acid levels of the stomach cancer patients before and after chemotherapy; (ii) to evaluate the importance of sialic acid and lipid bound sialic acid for gastric cancer.

Material and Methods

Patients and Blood Sampling

Totally 48 patients (33 male and 15 female, age of 45-76) diagnosed as stomach cancer in Yuzuncu Yıl University Faculty of Medicine Oncology Clinic and 20 healthy controls (12 male and 8 female, age of 35–64) were chosen to the study. Stomach adenocarcinoma was diagnosed by endoscopic biopsy in all the patients. The cancer were ranked into stages by lung graphy, abdominal computed tomography, biochemistry, hemogram and if needed magnetic resonans. The patients who are in localised stages were excluded from the study because they were chosen for surgical treatment. The advanced local and metastatic cancer patients were chosen to study because they were the candidates for systematic chemotherapy. Blood were taken before starting treatment and then cisplatin and 5-flourouracil based chemotherapy was started orally or intravenously. After it was repeated 3-4 times in two or three weeks, according to the chemotherapy protocols.

Cisplatin-5 FUFA (5Flourouracil-Folinic acid) was given biweekly or cisplatin-UFT (uracil tegafur) was given once in 21 days. Responses of all patients to this chemotherapy were investigated clinically and radiological after 3-4 cures. Chemotherapy protocol is listed in table 1- 2.

Blood samples were taken from all patients into the non-anticoagulant and sodium citrate tubes after the chemotherapy. They were centrifuged for 10 minutes in 2500 rpm, sera and plasma were separated.

Measurement of SA, LSA, Tumor Markers and Acute Phase Proteins

The levels of serum SA (13, 14) and LSA (15, 16) were determined spectrophotometrically. The LSA level were calculated by using calibration curve (13-17). The serum CA 125, CA 15–3, CA 19–9, CEA tumor marker levels were determined in autoanalyzer with chemiluminescent immunoassay method by using commercial kits (Immulite 2000 DPC, LosAngeles, USA) (18). The serum CRP measurement was done by nefelometer (Dade Behring, Model BN II) by using hsCRP kit (19,20) Plasma fibrinogen levels were determined by Clauss Clotting Method with STA Compact (21).

Statistical analysis: Statistical analyses were performed using SPSS (SPSS Inc, Chicago IL, USA) version 17.0. The statistical analyses were done by Wilcox Test and Mann Whitney-U Test.

Results

The levels of tumor markers (CA 125, CA 15–3, CA 19–9 and CEA), SA, LSA and the acute phase proteins (CRP and fibrinogen) of the stomach cancer patients and the controls before and after chemotherapy are shown in Table 3.

The levels of CA 125, CA 15–3, CA 19–9, CEA, SA, LSA, CRP and fibrinogen were found higher than the controls. They were declined after the chemotherapy but still high. As seen in table 3, there were statistical importances among the groups.

While serum level of CA 125 was found as 107.30 U/ml before chemotherapy and diminished to 36.46 U/ml after chemotherapy. The serum level of CA 125 of the control group was found as 8.64 U/ml.

The serum levels of CA 15-3 before chemotherapy in stomach cancer patients were higher (65.74–21.65 U/ml) than that of both the controls and after chemotherapy.

While the serum levels of CA 19-9 in stomach cancer patients were found higher compared than that of the controls (295.86-21.52 U/ml; $p<0.05$), this value was dropped to100.18 U/ml after chemotherapy and found as statistically important compared to before chemotherapy ($p<0.05$).

Before and after chemotherapy serum levels of CEA were found statistically high $p<0.001$ and $p<0.01$, respectively when compared to the controls. After chemotherapy serum levels of CEA (20.20 ng/ml) were found statistically low ($p<0.01$), when compared to before chemotherapy (108.57 ng/ml).

It was determined that the serum levels of SA were higher significantly (199.60 mg/dl–73.75 mg/dl; $p<0.001$) before chemotherapy when compared to the controls. While the level of SA was statistically lower after chemotherapy (87.67 mg/dl) compared to before chemotherapy groups.

Table 1. Chemotherapy protocol

	Total dosage	Application days	Application method
Cisplatin 30 mg/m^2	*	D1–2	Infusion for two hours in 1000 ml isotonic.
Folinic acid 20–35 mg/m^2	*	D1–2	Infusion for 30 minutes in 150 ml isotonic
Flourouracil 400 mg/m IV bolus+1000 1500 mg/m^2 IV infusion	*	D1–2	Dosage which should be applied after bolus dosage infused for 3-4 hours in 500 ml %5 D (Dextrose)

* Body mass index of patients were calculated according to their length and weight ratio. The drug dosage was given as mg per square meter.
1-Cisplatin 30 mg/m^2; two days intervals
Folinic acid 30 mg/ m^2; two days intervals
5FU 1000 mg/ m^2 ; two days intervals as biweekly

Table 2. Chemotherapy protocol

	Total dosage	Application days	Application method
Cisplatin 60-75mg/m2	*	D1–2	Infusion for two hours in 1000 ml isotonic
UFT tablet 300mg/m2	*	D1–14	It was taken in the morning and evening after meal.

* Body mass index values of the patients were calculated according to their length and weight ratio. The drug dosage was given as mg per square meter.
2-Cisplatin 60mg/m^2 D1
UFT 300mg/m^2 D1-14 (once in 21 days)

Table 3. Tumor markers, SA, LSA and the acute phase protein levels in the control group and the stomach cancer patients

	Control (n=20)	**Before Chemotherapy (n=48)**	**After Chemotherapy (n=24)**			
	X±SD	**X±SD**	**X±SD**	**A**	**B**	**C**
CA 125 (U/ml)	8.64 ± 4.45	107.30 ± 140.11	36.46 ± 51.45	p<0.001	p<0.05	p<0.01
CA 15-3 (U/ml)	21.65 ± 11.96	65.74 ± 76.47	34.00 ± 43.05	p<0.01	p=0.494	p<0.01
CA 19-9 (U/ml)	21.52 ± 7.78	295.86 ± 382.85	100.18 ± 278.05	p<0.05	p=0.054	p<0.05
CEA (ng/ml)	2.77 ± 1.60	108.57 ± 162.21	20.20 ± 42.22	p<0.001	p<0.01	p<0.01
SA (mg/dl)	73.75 ± 7.57	199.60 ± 7.64	87.67 ± 13.19	p<0.001	p<0.001	p<0.001
LSA (mg/dl)	27.47 ± 2.91	41.89 ± 5.98	31.06 ± 3.64	p<0.001	p<0.01	p<0.001
CRP (mg/l)	2.37 ± 1.45	86.03 ± 2.16	57.04 ± 75.45	p<0.001	p<0.001	p=0.054
Fibrinogen (mg/dl)	303.50 ± 58.22	469.42 ± 131.10	379.04 ± 114.39	p<0.001	p<0.01	p<0.01

A. Mann Whitney U Test results between the control and before chemotherapy group values
B. Mann Whitney U Test results between the control and after chemotherapy group values
C. Wilcox Test results between the before and after chemotherapy groups

Discussion

The serum levels of LSA were elevated significantly (41.89 mg/dl–27.47 mg/dl) before chemotherapy when compared after chemotherapy and control group. The level of LSA was significantly reduced after chemotherapy (31.06 mg/dl) when compared to before chemotherapy groups and the controls (p<0.01).

The level of CRP was higher before chemotherapy (86.03 mg/l- 2.37 mg/l; p<0.001) compared to the controls. Despite that it decreased down to 57.04 mg/l after chemotherapy, it still remained statistically higher when compare to the controls. The levels of fibrinogen were 469.42 mg/dl and 379.04 mg/dl before and after chemotherapy. Significantly differences were found between the groups.

Cancer is one of the severe disease cause death and mostly diagnosed at the latest stage or during metastasis. Therefore, early diagnosis is an important factor for the treatment and prognosis. CEA ve CA 19-9 and CA 125 can be used for the prediction of the stage and prognosis of the cancer (22, 23).

Yamamoto et al. (24) stated that CEA diagnosed and predicted the peritonal spread better than CA 125 ve CA 19-9 in stomach cancers which show peritonal spread. Takahashi (25) emphasized that CEA and/or CA 19-9 is the important biomarkers for observing the recurrence probability of stomach cancer after the operation. Webb et al. (26) stated that CEA ⩾5 mg/l and CA 125 ⩾ 350 U/l reflect the poor prognosis in

advanced stomach cancer patients before chemotherapy.

In the presented study, four different tumor markers (CA 125, CA 15–3, CA 19–9 and CEA) were measured in pre and post-treatment at stomach cancer patients and compared with the healthy controls. These tumor marker levels were determined higher before chemotherapy in stomach cancer patients. It was still found higher even there was a decrease in ongoing post-treatment level while the levels of the tumor markers were decreased following the chemotherapy. It can indicate the effectiveness of the treatment, positive improvement in prognosis and the extention of the patients' life time .

The tumor cells have got different surface charasteristics compared to the normal cells which were partly resulted from sialoglycoconjugate. The behaviors and metastatic characteristics of the cells are affected by them. The sialic acid level in malign cell surface is related with metastasis (5). Many researchers determined that total and lipid bounded sialic acid levels increased in different cancer types (27, 28). It is known that the sialic acid is necessary for cell adhesion and carries out the electrostatic impulse in thrombocyte, cancer cells and erythrocytes via the negative charge (29).

The high level of serum SA and LSA can originate from increased synthesis or sialic acid release which is found on the cell surface glycoconjugate (30). Furthermore, it was suggested that the sialic acid concealed the tumor cells or tumor specific antigens from the immunological attack, and protected the invasion and metastatic characters of malignant cells (31).

Total serum sialic acid levels increases in stomach cancer patients (32). A positive correlation was found between stage of cancer, metastasis grade and sialic acid level. The high serum sialic acid level shows poor prognosis (28,33). While Krasnodebski (34) put negative opinion for the biomarker probability of sialic acid level because of its 55.2 % sensitivity, the increased serum SA level in metastasis supports the metastatic cell existance.

As it can be seen in this study that SA and LSA levels increased in stomach cancer cases and decreased after chemotherapy. The increased levels of SA and LSA in stomach cancer were compatible with the previous literatures. The increased serum levels of SA and LSA in malignant cases must be carefully evaluated owing to the levels of them can be rised in some other diseases. Therefore, SA and LSA should be interpreted with the other markers and acute phase proteins. However, Raval et al. (35) reported that high level of SA is a sign of weak or poor prognosis of oral cavity cancer.

In other study, CRP and cytokine levels were investigated in stomach cancer patients. A correlation was found between poor prognosis and systemic inflammation. Furthermore, CRP was also related with the decrease of the patients' life span (36). Wu et al. (37) indicated that there was a moderate correlation between CRP and increased cytokine levels in stomach cancer.

Fukata et al. (38) determined that CRP level in liver cancer patients with stomach metastasis and also reported that the level of CRP was decreased following the gastrectomy. Tavaris et al. (39) evaluated the levels of CRP, transferrin, α-2 macroglobulin, ceruloplasmin, α-1 acide glycoprotein, retinol binding protein and prealbumin in 153 stomach cancer patients before surgical operation. The level of CRP was clearly higher in patients than the controls but any differences were not found in other parameters (39). It was concidered that CRP was more sensitive than the other acute phase proteins in cancer patients.

In this study, levels of CRP were found as 2.37 – 86.03 – 57.04 mg/l in all three groups (control, pre-treatment and post-treatment), respectively. The main reason of the high CRP level in stomach cancer patients is the stimulation of CRP synthesis by cytokine response to the cancer formation. The major inducer of CRP synthesis is IL-6. Likewise, Iijima et al. (40) stated that the high level of IL-6 was found in stomach cancer patients. In addition, CRP is the fastest responder of the acute phase proteins during the infection.

The high plasma fibrinogen level was found usually in malignant diseases. However, Di Micco et al. (41) showed that the fibrinogen level increased in 11 non-metastatic stomach cancer. Some studies have been done to explain the relationship between the plasma fibrinogen levels and tumor size, invasion depth and metastasis (42). While the hyperfibrinogenemia was related with cancer progression and metastasis, the low level of fibrinogen was a sign of weak metastasis (43). Yamashita et al. (12) evaluated the CEA, CRP and fibrinogen levels in the 649 operated patients with stomach cancer. They proposed that hyperfibrinogenemia could provide favorable circumstances for cancer cells to metastasize via the lymphatic system. The plasma level of preoperative fibrinogen could be a useful predictor of lymphatic metastasis in patients with intestinal-type gastric cancer.

Yamamura et al. (44) observed that fibrinogen activity was decreased in stomach cancer patients after total stomach resection. Brajerzki et al. (45) measured the plasma level of fibrinogen in patients with stomach cancer and ulcer. They could not determine any increase of fibrinogen in patients with ulcer but there was a high increase in 67% of cancer patients. Some hematological parameters such as fibrinogen,

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thrombocyte, hematocrit were investigated in 63 cancer patients, and all parameters in cancer patients were higher than the controls (46).

In this study, the fibrinogen level showed significant increase in pre-treatment group compared to the other two groups. The values of fibrinogen levels were at normal margins because the laboratory measurement intervals were 300–400 mg/dl. Our results with regard to fibrinogen level were compatible with investigated literatures. Likewise, Wang et al. (47) recommended that fibrinogen was related with cancer diagnose and prognose like the other parameters.

Conclusion

As a consequence, significant increases were determined in the serum levels of CA 125, CA 15-3, CA 19-9, CEA, SA, LSA, CRP and fibrinogen of patients with stomach cancer. It is strongly emphasized that SA and LSA may be considered as tumor markers, and also acute phase proteins such as CRP and fibrinogen should be used for diagnosis and prognosis in patients with stomach cancer before and after chemotherapy.

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Admission Characteristics and Outcomes of ED Patients With Rhabdomyolysis

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Abstract

Objective: Rhabdomyolysis is a potentially life-threatening syndrome characterized by muscle necrosis and the release of potentially toxic intracellular muscle constituents into the circulation. Acute kidney injury (AKI) is the most important complication of rhabdomyolysis and is associated with increased risk of all-cause mortality. The main objectives of this study were (1) to characterize the most common etiologies of rhabdomyolysis and (2) to determine the complications and outcomes (rhabdomyolysis-induced AKI, need for renal replacement therapy [RRT] and, 28-day mortality) in our sample.
Material and Methods: This retrospective, cross sectional and single-center study was conducted in the ED of university hospital between January 1, 2013, and December 31, 2013. We analyzed the clinical spectrum and evaluated the complications and outcomes for each patient.
Results: Forty-three eligible cases were enrolled in the study. The mean age was 52.0±21.9 years (range 16 to 92), and 81.4% were men. The two most common causes of rhabdomyolysis in this sample were trauma and infections (n=16; 37.2% and n=12; 27.9%, respectively). AKI occurred in 23 patients (53.4%), 13 of whom (30.2%) required RRT. All-cause 28-day mortality rate was 44.2% (n=19). The nonsurvival group had significantly increased peak creatinine level, increased phosphate level, and prolonged aPTT (P <.001, P =.003, and P =.001, respectively).
Conclusion: A substantial proportion of patients with rhabdomyolysis developed the complications of AKI and required RRT. Early recognition and aggressive fluid replacement should be considered for ED patients with rhabdomyolysis.

Key words: Rhabdomyolysis, acute kidney injury, renal replacement therapy

Introduction

Rhabdomyolysis is a potentially life-threatening syndrome characterized by muscle necrosis and the release of potentially toxic intracellular muscle constituents, including creatine phosphokinase (CK), myoglobin (Mb), electrolytes, lactate dehydrogenase, aldolase, alanine aminotransferase, and aspartate aminotransferase into the blood circulation (1-7).

There are numerous potential causes that can lead to rhabdomyolysis (eg, trauma and muscle compression, infections, myotoxins and drugs, marked exertion, prolonged immobilization, metabolic disorders, endocrine disorders, genetic disorders, hypothermia or malignant hyperthermia, seizure, acute extremity compartment syndrome, high-voltage electrical injury, or electrolyte abnormalities) (1-11). Although the causes are multiple, the final common pathway for injury is an increase in intracellular free ionized cytoplasmic and mitochondrial calcium. This may be caused by depletion of ATP, the cellular source of energy, and/or by direct injury and rupture of the plasma membrane and the release of aforementioned muscle constituents into the blood circulation (5,12).

Acute kidney injury (AKI) is the most important and serious complication of rhabdomyolysis independently of its etiology (12,13). Although it is widely accepted that AKI is caused by Mb deposition in the kidney, the mechanism by which it occurs is not clearly understood. The current consensus is that AKI is due to the combined effects of hypovolemia, aciduria, and direct cytotoxicity due to accumulation of renal tubular Mb (8,12-15). It has been reported that 10-40% of patients with rhabdomyolysis develop AKI, and that 5-15% of cases of AKI are attributable to rhabdomyolysis (9,13) Especially, the risk of

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rhabdomyolysis-induced AKI is higher in patients with CK levels at admission more than 5000 IU/L (16).

Although many case reports appear in the literature on rhabdomyolysis from Turkey, to the best of our knowledge, this is the first study to analysed the clinical spectrum, prevalence of various etiologies, and explored the frequency of AKI in adult patients with rhabdomyolysis that presented to the emergency department (ED) (17,18). The two main goals of this study were as follows: 1) to characterize the most common etiologies of rhabdomyolysis in our ED patients, 2) to determine the rhabdomyolysis-induced AKI, treatment modalities, and mortality in this sample. We believe that the present study will be useful and salutary for the progress of literature

Material and Methods

Study design and setting

This retrospective, single-center, cross-sectional study was conducted at the ED of university hospital (Manisa, Turkey) between January 1, 2013, and December 31, 2013. The annual number of adult ED patient visits is approximately 40,000 per year. Upon approval from the local ethics committees (Reference number 20478486-53), this study was conducted according to the Principles of the Declaration of Helsinki of 1975, as revised in 1983. The need to obtain written consent informs was waived because of the retrospective nature of the study.

Data collection and patient selection

This study was a medical record review of patients 16 years or older who presented to the ED with a diagnosis of rhabdomyolysis based on their medical histories and elevated serum CK levels within 72 hours after admission to the ED. We identified potentially eligible patient visits by searching the hospital patient records database. Furthermore, the hospital information system database was also searched to identify all of the serum CK levels above 5000 IU/L. We excluded patients who had 1) an age younger than 16 years 2) an elevated CK levels associated with an acute coronary syndrome (ST-elevation or non–ST-elevation myocardial infarction), 3) rhabdomyolysis that developed after admission to the hospital because of a coexisting condition or iatrogenic complication, 4) end-stage renal disease requiring haemodialysis or continuous ambulant peritoneal dialysis, 5) a cerebral vascular infarction or bleeding, and 6) a documented history of muscular dystrophy or other metabolic muscle disorder.

From all patients, the following variables were collected: age, gender, past medical history (epilepsy, hypertension, diabetes, history of renal insufficiency), medication use, recent physical exertion, recent trauma (crush injury, motor vehicle collision, fall, assault, burn, electrical injury), seizure, immobilization, dehydration, viral/bacterial illness, metabolic derangements (diabetic/ alcoholic ketoacidosis), hyper- or hypothermia, illicit drug use, vital parameters, therapeutic interventions, and length of stay (LOS) at the ED or hospital. In addition, we also obtained patients' clinical laboratory test results (initial and peak serum CK levels, white blood cell count, haemoglobin, platelet count, electrolytes, blood urea nitrogen, initial and peak serum creatinine, lactic dehydrogenase, alanine and aspartate aminotransferase, coagulation tests, and arterial blood gas values). Complications and outcomes (AKI, need for dialysis, and 28-day mortality) were recorded for each patient.

The concentrations of serum CK (reported as IU/L) were analysed using the Beckman Coulter chemiluminescent immunoassay on the Beckman Coulter Unicell DXC 800 immunoassay analyser. All serum CK values above the upper limit (1200 IU/L) were routinely assayed by dilution (10-fold), making quantitative assessment possible. The baseline serum CK, CK-MB, and creatinine value was obtained on admission in the ED; the peak serum CK, CK-MB, and creatinine value was considered as the highest level during the ED or hospital stay. In our ED laboratory, serum and urinary Mb are not routinely assessed.

Definitions

Rhabdomyolysis classically defined as a CK levels greater than five times the upper limit of normal (approximately 850-1000 IU/L) (9-19). In our study, patients with rhabdomyolysis were defined as new proposed diagnostic criteria having absolute CK levels >15.000 IU/L or CK levels >5000 IU/L and any of the following: 1) crush injury, 2) AKI or overt failure, 3) myoglobinuria, 4) acidosis, disseminated intravascular coagulation (DIC), hypocalcemia, or hyperkalemia, 5) massive muscle injury, 6) prolonged extrication or initial evaluation delayed longer than 4 hours (20). Patients with acute kidney injury were defined as the abrupt ($\leqslant$ 48 hours) reduction of kidney function: increased serum creatinine levels (absolute, $\geqslant$ 0.3mg/dl; percentage, $\geqslant$ 50%; or 1.5 fold from baseline), or oliguria (< 0.5ml/kg/h for more than 6 hours) by using the Acute Kidney Injury Network (AKIN) criteria (21). Renal replacement therapy (RRT) was defined as the use of peritoneal dialysis, haemodialysis or continuous renal replacement therapy. Indication for emergency RRT was determined by the consultant nephrologists.

Statistical analysis

All the patients were divided into two groups (survivors and non-survivors) based on their 28-day mortality. Continuous variables were expressed as mean ± SD or median (interquartile range [IQR])

according to normal or non-normal distributions. Categorical variables were presented as absolute values and percentages. The normality of data distribution was checked with Shapiro-Wilks test. Group differences in categorical variables were compared using the Pearson $\chi 2$ test. Differences in continuous variables were evaluated by the Mann-Whitney U test. For all tests, $P < .05$ was considered statistically significant. Statistical analyses were performed using SPSS software (version 20.0; SPSS Inc, Chicago, IL, USA).

Results

We identified 64 consecutive patient visits with an ED diagnosis of rhabdomyolysis over the 1-year study period. Twenty-one patients were excluded (9 had rhabdomyolysis develop only after admission as a result of another disorder; 6 cases of rhabdomyolysis occurred in patients younger than 16 years; 3 were transferred another hospital; 2 were missing data; and 1 patient on chronic dialysis). Thus, 43 patients met the inclusion criteria and comprised the study population.

In those patients with an ED diagnosis of rhabdomyolysis, the mean age was 52.0±21.9 years (range 16 to 92), and 81.4% were men. Table 1 summarizes the causes of rhabdomyolysis of patients in this study. The two most common causes of rhabdomyolysis in this sample were trauma and infections (n=16; 37.2% and n=12; 27.9%, respectively). Baseline demographic, clinical, and laboratory characteristics of the patients were described and divided according to the survival status at 28 days in Table 2. All the patients included in the study were hospitalized, total of 23 (53.4%) patients developed AKI, and 13 (30.2%) cases with AKI were treated with RRT. Rest of the patients treated with conservative treatment. All-cause 28-day mortality rate was 44.2% (n=19). Mortality was significant higher among patients who developed AKI then in patients without AKI, $P < .001$. Only 1 patient with AKI who treated with RRT discharged from the hospital with a full recovered kidney function. In addition, there was significant difference in terms of need for RRT between survivors and non-survivors groups, $P < .001$. And also, the most common cause requiring the use of RRT was infections (n = 5; 11.6%). The median hospital LOS was 5 days (IQR, 1-80) and there was no significant difference between the means of the two groups.

With regard to the admission and peak serum CK levels, there were no significant difference between the survivors and non-survivors groups (7890 ± 7353 vs. 9721 ± 19267, P= .282 and 12778 ± 8246 vs. 20515 ± 28144, P= .751). Patients who did not survived had significantly increased peak creatinine level (4.5 ± 2.0 vs. 1.7 ± 1.4, $P < .001$), increased phosphate level (5.4 ± 3.0 vs. 3.1 ± 0.9, P = .003), and prolonged aPTT (35.2 ± 13.8 vs. 24.6 ± 8.2, P = .001).

Discussion

As far as we know, this is the first clinical investigation of patients with rhabdomyolysis that presented to the ED in Turkey. In this study, we analyzed the prevalence of various etiologies, explored the frequency of AKI, and compared the demographic, clinical and, laboratory characteristics of the survivor and non-survivors adult patients with rhabdomyolysis.

The underlying causes of rhabdomyolysis are highly variable from hospital to hospital and, from country to country (22,23). In our study, trauma accounted for more than one-third (37.2%) of the causes of rhabdomyolysis. In the United States, data from the National Hospital Discharge Survey in 1995, the main underlying cause of rhabdomyolysis is alcohol intoxication, followed by illicit drug use (24). However, in the recently larger adult study from United States conducted by McMahon et al identified 2371 patients and they found the main causative factor of rhabdomyolysis was trauma (25). In another important retrospective study from Spain performed by Rodriguez et al, the researchers examined 126 patients with severe rhabdomyolysis (defined as serum CK level > 5000 IU/L), the most frequent cause was prolonged immobilization due to consumption of illicit drugs abuse (16). Interestingly, rhabdomyolysis due to illicit drugs abuse were not observed in our study of ED patients. Furthermore, in contrast to adult studies, the leading cause of rhabdomyolysis in pediatric patients is viral myositis (26,27). On the other hand, traumatic injuries are the leading cause of youth adult's morbidity and mortality in the United States and Turkey (28-32). Therefore, all emergency physicians should be aware of the association between trauma and the risk of rhabdomyolysis.

Electrolyte abnormalities are the most feared complications and are common in patients with rhabdomyolysis. Hyperphosphatemia, one of them, results from the release of inorganic phosphate from damaged muscle cells. The subsequent development of AKI and acidosis can also lead to further increases in serum phosphate. Hyperphosphatemia has been shown to be a powerful risk factor for either predicting renal failure or death in rhabdomyolysis. In our study, with regard to the admission phosphate levels, there was significant difference between the survivors and non-survivors groups. Recently, a large study conducted by McMahon et al showed that hyperphosphatemia was associated with increased risk of developing AKI and mortality even when it was mild degree (25). It remains unclear whether the relationship between hyperphosphatemia and adverse outcomes is causative or only associative.

Table 1. Causes of rhabdomyolysis

Causes	Study population (n = 43)
Trauma	16
Infections (sepsis or septic shock)	12
Vascular occlusion (embolism or thrombosis)	5
Toxins	2
Seizures	2
Malignant hyperthermia	1
Ethanol withdrawal	1
Metabolic disorders	1
Recent abdominal surgery	1
Inflammatory myopathy	1
Idiopathic	1

Table 2. Demographic, clinical and laboratory characteristics of patients with rhabdomyolysis

Variables	Survivors (n= 24)	Nonsurvivors (n= 19)	*P* value
Demographic and clinical data			
Age (y)	46.3±23.0	59.1±18.6	.056
Sex (Female/Male)	4/20	4/15	.507
AKI (%)	5 (11.6)	18 (41.8)	<.001
RRT (%)	1 (2.3)	12 (27.9)	<.001
Hospital LOS (days)	10.9±15.9	7.3±7.9	.296
Hematology profile			
White blood cell count ($x10^3/\mu L$)	13.8±6.8	15.2±6.8	.501
Hemoglobin (g/dL)	12.7±1.9	11.6±2.2	.080
Hematocrit (%)	37.2±6.1	34.7±5.2	.151
Platelet count ($x10^3/\mu L$)	200.6±82.2	169.1±91.2	.242
Coagulation profile			
INR level	1.0±0.1	1.8±1.4	.011
PT (s)	12.5±1.8	20.9±16.9	.015
aPTT (s)	24.6±8.2	35.2±13.8	.001
Serum chemistry			
Glucose (mg/dL)	152.5±74.1	159.6±94.5	.590
Blood urea nitrogene (mg/dL)	30.5±34.6	48.5±39.6	.117
Uric acit (mg/dL)	6.0±1.9	9.0±6.1	.065
Admission creatinine (mg/dL)	1.4±0.7	1.7±1.0	.031
Peak creatinine (mg/dL)	1.7±1.4	4.5±2.0	<.001
Sodium (mEq/L)	136.6±6.3	136.9±5.1	.941
Potassium (mEq/L)	4.2 ±0.6	4.7±1.1	.276
Chloride (mEq/L)	104.1±6.9	102.5±5.7	.225
Calcium (mg/dL)	8.5±0.8	8.1±1.0	.107
Phosphate (mg/dL)	3.1±0.9	5.4±3.0	.003
Magnesium (mg/dL)	1.9±0.2	2.3±0.6	.006
Admission CK (IU/L)	7890±7353	9721±19267	.282
Peak CK (IU/L)	12778±8246	20515±28144	.751
Admission CK-MB (IU/L)	233±237	316±562	.549
Peak CK-MB (IU/L)	375±372	507±624	.980
Total protein (g/dL)	6.1±1.1	5.9±0.9	.677
Albumin (g/dL)	3.4±0.7	3.1±0.5	.086
Aspartate transaminase (IU/L)	203.5±174.7	424.2±774.6	.608
Alanine transaminase (IU/L)	116.7±124.3	251.8±445.0	.633
Blood gas analysis (arterial)			
pH (pH units)	7.36±0.06	7.25±0.21	.084
HCO_3^- (mmol/L)	22.3±3.9	18.4±5.4	.009
Lactate (mmol/L)	2.7±2.9	5.2±4.5	.019
BE^{ecf} (mmol/L)	-3.3±3.3	-7.6±8.2	.082
Anion Gap (mmol/L)	2.9±4.9	3.1±5.6	.905

Data are expressed as mean ± SD or count (percentage of the 43 subjects) for categorical variables unless otherwise indicated.

Abbreviations: AKI, Acute Kidney Injury; RRT, Renal Replacement Therapy; LOS, Length of Stay; INR, International Normalized Ratio; PT, Prothrombin Time; aPTT, Activated Partial Thromboplastin Time; s, Seconds; CK, Creatine Kinase; CK-MB, Creatine Kinase-MB; pH, power of Hydrogen; BEecf, Base Excess of extracellular fluid

Coagulation studies (PT, aPTT, fibrin split products and fibrinogen) should be obtained in all suspected cases of rhabdomyolysis. Because, severe rhabdomyolysis may be associated with the development of disseminated intravascular coagulation (DIC) due to activation of the cytokine network and the release of thromboplastin and other prothrombotic substances from the damaged muscle. DIC is more frequently observed in patients with post-traumatic rhabdomyolysis with manifesting the systemic inflammatory response syndrome. Rodriguez et al found that decreased PT can confer a 4.4-fold increased risk for development of the AKI in study population (16). In our study, prolonged aPTT was found associated with increased risk of mortality.

AKI is a serious and often life-threatening complication of rhabdomyolysis and requires immediate diagnosis and emergency treatment (9,33,34). AKI is believed to be due to decreased extracellular volume, which results in renal vasoconstriction. It is also believed to be due to ferrihemate, which is formed from Mb at a pH level of 5.6 or less. Ferrihemate produces free hydroxy radicals and causes direct nephrotoxicity, often through lipid peroxidation (2,5,12,13). Previous studies on rhabdomyolysis have reported rates of AKI with or without the need for RRT ranging from 14-59% in adults (9,35). In all these studies various population settings and different definitions of AKI have been used. Consequently, the exact incidence of AKI is difficult to determine. Delaney et al recently conducted a retrospective study showing that based on the RIFLE criteria, 59% of the patients with rhabdomyolysis had AKI, most of which were prerenal.35 However, a study by Chen et al found that only 14.4% patients with rhabdomyolysis developed AKI (9). In a recent study of 521 pediatric patients with posttraumatic rhabdomyolysis, AKI occurred in 70 (13.4%) patients (36). In our study based on the AKIN criteria, total of 23 (53.4%) patients developed AKI. This suggests that various factors and conditions may play a role in the development of the AKI in patients with rhabdomyolysis.

Currently, there is no way to accurately predict or stratify mortality risk or risk of AKI among patients with rhabdomyolysis. Several studies have attempted to predict the likelihood of AKI by means of biochemical and clinical markers. In a recent study, McMahon et al developed a new risk score for predicting death or AKI in rhabdomyolysis. The independent predictors of death or AKI were age (50-70 years, 1.5 points; 71-80 years, 2.5 points; >80 years, 3 points), female sex (1 point), cause of rhabdomyolysis (origin not seizures, syncope, exercise, statins, or myositis, 3 points), and values of initial creatinine (1.4-2.2 mg/dL, 1.5 points; >2.2 mg/dL, 3 points), CK (>40.000 U/L, 2 points), phosphate (4.0-5.4 mg/dL, 1.5 points; >5.4 mg/dL, 3 points), calcium (>7.5 mg/dL, 2 points), and bicarbonate (>19 mEq/L, 2 points). Mortality rate or AKI for patients with a score under 5 was 3% and with a score over 10 was 59.2% (25). According to another recent study of 126 patients with rhabdomyolysis, the following variables on admission were independently associated with AKI; peak CK (>12.750 U/L; [odds ratio (OR), 4.9; 95% CI, 1.4-16.8]), hypoalbuminemia (<33 mg/dL; OR, 5.1; 95% CI, 1.4-17.7), metabolic acidosis (OR, 5.3; 95% CI, 1.4-20.3), and decreased PT (<82%; OR, 4.4; 95% CI, 1.3-4.5) (16).

The degree of CK elevation correlates with the degree of muscle injury, but it remains unclear if the degree of elevation corresponds to the risk for development of AKI or mortality. In a prospective observational study by Bhavsar and colleagues examined 50 patients with rhabdomyolysis due to trauma and electrical burns. They identified a cutoff value of CK 3805 U/L to be 76.5% sensitive and 87.9% specific in predicting AKI after 48 h of injury (36). In another important study performed by Brown et al reviewed the case records of 1771 trauma patients with increased CK levels. Overall 217 patients (12%) developed renal failure, with 97 requiring RRT. In this study, peak CK >5000 IU/L was associated with an increased risk of developing AKI (37). The risk of AKI is low when initial CK levels are lower than 15000-20000 IU/L. Lower CK levels may lead to renal injury in patients with sepsis, dehydration, or acidosis (13). On the other hand, in our study, neither initial nor peak value of CK were not correlated with AKI and mortality.

Our findings may help to progress of literature about rhabdomyolysis. However, the study has some limitations. First, this crosssectional study has a relatively small sample size. Therefore, future prospective and multicenter studies with larger sample sizes will be needed to validate our results. Second, the study population consisted of patients at only one center, and therefore, the outcomes may not be applicable to different socioeconomic communities. Third, we could not measure the levels of Mb in urine and blood. As a result, we could not ascertain the potential interaction effect of Mb and AKI on the selected outcomes. Fourth, it is not easy to determine accurate and definitive causes of-death in patient with rhabdomyolysis. Another limitation of our study was that we did not discuss the treatment details such as early fluid therapy, mannitol or bicarbonate therapy. Finally and the most important limitation of the current study was that the relatively small sample size may fail to address definitely predictive factors of AKI or need for RRT.

In conclusion, these data clearly demonstrate that the substantial proportion of ED patients with rhabdomyolysis developed the complications of AKI and required RRT. The all-cause mortality rate was relatively high. Increased peak creatinine level,

increased phosphate level, and prolonged aPTT were found associated with mortality. Early recognition and aggressive fluid replacement should be considered for patients with rhabdomyolysis.

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The Effect of Group-Discussion on the Nurses' Performance in Recognizing Patients' Rights

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Abstract

Objective: Group discussion enhances the knowledge and the quality of cares provided for patients and reinforces nurses' skills and diagnostic approaches. This paper, aims to study the effect of group discussion on nurses' performance in respecting the rights of patients staying in Madani Hospital in Tabriz Iran in 2014.
Methods: This is a semi-empirical research study conducted on nurses using a pre- and post-test design. A research sample of 71 nurses randomly selected with negative attitude scores or less than 80 on respecting patients' rights. Data were gathered by an observation checklist including the principle components of patients' physical, mental and social rights. Data were analysed in SPSS.
Results: Mac Nemar Test was used to compare results before and after intervention. Results indicated that there was a significant statistical difference in the group on respecting patients' rights ($p < 0.05$).
Conclusion: According to results, group discussion may contribute to the improvement of nurses' performance in respecting and understanding patients' rights. Group discussion is recommended to be held as an appropriate method in educational therapy centers to improve nurses' perception of patients' rights.

Keywords: Patients' rights, Group Discussion, Performance, Intervention

Introduction

As the highest form of God's creation, human being has been merited rights to his/her needs in health or illness (1). Patients are perhaps one of the most vulnerable social groups, because they not only lose their physical qualities of their healthy times, but are under grave mental, social, and economic pressures (2). Because of the Suffering from the pains of illness and seeking to improve their inabilities, they usually trust healthcare systems and should be protected by some special mechanisms (3), and in this regard, hospitals as an important part of the health care services that should be an institution for understanding and respecting patients, and their families, rights (4).

Patients' rights refer to protecting them and providing a good ground for enjoying human dignity in all stages of treatment in therapy center at the same time ensuring an unprejudiced care in a high-quality environment full of respect and affection (5, 6).

Improved patients' satisfaction of care services and increased respect for patients' rights are a measure of the effectiveness, productivity and the quality of health and therapy services (7, 8), and non-compliance can result in patient injury and compromised health, life and safety of patients and the weakening of the relationship between patient and nurse and reduce the effectiveness of services for patients (6) and legal complaints by patients (9). Nursing is generally defined as the care of others and all that focus on individual nursing care he receives (7), and that care should be taken to represent the interests and concerns about the health of the patient as a person, he is vulnerable (8). Since nursing is one of the most important principles of respect for human rights and respect the dignity of all patients and nurses, one of the main pillars of the rights of patients in hospitals (7). Except profession that has the appropriate knowledge and respect for the patients' rights sensitive.

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In turn, lack of respect for patients' rights may compromise their health, life, and security, weaken the relationship between caregivers and patients, and ultimately reduce the effectiveness of services (6, 9).

Nursing, in general, is defined a care provided for others. All nursing interventions focus on those receiving care (7). Such care should be delivered as representing the caregivers' interest and concern about patient's health as a vulnerable person (8). As one of the most important column of nursing is respecting human rights and esteeming all patients' dignity, as nurses are one the most important column of protecting patients' rights in hospitals (7), and as nursing is a profession full of required knowledge on respecting patients' rights, the more nurses are informed of patients' rights, the better they can provide nursing care to satisfy patients' physical and mental needs. This also improves the quality of nursing services and patients' satisfaction. Therefore, an inclusive care encompassing the respect for patients' rights requires nurses to raise their knowledge on this (10). Nurses' knowledge can be raised by study, passing training courses on patients' rights, participating in seminars and congresses, adding related courses to nursing field (11). Another useful way of enhancing nurses' knowledge and information is the group discussion. Group discussion is a valuable way for gathering information. People can acquire deep information on their interested subjects including patients' rights and add to the quality and quantity of their information (12). Krocshan et al. stated that group discussion was a useful method of provoking deliberation, challenging insights and beliefs, and developing interpersonal skills such as listening to others, accepting the dissenting opinions, and respecting people's freedom and rights (13). Barret et al. (2007) claimed that group discussion could elevate people's awareness of health, illness, and healthcare services and caregivers' needs. This consequently improves nurses' performance (14). Since the group discussion is aimed at studying patients' problems including their rights, nurses' knowledge and information may be raised with this and the required ground is provided for respecting patients' rights. Nurses play a vital role in healthcare system and they are more in connection with patients and their families, studies though indicate that they do not think high enough of patients' rights (15). Salami et al. reported that the level of respect for patients was lower than average on the side of nurses (16). Khodamardi also claimed weak the level of respect nurses have for patients' rights (17). Since it is important for nurses to recognize patients' rights during care delivery, and as this subject has not widely studied in Iran, this research aims to identify the effect of group discussion on nurses' performance and find a way for nurses to better understand patients' rights

Materials and Methods

This is a semi-empirical research study conducted on nurses using a pre- and post-test design. The statistical population includes all nurses employed in Madani Educational Therapy Center in Tabriz. The research sample of 142 nurses randomly selected with negative attitude scores or less than 88 on respecting patients' rights. At first, 10 general wards qualified for the researches were selected 142 nurses were then randomly chosen from these wards. Using random sampling of 71 nurses entered into the study group and the control group were 71 cases. Before training by group discussion, entered group members were evaluated clinically by the researcher in three shifts (morning, afternoon, night). Six 45 to 60 minute sessions of discussion group were held for six groups of 12. At the beginning of sessions, the researchers' objectives were defined. Any of the principles of the chart of patients' rights were then discussed in each session. At the end, discussed subjects were concluded. Chairs were arranged as to facilitate discussion and knowledge exchange. One week later when classes finished, post-test were conducted. Entered Group members were re-evaluated clinically by the researcher in three shifts. During this period, the control group received no training. Finally, for both groups a pamphlet on the chart of patients' rights and discusses subjects were distributed among members.

Statistical Analysis: An observation checklist of 22 phrases including 11 items on patients' physical rights, 7 items on patients' psychological rights, and 4 items on patients' social rights was used. The checklist was measured by "Yes" or "No" answers. The study was scientifically validated on content. Ten faculty members of Tabriz University of Medical Sciences were asked to assess it. Having gathered their specialized comments, the required modifications were done. As the internal consistency reliability were measured by Cronbach's alpha at greater than 0.7, the reliability and generally the whole checklist was confirmed. Data were analysed by descriptive statistic (frequency and percent) and Mac Nemar Test (to compare results before and after intervention) in SPSS

Results

Regarding the working ward, the highest frequency (18.3%) related to female ward and the lowest frequency (1.4%) related to CCUs. In terms of work shift, the highest frequency (38%) was for night and the lowest frequency (29.6%) related to morning. Table 1 displays the qualitative variables of frequencies. Mac Nemar Test was used to compare results before and after intervention. Results indicated that there was a significant statistical difference in the group on respecting patients' rights ($p<0.05$) (Table 2).

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Table 1: Study population specifications

		Count	Table N %
Shifts	**Morning**	21	29.6%
	Afternoon	23	32.4%
	Night	27	38.0%
Service	**Children**	8	11.3%
	Female Surgery	6	8.5%
	Male Surgery	10	14.1%
	Male General Ward 1	9	12.7%
	Male General Ward 2	6	8.5%
	Female General Ward	13	18.3%
	CCU2	6	8.5%
	CCU3	1	1.4%
	ICU	9	12.7%
	Dialysis	3	4.2%

Table 2: Comparing results before and after intervention by Mac Nemar Test. Results indicated that there were significant statistical differences between the group on respecting patients' rights ($p < 0.05$)

	N	Yes %	No %	Exact Sig. (2-tailed)	Exact Sig. (1-tailed)	Alteration%
QA1 & QB1	71	30.98	69.01	.000	.000	100
QA2 & QB2	71	36.61	63.38	.000	.000	100
QA3 & QB3	71	1.Nis	97.18	.000	.000	98.59
QA4 & QB4	71	1.Nis	98.58	.000	.000	28.16
QA5 & QB5	71	0	98.59	.000	.000	98.59
QA7 & QB7	71	0	100	.000	.000	100
QA8 & QB8	71	0	100	.000	.000	100
QA9 & QB9	71	81.69	18.Mar	.000	.000	100
QA10 & QB10	71	0	100	.000	.000	100
QA11 & QB11	71	0	99.99	.000	.000	80.28
QA12 & QB12	71	71.83	20.26	.000	.000	98.59
QA13 & QB13	71	18.59	1.Nis	.000	.000	100
QA14 & QB14	71	14.Ağu	85.91	1.000	.500	100
QA15 & QB15	71	97.18	Şub.81	0.500	.250	100
QA16 & QB16	71	19.71	80.28	.000	.000	100
QA17 & QB17	71	97.71	Şub.81	0.500	.250	100
QA18 & QB18	71	97.18	Şub.81	0.500	.250	100
QA19 & QB19	71	0	100	.000	.000	45.07
QA20 & QB20	71	0	100	.000	.000	66.19
QA21 & QB21	71	1.Nis	97.28	.000	.000	100
QA22 & QB22	71	73.23	27.76	.000	.000	100

QA1: question 1 after intervention QB1: question 1 befor intervention

Discussion

One of the most important measures of high-quality and moral care is the recognition of patients' rights (18). Considering patients' basic rights when delivering care, nursing staff can maximize the quality and efficiency of healthcare. Hospitals should educate therapy team the chart of patients' rights to raise their satisfaction (19). Research results showed that in more than half of cases, nurses' approaches to understanding patients' rights had highly changed.

Amani et al. reported that the respect for the chart of patients' right was 54.5% in good level. This agrees with our research results (2). Rangrazjedi and Rabiei revealed that the respect for the chart of patients' right was 67.74% in good level. This agrees with our research results (20).

Ghelje et al. claimed the physicians' and nurses' attitude toward patients' right in an average level which did not agree with our results. Our study also disclosed that high number of patients, being under high work pressure, numerus work shifts, and doing overwork were all factors affecting nurses' performance. Understanding and respecting patients' rights requires good and standard workplace and facilities (11). Hooshmand et al. enumerated noninstitutionalized rules and lack of sufficient time to study and research due to improper economic conditions, lack of a positive professional view among nurses, high number of patients, shortage of caregivers and facilities as the reasons of low awareness of the study units of patients' rights (18).

Another study referred to the patients' higher awareness of their rights as a facilitating factor of understanding patients' rights. According to most findings, improved knowledge among patients encourages them to expect higher quality services and ask for respecting their rights. It is, therefore, necessary to both educate the therapy team and raise the information among patients on their rights to be more satisfied of received care (21).

Table 2 showed that in more than half of cases, nurses' approaches to understanding patients' rights had highly changed. Mac Nemar Test was used to compare results before and after intervention. Results indicated that there was a significant statistical difference in the group on respecting patients' rights. For most items, the performance changed from 30% to 100%. This shows that teaching and learning is always an efficient tool for raising people's awareness, especially nurses. Improved knowledge may be then followed by improved clinical performance in various contexts such as patients' rights. Nurses should acquire the needed knowledge in order to better understand patients' rights. Put it differently, the higher the knowledge, the better the patients' rights are understood (16) and the more satisfied they are of care services. Patients' satisfaction is a measure of the effectiveness, productivity, and the quality of healthcare services (22).

Our research showed that group discussion can be useful for changing nurses' approaches to patients' rights. Nursing is a valuable and moral act by nature and the quality of nursing care highly depends on nurses' performance (23). Studying the effect of educating nurses through group discussion on the nursing care quality for patients with heart attack, Safari et al. claimed that just two nurses had good performance before the intervention. However, the number elevated to 8 after the group discussion. The mean score before the intervention was 24.6 raised to 38 after the intervention.

The effectiveness of the group discussion on nurses' performance was calculated 54.4% by paired t-test which agrees with our results (8). Aiming to employ clinical training through group discussion for nursing students, Hajbagheri et al. concluded that higher mean scores were achieved by adopting the group discussion technique than the traditional method. This agreed with our study (24).

Comparing the effect of educating through lecturing and group-discussion on learning level among nursing students, Karimi et al. reported a significant increase through group discussion than the other approach which agreed with our findings (25). Kazemnezhad et al. examined how much physicians and nurses in the hospitals of the Mazandaran University of Medical Sciences respected the chart of patients' rights. They evaluated the recognition of patients' rights in poor or average level. The mean score was reported 2.65 (0.83) which did not agree with our results (26).

Babamahmoudi et al. also investigated how much physicians and nurses in the hospitals of the Mazandaran University of Medical Sciences respected the chart of patients' rights. Their results showed the mean score in poor level which did not agree with our results. They claimed lack of knowledge on patients' rights as a reason of not recognizing such rights (27).

According to Johnson, using group discussion helps participants to be in contact and coordinate with each other, and raise their self-confidence (11).

Regardless of educational aspects and a good chance of analyzing discussion details, such learning offers undeniable effects in terms of improving social culture and communication. This method is useful in improving communication skills, self-confidence, the ability to express intends, listening skills, observation of others' reaction to what is said, freedom to express opinions, and ability to pose questions considered a start point of a research study. Discussion and communication, in general, develop thinking, understanding, learning, and remembering skills. And all interested people can take the required advantages of it (28).

Conclusion

Emphasizing on using group discussion to identify complex issues for the audiences, Light and Cox considered it helpful for evaluating previous learning, identifying people's experiences about healthcare services in a group, and discovering personal differences in their perceptions (29). Ledo et al. concluded that group discussion was a good way for raising people, especially nurses', knowledge (30).

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Factors triggering epileptic seizures in patients over 50 years

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Abstract

Objective: In this study the factors that trigger the seizures in epileptic patients over the age of 50 were investigated and the frequencies of seizures were analysed regarding to different age, gender, type of seizure and etiological groups.

Material and Methods: For this purpose, 387 patients were included in the studies who were admitted to neurology outpatient clinic with the diagnosis of epilepsy. The patients are divided into groups based on those characteristics: male / female, generalized seizure / partial seizure, age between 50 and 65 / age over 65, they were evaluated in terms of seizure triggers.

Results: The most common precipitating factor in all groups were found as stress (37%), sleeplessness (27%) and forgetting to take the medication (20%). 31% of the patients were on Carbamazepine, 21% were on Levetiracetam and 19% were on Valproic Asid. The most common etiological causes were identified as idiopathic (39%), post stroke (24%) and dementia (15%). Regarding the triggering factor, some statistically significant differences were found between the following groups and control groups; the group with patients between the age 50 and 65: stress, fatigue, waking and sleeping; the group with female patients: sleeplessness; the group with the generalized seizures: alcohol and sleep.

Conclusion: In conclusion 68% of our patients complained about at least one seizure precipitant and the most common precipitants were stress, sleeplessness and missing dose of medication. In this study, age between 50 and 65 group is more affected by triggers.

Keywords: Epilepsy, Seizure precipitants, Stress, Sleeplessness, Missing

Introduction

Epileptic seizure is the unavoidable overactivity of a part or the whole of the central nervous system (CNS) as a result of sudden, paroxysmal, high-voltage electrical discharges (1). If the loss of consciousness, abnormal sensory or motor activity and behavioural dysfunction that is seen during a seizure is of a repetitive nature, the term 'epilepsy' is used (2). Epilepsy is a common health problem in the whole world.

Neurological problems are seen fairly commonly in patients of the geriatric age group. Epilepsy is the most common neurological disease after cerebrovascular disease and dementia in the elderly. Since it is projected that by the year of 2050, 20% of the world's population will be the aging, it is necessary to focus more seriously on diseases of elderly (6,7).

The studies done in patients from other age groups should also be done in older patients; elderly epileptics are equally entitled to research on diagnosis and treatment of epileptic seizures (8). Many studies have been done on the factors triggering seizures and therapy in children and young adults and many endogenous (stress, fatigue, fever, menstrual cycle, sleep, etc.) and exogenous (alcohol, caffeine, eat, sleep, flickering light, temperature, humidity etc.) triggers have been defined. Yet, there aren't enough studies on these issues in the elderly (9). Information on this subject for epileptic people over 50 years is mostly based on data from personal experiences or claims. In this article, we are presenting the results of the survey study which we think is addressing these missing issues, and want to share the results to attract attention to the issue.

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Material and Methods

In this study, 387 patients over 50 years of age, who were evaluated between February 2013-June 2013 in GATA Haydarpaşa Training Hospital Neurology Department Outpatient Policlinic, GATA Ankara Neurology Department Clinic, Cerrahpaşa Faculty of Medicine Neurology Department Epilepsy Policlinic and Haydarpaşa Numune Training and Research Hospital Neurology Department Epilepsy Outpatient Policlinic, who have been diagnosed as having epilepsy by a neurologist, who were over 50 years of age, and who have been followed up for more than 6 months were included. These patients were evaluated for the "factors that trigger seizures in epileptic patients over the age of 50". Metabolic disorders, post-infectious causes, fever and other causes that may present with symptomatic seizures that last less than six months were excluded from the study. To investigate this issue, a random sample of 387 epilepsy patient volunteers selected from those being followed up in the outpatient departments were asked to complete the screening questionnaire. While developing the instrument, a pre-test consisting of open-ended questions was administered to 30 patients in order to determine the factors that determine the factors that trigger the seizures. The information obtained from these patients was used to identify the triggering factors and these factors were added to the survey. An open-ended item was also included; thus nothing was left out and all the factors could be evaluated.

Statistical method:

Statistical analysis of the study was carried out by using the SPSS 18:00 program. Qualitative variables were summarized with frequency and percent values, numerical variables were summarized by mean ± standard deviation values. Basic topics investigated in this study are the age group with the triggering factors, age of onset of seizures, sex, disease, type of seizure types. The relationship between all variables was investigated. To investigate this relation, chi-square test, which is the statistical test to investigate the difference between qualitative variables, was used. To investigate the relation between the treatment groups and the variables evaluated, Spearman's rho coefficient was used. Since the types of treatment and the types of disease variables were more than two level, linear association test statistic, which is a specialized version of Chi-squared test was used.

Our study was given "ethical approval" by the GATA Haydarpasa Training Hospital Non-Invasive Clinical Research Ethics Committee with project number 2013-14 in the 13th session on February 28, 2013.

Results

387 patients were included in the study and 52 % were men. 59% were between 50-65 years, 54% were patients whose seizures started after the age of 50 and 52% had partial seizures. (Table 1). The 31% of the patients in the study were using carbamazepine as therapeutic, and 21% levetiresetam 19% valproic acid and %9 fenitoin for epilepsy treatment (Table 2).

Table 1: Sex, age group, age of seizure onset and type of seizures descriptive statistics

Groups		n	%
Sex	Male	201	52%
	Female	186	48%
Age group	> 65 years	160	41%
	50-65 years old	227	59%
Age of seizures	<age 50 years	209	54%
	>50 years	178	46%
Type of seizure	Generalized	184	48%
	Partial	203	52%

Table 2. Treatment type variables descriptive statistics

Drugs type	n	%
Carbamazepine	119	31
Levetirecetam	83	21
Valproic Acid	75	19
Fenitoin	35	9

Idiopathic causes were found in 39% of patients, cerebrovascular diseases in 24%, and dementia was present in 15% (Table 3).

Table 3. Etiology variables summary statistics

Disease	n	%
İdiopathic	151	39%
Cerebrovascular disease	92	24%
Dementia	57	15%
Brain tumour	49	13%
Post-traumatic	38	10%

At this point 68% of the participants (n = 122) reported at least one triggering factor for seizures. At Table 4 all factor that are thought to trigger seizures and their frequencies are listed. 37% of the patients have reported seizures triggered by stress. Insomnia was a triggering factor in 27%, while missing doses was mentioned as a triggering factor in 20%.

Table 4 Seizure Triggers

Triggering factor	n	%
Hunger	27	7%
Insomnia	104	27%
Sleep	36	9%
Waking	6	2%
Stress	145	37%
Weather Changes	12	3%
Heat	4	1%
(high sound)	4	1%
Photosensitivity	6	2%
Missing doses	79	20%
Fatigue	45	12%
Alcohol	21	5%

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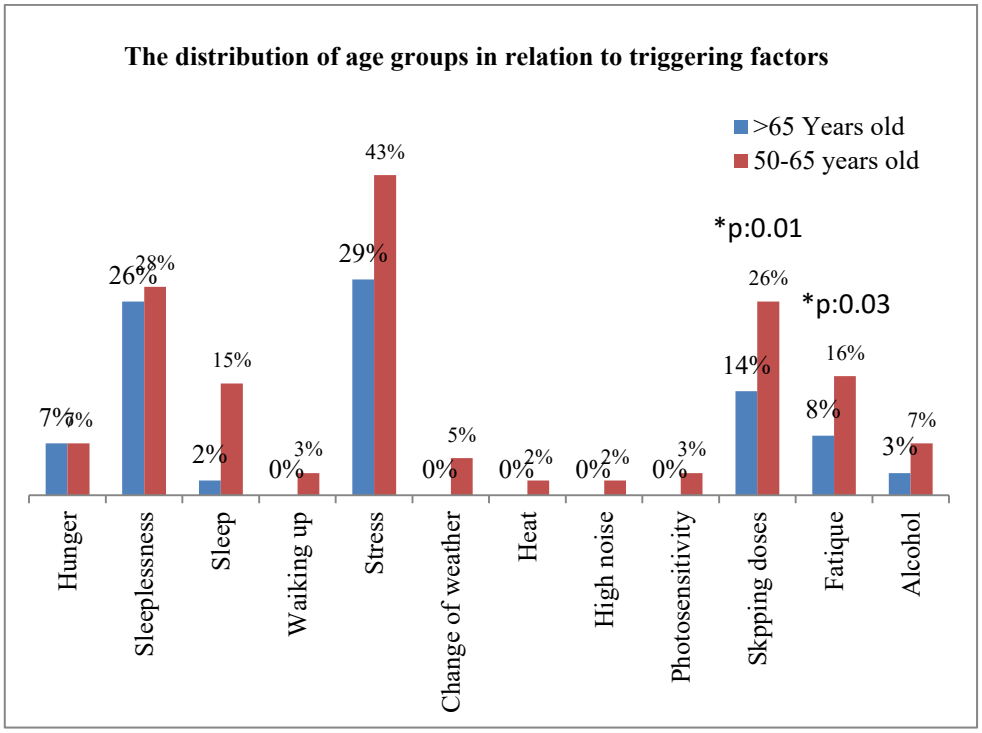

Figure 1: The distribution of triggering variables in relation to age

Comparing sex groups, females were found to have significantly more seizures in case of insomnia (p = 0.039) (Figure 2).

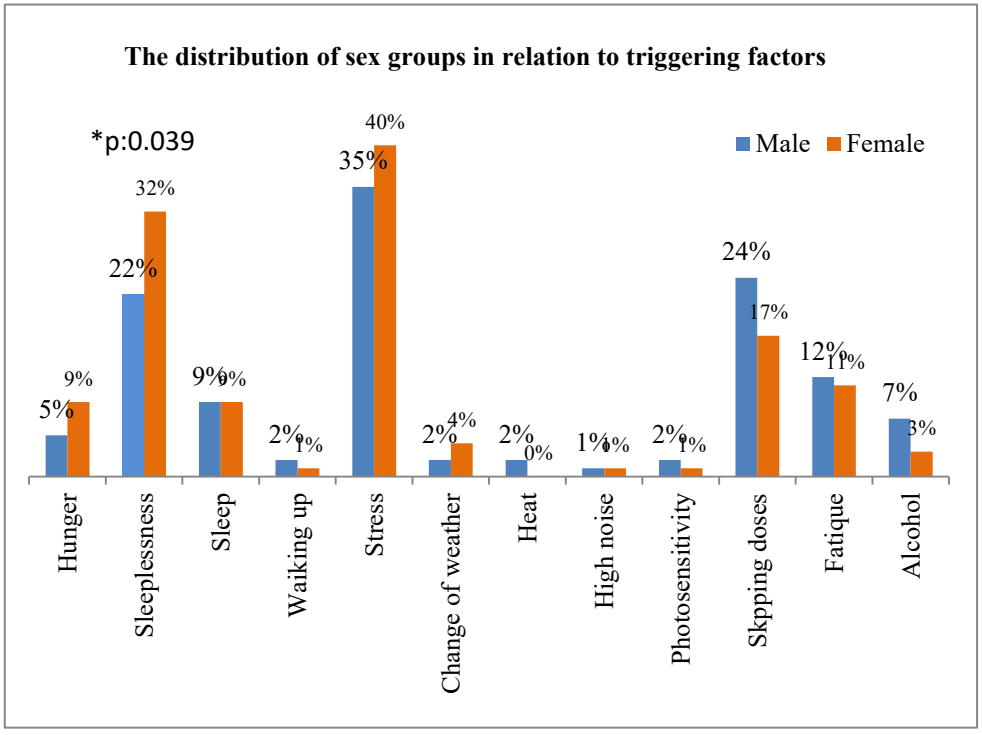

Figure 2: The distribution of triggering variables in relation to sex groups

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In patients with generalized seizure types, sleep (p = 0.006) and alcohol (p = 0.000) were found to trigger seizures at a significantly higher frequency. (Figure 3).

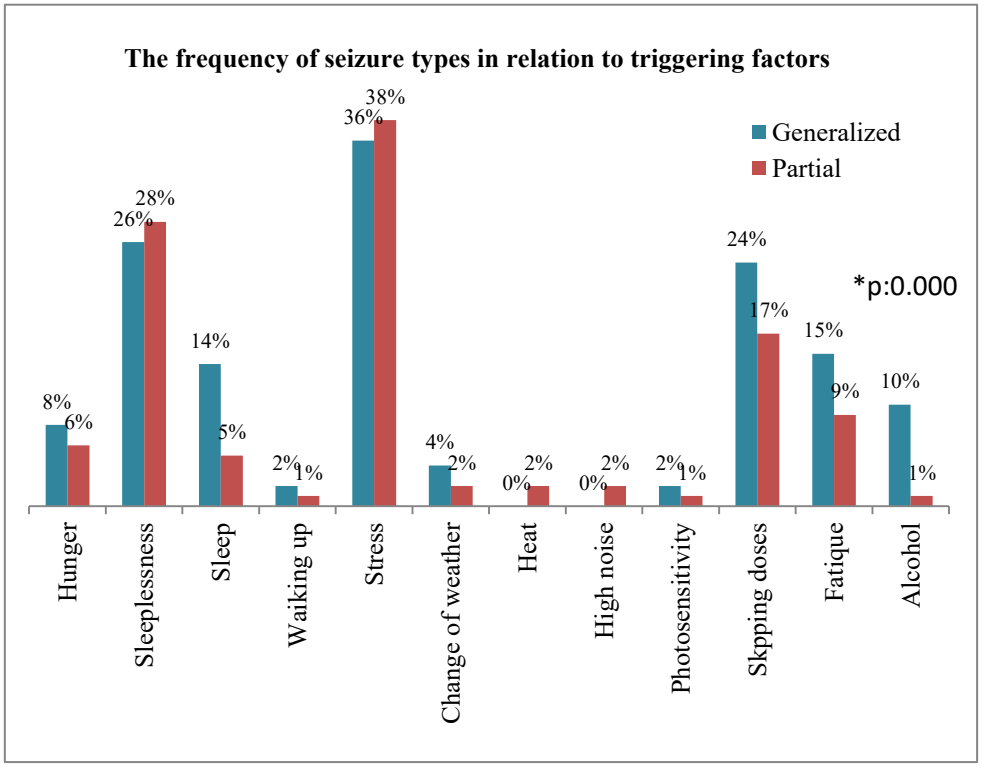

Figure 3: The frequency of seizure types in relation to triggering factors

When the two age groups were compared, patients in the 50-65 years age group had significantly more seizures during sleep (p = 0.000), while waking up (p = 0.038), with stress (p = 0.006), weather changes (p = 0.003), photosensitivity (p = 0.038), missing doses (p = 0.013) and fatigue (p = 0.033). Additionally, patients in the 50-65 years age group had significantly more seizures. In general, triggering factors had a significantly higher probability to trigger seizures in the 50-65 age group. (Figure 1).

Discussion

Epileptic seizure is the unavoidable overactivity of the whole or a part of the central nervous system (CNS) as a result of sudden, paroxysmal, high-voltage electrical discharges (1). Its incidence increases again after the age of 50 years and after 65 years the incidence of epilepsy reaches the highest incidence of all age groups. The incidence of epilepsy is at its lowest values in the 40s (30-40 / 100,000), its incidence rapidly increases in the 50s. In ages around 80s, the average value is at the 140- 160/100,000 level (6-8).

Although definitions vary according to the resources, the term “elderly” is mainly used for individuals over 65 years.

Meanwhile, after the age of 50 years, the incidence of epilepsy increases along with the increasing incidence of many systemic diseases. In our study, we described pre-senile age group as the patients between 50-65 years of age (5-8).

It is not easy to diagnose epilepsy in elderly patients. Usually a generally reliable story cannot be obtained from these patients, and these patients may have different seizures that are not observed by their relatives or that may be confused with or misinterpreted as other conditions. Epilepsy may present very different from young people in the elderly (9).

The etiology of epilepsy in our study was; idiopathic in 39%, cerebrovascular disease in 24%, dementia in 15%. Compared to the literature, our higher rate of idiopathic epilepsies may be due to undiagnosed other etiologies (e.g. meningioma, dementia, or head trauma overlooked in medical history etc.) and also be due to cryptogenic epilepsy patients been considered in this group. There are studies suggesting Alzheimer's disease as a cause of late-onset epilepsy with no identified etiology (10).

The diagnosis of epilepsy in older patients with different presentations may also be difficult because of the patient's current disease and seizures. These patients may respond to low-dose antiepileptic agent. Side effects in a wide range may occur, including sedation, tremor and cognitive disorders, depending on the patient and the AEDs used. The combination therapy should be avoided if possible, due to combination therapies may increase side effects (11). Since elderly patients often use other drugs (antihypertensive, antidiabetic, antidementia, etc.), agents with lower drug interactions, drugs that do not bind to proteins and do enzyme induction should be preferred. Cognitive and psychological effects should be positive. In this age group, the seizures can be controlled with proper treatment at correct doses in 70% of the patients (11,12).

The most common agents used were carbamazepine (31%), levetiracetam (21%) and valproic acid (19%). The relatively high frequency of partial seizures may have been a reason for the neurologists' choice of carbamazepine. The possibility to follow blood drug levels of carbamazepine and valproate, and the long experience related to these agents may be other reasons for their selection of these agents. However, unlike the literature, the second most preferred drug is levetiracetam. The reason for the selection of this drug may be the low drug interactions, its side effect profile being lower than other AEDs, and easy dose titration, with going up to high doses in a relatively short time (13).

68% of the participants in our study reported at least one seizure triggering factor. Results of different studies has revealed a seizure triggering factor (at least one) at a ratio between 53-86.6%. (14-18).

Stress is an automatic response when a condition or force that exceeds the person's ability to deal with is detected. Fear, anxiety and concern are moods that are the reflections of stress in everyday life (19-21). Epilepsy is one of the common areas of study for different disciplines such as neurology, psychiatry, neurosurgery and pediatrics. Specifically, many studies have been done on the neuropsychological aspects of epilepsy in the last century (22-27). Meanwhile, individuals are exposed to stress factor more at old age than young individuals due to affective problems due to physical challenges, loss of self-confidence, feeling helpless, loneliness, hopelessness, inability to fulfill one's responsibilities, and social challenges such as those due to retirement, loss of productivity and economic difficulties. Jalava et al. have demonstrated in their 35- year follow study that patients with epilepsy have a 4-fold increased risk of developing psychiatric disease and are sensitive to stress than normal individuals (28). On the other hand, the relationship between stress and seizures is usually accepted by clinical experience and Nancy et al. have demonstrated in the work they have done that stress is a factor that triggers seizures (29). In their study on the quality of life of epilepsy patients, Baker et al. have shown that stressful experiences tend to increase seizure frequency. Again it was concluded in this study that the mental and physical fatigue caused by stress results in an increase in seizure frequency (30). Other studies demonstrating that seizures may be triggered by stress are also present (15,17,31-35). Although quite a number of hypotheses have been put forward on how stress triggers seizures, the exact mechanism has not yet been clearly explained (36).

There is an interaction between sleep and epilepsy. The effect of sleep on epilepsy and the effects of epilepsy on sleep, has been intriguing scientists for many years, and despite a number of studies conducted on the subject, it is still not yet fully clear (37,38). In particular, the occurrence of SUDEP usually happening during sleep has increased the interest on the relation of sleep and epilepsy. Especially childhood epileptic syndromes are known to have close relationship with sleep.

In our study, the second most triggering factor was found to be insomnia with 27%. In patients between 50-65 years of age and in women insomnia was found to trigger seizures significantly. At the same time, stress is also a cause of insomnia in women and in the elderly. Stress and insomnia are closely related to each other as triggering factors. Insomnia also may create stress (39). In studies comparing the two sexes, insomnia problem was more prevalent in women than men, similar to our study. Women may not spend enough time to sleep like men, due to their tempo of business life and their responsibility associated with family business and housework. According to the data from the US National Sleep Foundation, women aged 30-60 years allocate only 6 hours 41 minutes to sleep. To be a woman and to have insomnia are associated with each other (40

Although skipping doses of medication is not counted among endogenous or exogenous triggers, it is one of most common causes of status epilepticus. Antiepileptic drugs are effective with a particular concentration in the blood and instant withdrawal or decrease in concentration is thought to trigger seizures. Usually studies that investigate seizure triggers do not evaluate skipping doses; we wanted to address this issue with the result of our study. In this study, skipping doses was found to be the third most common triggering factor with 20%.

In conclusion, there is at least one trigger for seizures in 68% of our patients. The most common seizure triggers were found to be stress with 37%, insomnia with 27% and skipping doses with 20%. Etiological causes were, idiopathic 15%, Cerebrovascular disease 24%, dementia 39%, brain tumor 13% and posttraumatic 10% respectively. Most commonly used three agents were identified as; carbamazepine 31%,

valproic acid 19% and levetiracetam 21%. When our study groups were evaluated, the effect of seizure triggering factors are statistically significant in the group whose seizures started before the age of 50 and the group with seizures starting 50-65 years of age.

Conflict of Interest: The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article. The first case was presented as poster presentation at the American Academy of Neurology 67th Annual Meeting , 18-25 April 2015, Washington DC, USA.

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The effect of the time interval between the last breastfeeding and Tc-99m MIBI injection on the intensity of Tc-99m MIBI uptake in breast tissue

Bekir Tasdemir[1*], Zeki Dostbil[1], Ilhan Sezgin[1]

Abstract

In this case report, we present a 36-year-old lactating woman, 10 months after delivery, who was referred to our clinic for a myocardial perfusion scintigraphy (MPS) due to chest pain. A scintigraphic procedure was performed according to the two-day protocol. On the first day, dipyridamole pharmacological stress Tc-99m MIBI MPS was performed, and on the second day, the same test was repeated while in a resting state without the administration of any pharmacological agent. The stress scan, compared to the rest scan, presented a higher uptake of Tc-99m MIBI in the breast tissue. The patient query revealed that the last breastfeeding was 12 hours before the stress scan and she did not breastfeed or express breast milk prior to the rest scan. Our findings suggest that ceasing the emptying of the mammary glands prior to the Tc-99m MIBI injection might be appropriate to decrease the radiation exposure of the mammary glands and the breast-fed baby.

Key words: molecular imaging, myocardial perfusion imaging, SPECT, technetium Tc 99m sestamibi

Introduction

Technetium-99m (Tc-99m) 2-methoxy-2-methyI-isopropyl-l-isonitrile (MIBI) is one of the most common radiopharmaceuticals used in myocardial perfusion scintigraphy. Tc-99m MIBI concentrates in the myocardium in proportion to myocardial blood flow and shows slow washout and redistribution (1). Tc-99m MIBI is a lipophilic cationic agent that mainly penetrates into the mitochondrial compartment as a response to the high negative transmembrane potential in the myocytes (2). However, Tc-99m MIBI is not unique to the myocardial cells and may also concentrate in other tissues and organs (3). Breast tissue in lactating women is one of these tissues where diffuse Tc 99m MIBI uptake tends to concentrate (4, 5). In this case report, we present a lactating woman whose clinical profile indicated that the time interval between the last breastfeeding and the Tc-99m MIBI injection might affect the intensity of Tc-99m MIBI uptake in her breast tissue

Case

A 36-year-old lactating woman, 10 months after delivery, was admitted to our cardiology clinic due to chest pain. In line with her clinical history, the chest pain was considered to be of cardiac origin. Although the electrocardiogram was normal, the patient was required to undergo an exercise stress test since she presented with typical cardiac symptoms.

However, the patient refused to take the treadmill exercise stress test due to her orthopaedic problems and thus was referred to our clinic for myocardial perfusion imaging with pharmacological stress. Scintigraphic procedures were performed according to the two-day protocol.

On the first day, pharmacological stress imaging with dipyridamole was performed, and on the second day, the test was repeated in a resting state without the administration of any pharmacological agent. The patient fasted for a minimum of four hours prior to both the stress and rest scans. For each scan, 15 mCi (555 MBq) of Tc-99m MIBI was injected intravenously and the scans began 30 minutes following the injections.

The scans were performed using a Philips Brightview dual-headed gamma camera (Philips Medical Systems, Inc., Cleveland, OH, USA), and low-energy general purpose collimators were used for the imaging.

The patient was placed on the table in the supine position and perfusion single-photon emission computed tomography (SPECT) acquisition was performed using a 180° circular orbit, starting at 45° right anterior oblique and ending at 45° left posterior oblique. The patient's myocardial perfusion scintigraphy (MPS) was evaluated as normal.

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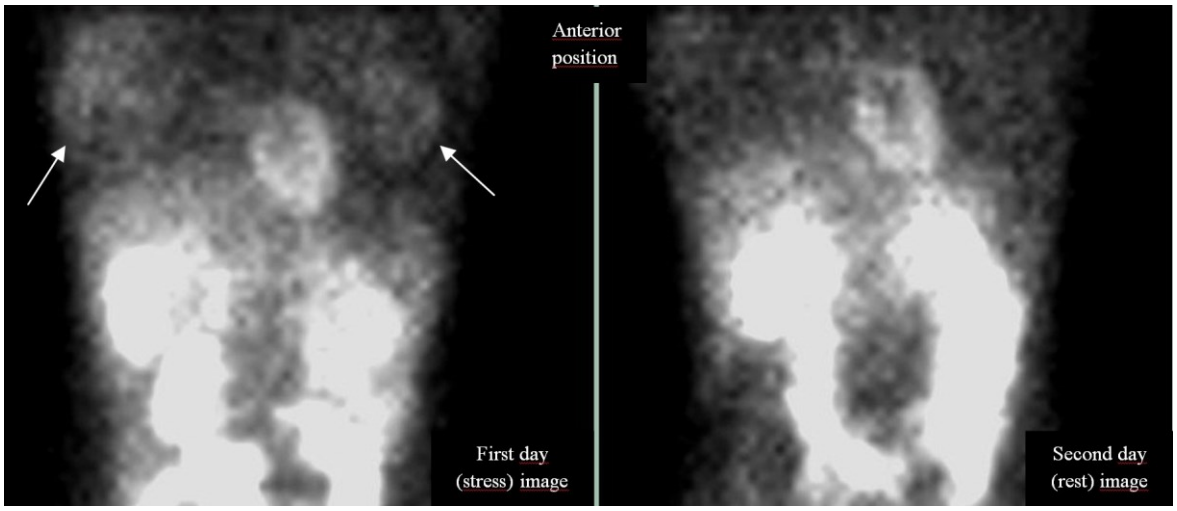

Figure 1: Tc-99m MIBI uptake in both breast tissues (arrows) is higher on the first-day (stress) image than on the second-day (rest) image.

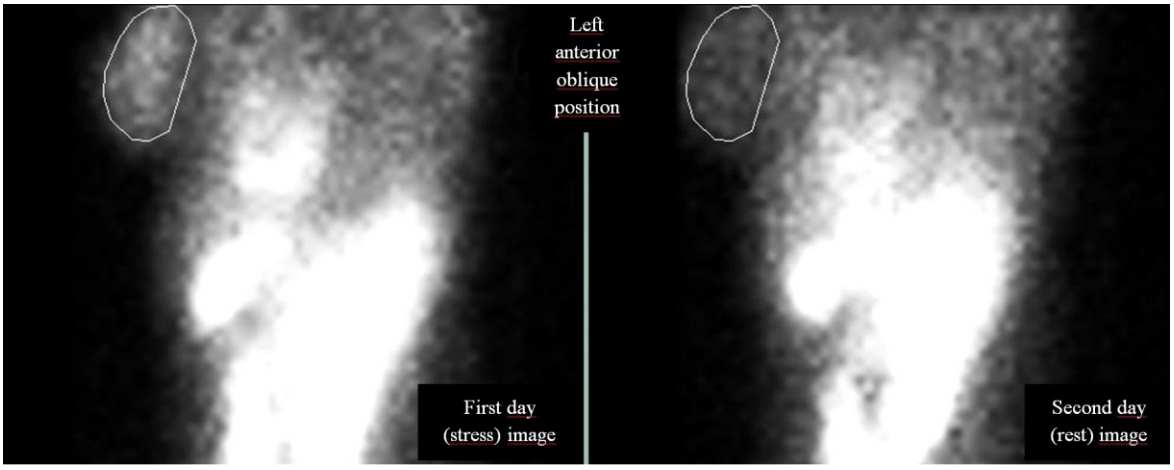

Figure 2: Quantification was achieved on both images by drawing same region of interest on the right breast tissue, and 88% higher Tc-99m MIBI uptake was measured on the first-day (stress) image compared with the second-day (rest) image.

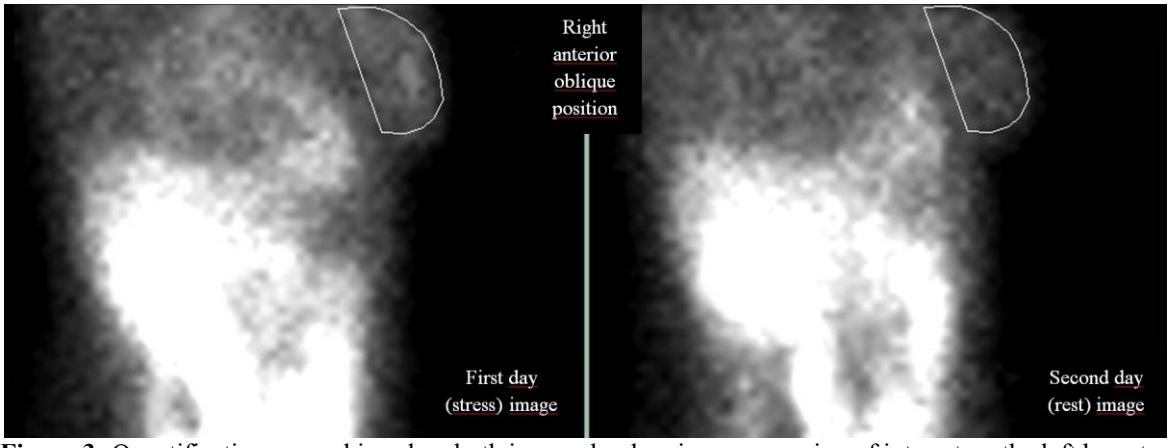

Figure 3: Quantification was achieved on both images by drawing same region of interest on the left breast tissue, and 52% higher Tc-99m MIBI uptake was measured on the first-day (stress) image compared with the second-day (rest) image.

However, it drew our attention that the first-day scan, compared to the second-day scan, presented a higher uptake of Tc-99m MIBI in the breast tissue, particularly in the right breast, when we were evaluating the raw data images (Figure 1).

Quantification was achieved by drawing a region of interest (ROI), including the glandular regions, on both breasts (Figures 2 and 3). During the quantification, in order to distinguish the breast tissues from other surrounding tissues, the right breast was evaluated on the left anterior oblique image and the left breast was evaluated on the right anterior oblique image (Figures 2 and 3).

The results of the quantification revealed that the Tc-99m MIBI uptake in the breast on the stress images was 88% higher in the right breast and 52% higher in the left breast than that of the images taken at rest. To investigate this situation, the patient was queried about the last breastfeeding time, and she revealed that the last breastfeeding was 12 hours before the stress scan and thus, 36 hours prior to the rest scan. We also determined that the patient had not taken any drugs, undertaken any invasive/non-invasive procedures related to the breast tissue, or undergone any extraordinary events in her daily life before the scanning processes. To prevent the baby from incurring any radiation exposure, the patient had been advised not to breastfeed her baby within the 24 hours following the stress scan and also to express her breast milk and discard it.

The patient stated that she did not breastfeed her baby during that period, as advised, however, she did not express and discard her breast milk. This means that the patient did not empty her mammary glands within the 36 hours prior to the rest scan. This situation was considered as a possible reason for the decrease in the Tc 99m MIBI uptake on the rest images and also for the difference between the intensity of Tc-99m MIBI uptake of the right and left breasts on stress images. On the other hand, the patient was also asked as to which breast she had last used for breastfeeding, unfortunately, no data was obtained since she could not remember which breast was used. We also calculated the liver to lung uptake ratios of Tc-99m MIBI in the stress and rest images to rule out the potential for dipyridamole to change the biodistribution of Tc-99m MIBI. However, we did not find any significant difference between the uptake ratios of the stress (2.324) and rest (2.321) images

Discussion

In this case, we observed different intensities of Tc-99m MIBI uptake in breast tissue on two different days. We considered that this difference was primarily concerned with the time interval between the last breastfeeding and the Tc-99m MIBI injection as we ruled out the majority of the other possibilities in line with the patient's responses to our queries. The possible mechanism of the increased Tc-99m MIBI uptake in the breast tissue may be that breast alveoli may be filled with new milk early after the breastfeeding (6) and, this situation may be cause of the increased Tc-99m MIBI uptake in the breast tissue in our case. As another possibility, we also focused on the dipyridamole, which was administered for the pharmacological stress testing. However, in our literature review, we found no information that dipyridamole may increase Tc-99m MIBI uptake in breast tissue. We also did not find any significant difference between the liver to lung uptake ratios of the stress and rest images in our calculations.

It has been reported that the radiation exposure of a patient's baby should be avoided by ceasing any breastfeeding for a certain period of time following scintigraphic procedures, and that the breast milk should be expressed and discarded during this period (7).

However, Rubow et al. studied the retention and secretion of 11 different radiopharmaceuticals in breast tissues and reported that, among all of them, Tc-99m MIBI is the lowest excreted radiopharmaceutical in breast milk (5). As a result of our findings, in order to decrease the radiation exposure of both the mammary glands and the breast-fed baby, the mother should cease emptying the mammary glands for a certain period of time prior to a Tc-99m MIBI injection. We feel this may be more appropriate than expressing and discarding the breast milk following the scanning procedure with Tc-99m MIBI. Moreover, this hypothesis might also be valid for other pharmaceuticals such as F-18 FDG (2-fluoro-2-deoxy-D-glucose) and Tc-99m tetrofosmin, both of which have shown high uptakes in breast tissues of lactating women (8, 9)

In conclusion, ceasing the emptying of mammary glands prior to the Tc-99m MIBI injection might be appropriate in order to decrease the radiation exposure of maternal mammary glands and the breast-fed baby. Nevertheless, additional more detailed prospective studies are needed to confirm this hypothesis and to determine the appropriate time for ceasing the breastfeeding prior to a Tc-99m MIBI injection

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Prenatal diagnosis of a giant fetal cervical teratoma by magnetic resonance imaging: a case report

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Abstract

Fetal cervical teratomas are the rare forms of congenital teratomas with a high risk of perinatal morbidity and mortality. Imaging plays an essential role in the management of cervical teratoma and also helps in counselling parents. Ultrasound may be inadequate in the prenatal diagnosis of cervical teratoma due to large tumor size and fetal position. Magnetic resonance imaging could be useful in the work-up of tumours detected by ultrasound. We reported a 29-year old pregnant woman referred to our hospital with a finding of giant solid mass at the fetal neck. Ultrasound examination revealed a right-side mass sized 87x64x51 mm that extended from mandible to the anterior thoracic wall. Fetal magnetic resonance imaging provided additional information regarding exact anatomical location and extent of the mass. Thus, we found that fetal magnetic resonance imaging is a complementary diagnostic modality to antenatal ultrasound examination in the differential diagnosis of cervical teratoma.

Key words: Fetal, Cervical, Teratoma, MRI, Prenatal diagnosis

Introduction

Fetal teratomas are congenital tumors containing more than one embryonic germ cell layer. Although teratomas are the most common fetal tumors, those of cervical origin constitute less than 5% of all teratomas with an incidence of 1/35000-200000 live births (1). The prenatal diagnosis of cervical teratoma is critical as it is associated with polyhydramnios, non-immune hydrops, cardiac failure and preterm birth (2). Ultrasound is the preferred primary imaging technique for the fetal neck tumors, but its ability to detect nature of the mass is limited. However, magnetic resonance imaging (MRI) could be a valuable tool for differential diagnosis of cervical teratoma and accurate identification of location and extension of the tumor (3). Together with ultrasound, MRI may thus be useful in selection of foetuses that require an ex utero intrapartum treatment procedure (EXIT). Here, we report prenatal diagnosis of a giant cervical teratoma diagnosed by sonographic and MRI findings.

Case

A 29 year old gravida 3, para 2 woman was consulted to perinatology clinic with a fetal neck mass which was identified on routine ultrasound examination at 16 weeks of gestation. The woman has two healthy children and her past medical history is unremarkable. On ultrasound examination, there was a right-side mass sized 87x64x51 mm that extended from mandible to the anterior thoracic wall (Figure 1).

It was composed of solid and cystic components with no calcifications. The border between normal tissue and mass was not clearly visualized. Colour Doppler flow revealed that mass was not particularly vascular. There were no accompanying anomalies and amniotic fluid was normal. We considered that the tumor was probably neuroblastoma, goiter or teratoma. For differential diagnosis, half-Fourier acquisition single-shot turbo spin-echo sequence in T2-weighted MRI of the fetal neck was performed. MRI revealed that mass was extending from mandible through supraclavicular level and compressing tracheoesophageal structures without thoracic infiltration (Figure 2).

The epicentre of the lesion was thought to be the cervical canal. Amniocentesis was performed and fetal karyotype was obtained normal 46 XY. Ultrasound and MRI findings suggested that the mass was most likely a cervical teratoma.

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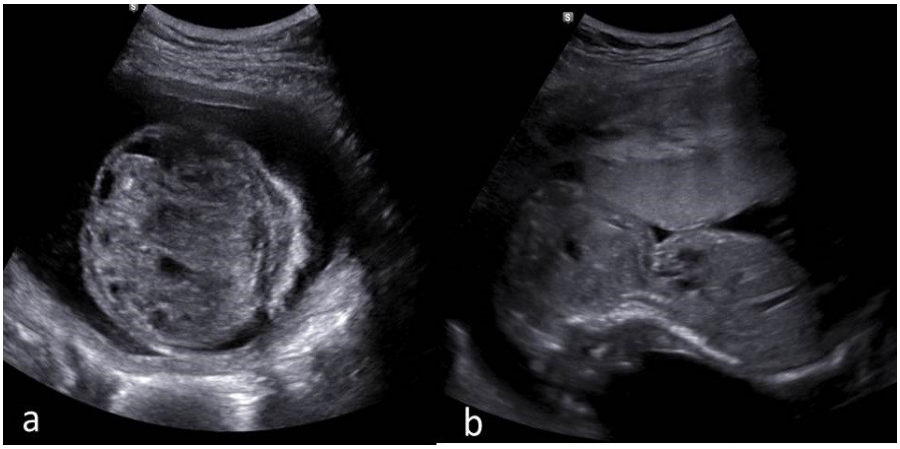

Figure 1. Ultrasound images showing solid-cystic mass extending from anterior neck on axial (a) and sagittal (b) planes.

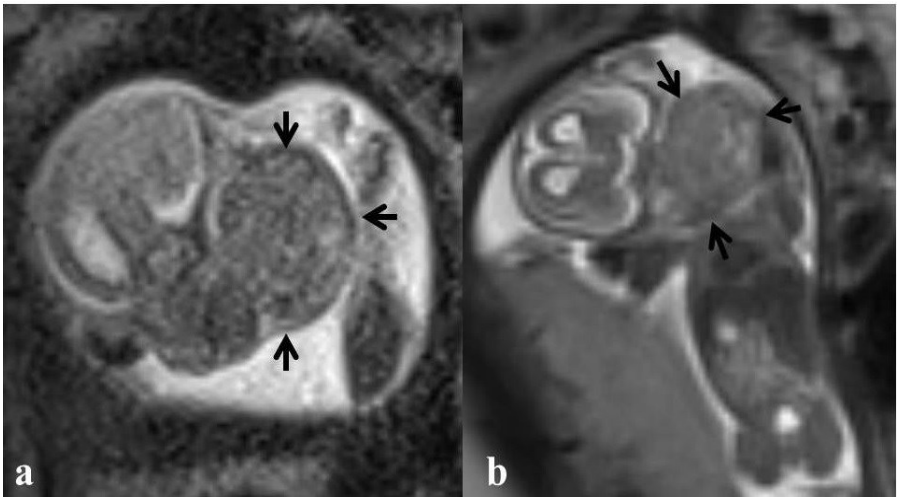

Figure 2. T2-weighted MRI is demonstrating tumor-like mass which compress adjacent structures on axial (a) and sagittal (b) planes.

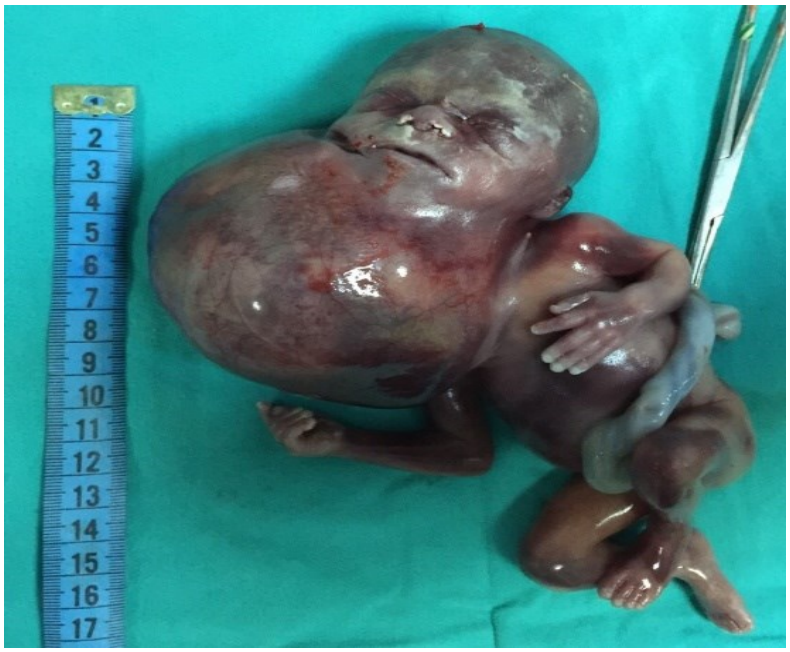

Figure 3. Postnatal findings of infant with cervical teratoma.

The MRI findings, prognosis and treatment options were discussed with consultants from pediatric surgery. Due to large tumor size, poor perinatal outcome and lack of experience with EXIT procedure, termination of pregnancy was offered to the parents. Since the patient had a caesarean section six months ago, pregnancy was terminated at 20 weeks by cesarean section. Postpartum examination revealed 10x7x6 cm well-defined mass originating from anterior portion of the neck (Figure 3). Histologic examination has showed grade 3 teratoma with immature neuro-ectodermal elements. No other structural anomalies were identified.

Discussion

Teratomas are tumors composed of abnormal tissues derived from three germ cell layers (mesoderm, ectoderm, endoderm) and may originate from nasopharyngeal, sacrococcygeal, facial or cervical region (1). Fetal cervical teratoma constitutes only 5% of all teratomas. Malignant transformation of cervical teratoma, which relies on the presence of primitive undifferentiated cells, has been reported in less than 5% of the cases (4). Fetal cervical teratoma is usually considered benign tumor, however, it may result in significant perinatal morbidity and mortality by causing fetal airway obstruction and extensive soft tissue distortion.

Although rare, fetal cervical teratoma may be associated with other structural malformations including imperforate anus, cystic fibrosis, chondro dystrophy fetalis, and maxillar deformity (5-7). It is also reported that teratomas are associated with chromosomal abnormalities such as gene mutations, trisomy 13, ring X-chromosome mosaicism and gonosomal pentasomy 49, whereas cervical teratoma often display normal karyotype (1). In this case, both prenatal and postpartum examinations revealed isolated teratoma and karyotyping turned out to be normal.

Perinatal complications of cervical teratoma include polyhydramnios (from impaired fetal swallowing of amniotic fluid), non-immune hydrops (from arteriovenous shunting) and pulmonary hypoplasia (due to mass effect) (8, 9). Obstruction of circulation and arteriovenous shunting through the tumor may also lead to high-output cardiac failure and, ultimately, fetal demise. Giant cervical teratoma and polyhydramnios increase the risk for preterm labor and may give rise to difficult labor. However, these complications are infrequent findings in the first half of pregnancy, as in our case.

Most of the congenital cervical teratomas can be diagnosed with antenatal ultrasound between 15 and 29 gestational weeks, but the tumor can develop later in pregnancy (4). Typical ultrasound features are well defined, solid or mixed solid-cystic masses extending along the midline with calcifications in about half of the cases. Colour Doppler flow imaging may reveal varying degrees of blood flow within the mass. In this case, the striking feature was presence of poorly vascularized large mass on the anterior neck region without calcifications.

Differential diagnosis of cervical teratoma includes cystic hygroma, haemangioma, goiter, cervical neuroblastoma and nasopharyngeal tumor (10). Cervical teratoma is generally seen at the anterior and midline region of the neck while cystic hygroma, lymphangioma, haemangioma and bronchogenic cyst are usually seen at the posterior and lateral region. However, differential diagnosis of nasopharyngeal tumors, congenital cervical neuroblastomas and goiter are often difficult (11).

MRI could be helpful as a complementary diagnostic tool in the differentiation of these fetal neck masses. MRI enables different image contrasts and provides high spatial resolution and large field of view as compared to conventional ultrasound. Nemec et al. demonstrated the ability to visualize tumors on prenatal MRI in a study of 18 fetuses with tumors (12). In that study, MRI findings changed 50% of suspected ultrasound diagnosis and postpartum histopathology examination confirmed 73% of MRI diagnosis (12). Fetal MRI has shown the potential to provide significant additional information in terms of tumor extent, composition and complications caused by the tumor (3). It is found that fetal MRI was a reliable diagnostic method in the classification of some congenital tumors (7). In our case, MRI clarified the diagnosis of cervical teratoma by identifying the exact anatomical location and extent of the mass.

The recommended therapy for cervical teratoma is surgical excision of tumor mass following establishment of the airway by EXIT procedure. The EXIT procedure involves partial delivery and airway assessment of infant while uteroplacental circulation and gas exchange is maintained. If EXIT procedure is not performed, fetuses with cervical teratoma have high mortality rates from respiratory distress immediately postpartum (6). The EXIT procedure provides time to secure the airway, administer resuscitation medications and resect cervical masses. Hedrick et al. have been used EXIT procedure in the delivery of 10 fetuses with cervical teratomas. They managed to intubate all neonates and long-term survival was reported as 80% (13).

During antenatal surveillance, it is essential to identify fetuses that require EXIT procedure at the time of delivery. Thus, MRI may be of critical importance to assess the relationship between cervical teratoma and structures of the airway and may aid in the selection of fetuses requiring respiratory support. Our MRI studies allowed us to better understand the difficulty in surgical resection of entire mass. Therefore, huge size of the tumor at this stage of gestation period, poor perinatal prognosis and lack of experience with EXIT

procedure were discussed at our institution with the family and termination of pregnancy was offered.

Conclusion

In conclusion, this case report demonstrated that fetal MRI can contribute to a more reliable evaluation in the differential diagnosis of cervical teratomas, particularly in cases where ultrasound is technically unable to establish site of origin and tumor extension.

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Bilateral frontal sinus mucocele: Histopathological and clinical review of a case

Seyda Belli[1*], Mehmet Faruk Oktay[1]

Abstract

Paranasal sinus mucoceles are cystic lesions that occur as a result of accumulation of mucoid secretion and desquamated epithelium, leading to distension by growing in an expansile and destructive manner within the sinus wall. The frontal sinus is most commonly involved, whereas sphenoid, ethmoid, and maxillary mucoceles are rare. However, bilateral frontal sinus involvement is more rare. If the cyst invades the adjacent orbit and continues to expand within the orbital cavity, the mass may mimic the behaviour of many benign growths primary in the orbit. Here, we present a case with frontal mucocele involving bilateral sinuses. It was manifested with proptosis and exophthalmia of the left eye in a forty years-old male patient. Paranasal computed tomography scan and magnetic resonance imaging revealed an image consistent with mucocele. We performed intranasal frontal sinusectomy via endoscopic approach. No orbital and intranasal complication developed at the end of the surgery. We report here that endoscopic drainage, performed by experienced hands, could be preferred surgical approach in rare case of bilateral frontal mucocele case.

Key words: Mucocele, Paranasal Sinuses, Proptosis, Exophthalmos

Introduction

Mucoceles are benign lesions, covered by pseudostratified epithelium, that affect paranasal sinuses (1, 2). Mucoceles of the paranasal sinuses were first described by Langenbeck (1820) under the name of hydatids. Rollet (1909) was the first author who used the term mucocele (3). Mucoceles are most commonly located in the frontal sinuses (60%), whereas sphenoid, ethmoid, and maxillary sinus involvement is rare (1, 2, 3). Frontal sinus mucoceles can develop due to obstruction of ostium by chronic sinusitis, polyp, tumor, trauma or surgical intervention. Mucoceles are formed as a result of accumulation of mucus and desquamated epithelium that lead to erosion due to increased pressure on the sinus wall. Mucoceles can lead to various complications with expansions in orbita, nasal cavity and intra cranium due to proximity (3, 4).

Both computed tomography (CT) and (MRI) are used in differential diagnosis and evaluation of mucoceles. CT is used for both assessment of regional anatomy and detection of particularly intracranial and intra orbital expansion, and bone erosion. MRI is helpful in differentiating mucoceles from neoplasms (3, 5). Treatment of mucoceles is achieved by craniotomy or functional endoscopic sinus surgery. Sinus obliteration may or may not accompany these surgical techniques. (3, 5).

Case

A 40 years-old male patient presented to the ophthalmology outpatient clinic with a complaint of rolling of the left eye to left and down for the past 3 months (Image 1). Paranasal CT revealed bilateral frontal mass image, and patient was referred to our clinic (Image 2). There was not any head trauma or previous nasal surgery in patient's medical history. He did not report any complaints regarding nasal pathology. Nose examination did not reveal any pathology. There was a shift to the left and exophthalmos in the left eye. No pathology was detected in bilateral light, and cornea reflexes and visual field examination was normal. There was not any finding in examination of the eye suggesting intra orbital pathology. Paranasal CT revealed a large, expansile cystic lesion filling both frontal sinuses. Frontal sinus anterior and posterior walls were intact, whereas medial wall of the left orbita was eroded by the mass (Image 2). A lesion consistent with mucocele, eroding left orbital medial wall and filling both frontal sinuses was found. Frontal sinus posterior wall was not destructed. Mass was isointense on T1 and hyper intense on T2 in MRI scans (Image 3). The patient underwent endoscopic bilateral frontal ethmoid sinusectomy. Both frontal recesses were widened by shaving and mucocele content was drained (Image 4). During six month of follow up controls, no finding of recurrence was found.

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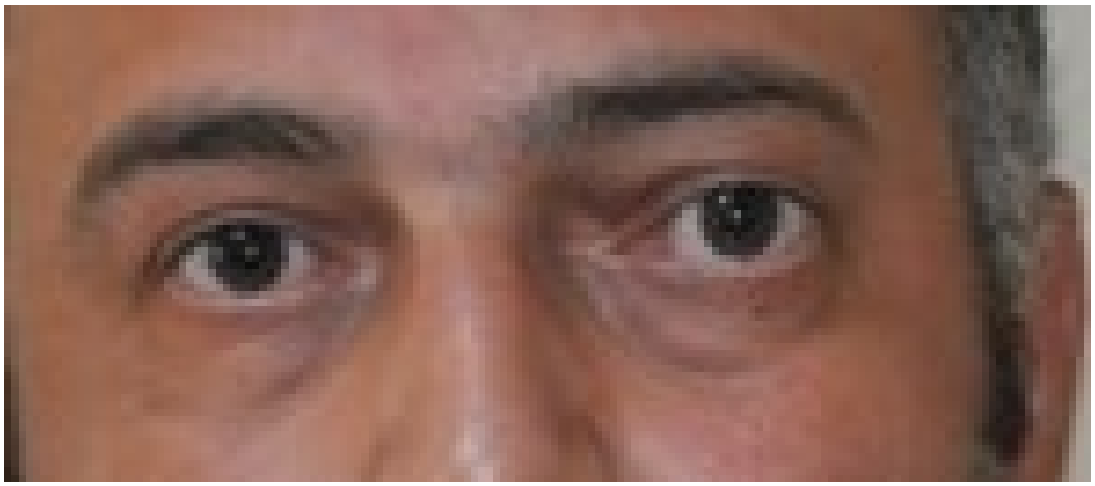

Image 1: Exophthalmia on the leftside.

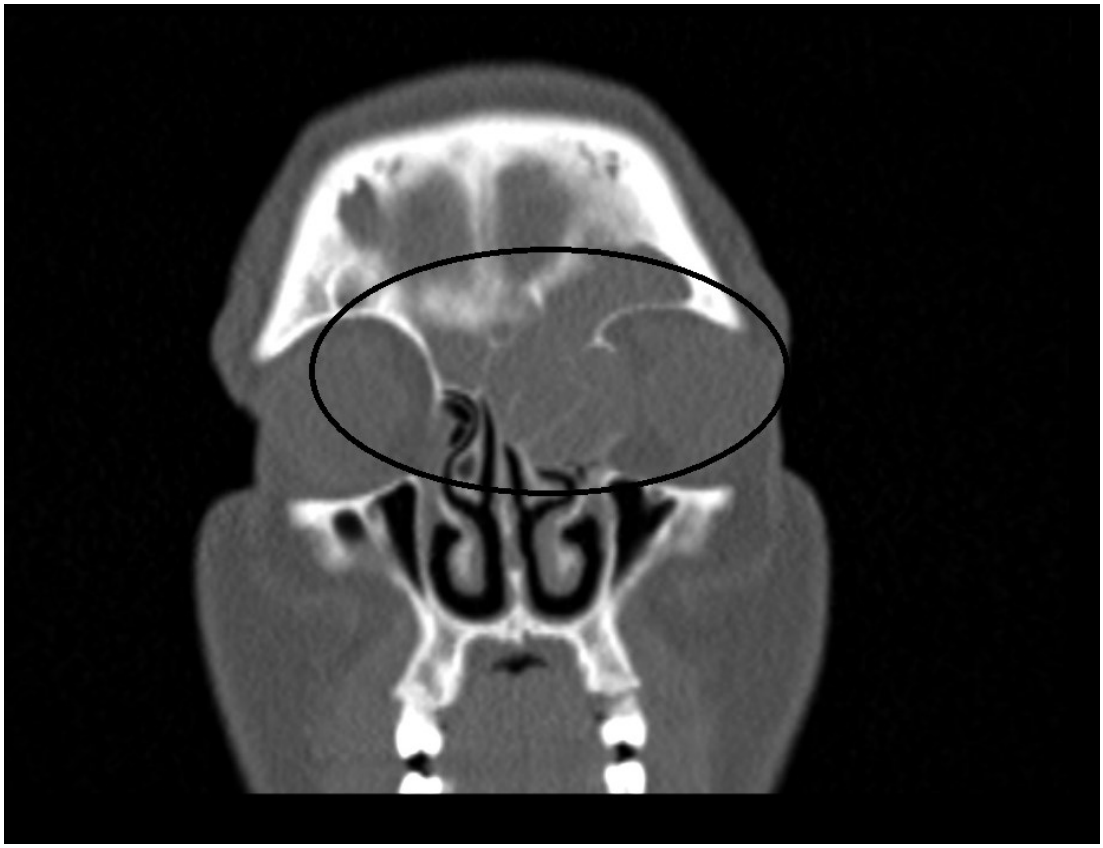

Image 2: Paranasal CT section of bilateral frontal mucocele.

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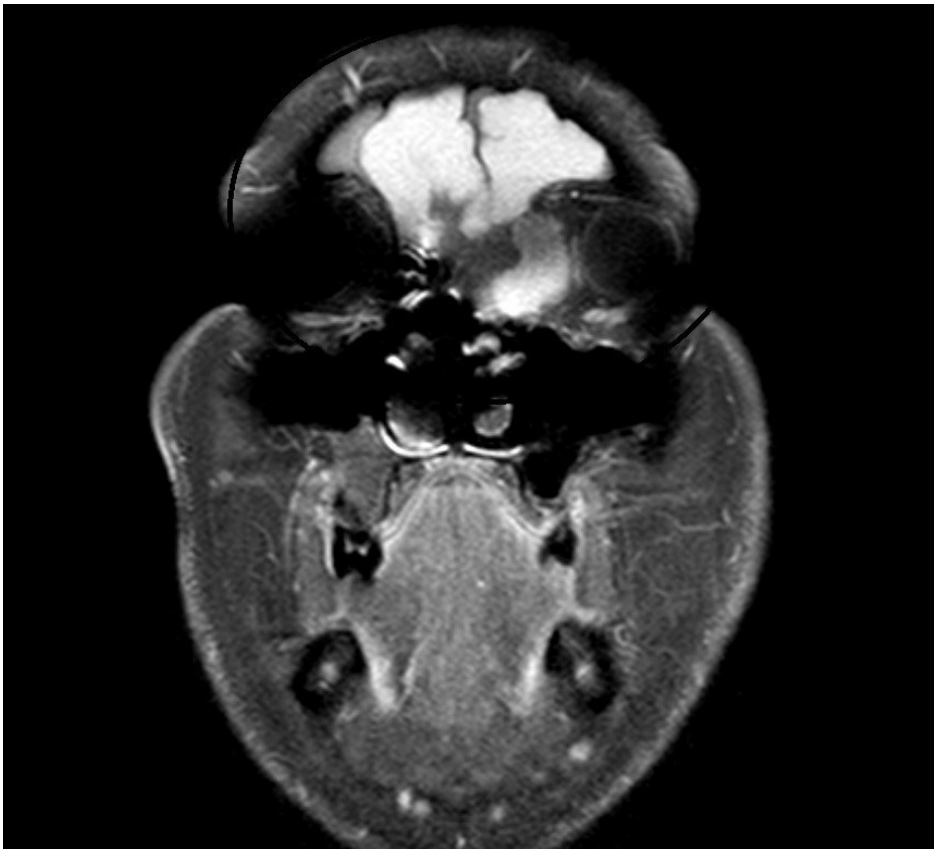

Image 3: MRI image of bilateral frontal mucocele (T1 weighted coronal section)

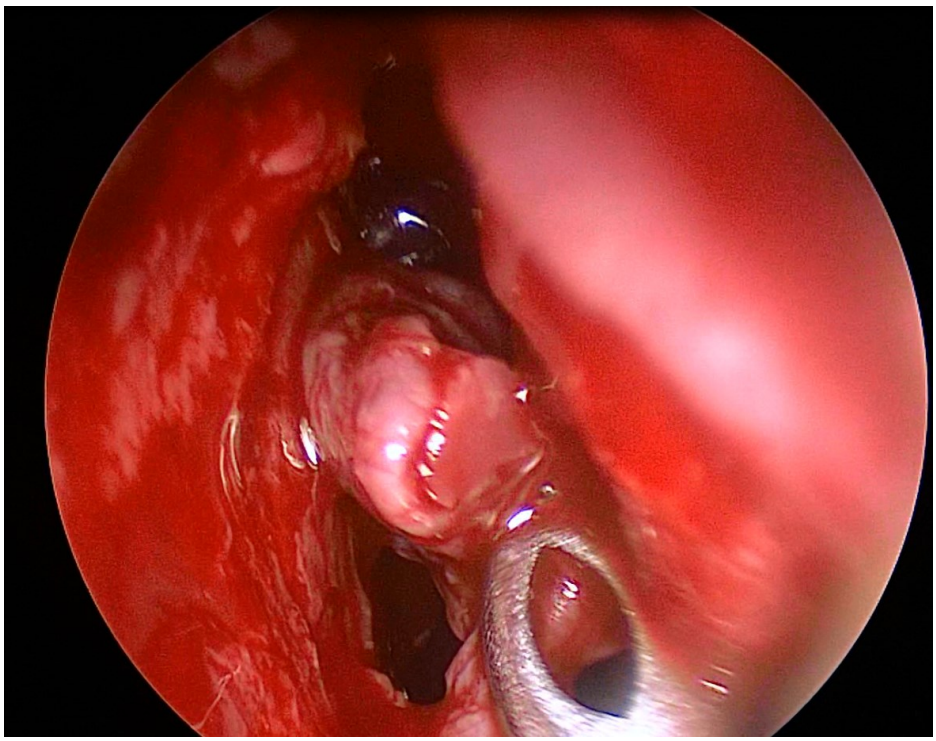

Image 4: Endoscopic examination image of mucocele.

Discussion

Mucoceles are benign lesions that occur following obstruction of sinus drainage ostium and enlarge rather subtly by eroding the surrounding bone structures within the sinus (1, 3). In literature, etiology was attributed to inflammatory process, neoplasm (e.g. osteoma, ossifying fibroma), postoperative complication, allergy, anatomic anomaly, fibrous dysplasia and posttraumatic sequel formation (2, 3, 6, 7). In our case, however, there was not any pathology except for partial stenosis in the frontal recess.

Although mucoceles involve frontal sinuses is common, bilateral involvement is very rare (2, 3). To our knowledge, only 6 cases were reported in the literature. Mucoceles can be seen in any age, but the majority are diagnosed in patients 40 to 60 years-old. This kind of mucocele affects Both Male and female are equally (3).

Microbiologic studies demonstrated that the most common isolated Bacteria were *Staphylococcus Aureus, Alpha-Haemolytic Streptococcus, Haemophilus Species,* and *gram-negative Bacillus*. The anaerobic bacteria species such as *Propionibacterium Acnes, Peptostreptococcus, Prevotella,* and *Fusobacterium* were also isolated (3, 9).

In detailed histopathologic studies, it was shown that a sustained infection develops following obstruction of the frontal recess. Continued stimulation of lymphocytes and monocytes leads to the production of cytokines by the lining fibroblasts in the sinus. These cytokines, in turn, initiate a cycle of resorption and re-modelling in the bone, resulting in expansion of the mucocele (10). Cultured fibroblasts have been shown to have significantly elevated levels of prostaglandin E2 and collagenase. Studies have found that high levels of prostaglandin E2 plays a role in the osteolytic process (3, 11, 12).

Diagnosis is mainly based on the history, physical examination and radiologic imaging. Patients usually complain of frontal headache, facial asymmetry and visual pathologies (impaired visual acuity, restricted eye movements, proptosis) (3,6). Only complaint of our patient was rolling of left eye towards left and down. Proptosis and diplopia are the most common complaints (3, 7).

Mucocele is seen as a homogenous isodense mass showing a regular contrast uptake, if not infected, and leading to irregularity in sinus contours in CT (Image 1). Same mass is seen as an isointense lesion on T1 scan and hyper intense on T2 scan, and thus findings are typical for mucocele (Image 2) (2, 3, 7).

Current treatment technique of mucoceles is surgical drainage with endoscopy. Low morbidity, complication rate and rare recurrences were reported via this treatment modality (2). In our case, we performed fronto ethmoidal sinusectomy and we did not encounter any recurrence during following 6 month.

Mucoceles are important clinic entity because of their proximity to the vital organs such as eyes and brain; moreover they could destruct the close tissues by local invasion. Endoscopic drainage method was performed as the most convenient treatment modality in protecting the vital organs and in avoiding recurrences.

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