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Reviews

Therapeutic Drug Monitoring of Protein Kinase Inhibitors
in Breast Cancer Patients / *Roušarová J., Šíma M., Slanař O.* page 243

Short Review of Liposteroid: A Novel Targeted
Glucocorticoid Preparation for Treatment of Autoimmune
and Inflammatory Diseases / *Saha B. K., Milman N. T.* page 257

Primary Scientific Studies

Evaluating the Effect of Conservative Therapy in Patients
with Wilkes Stage III Temporomandibular Joint Derangement /
*Machoň V., Levorová J., Beňo M., Hirjak D.,
Drahoš M., Foltán R.* page 269

Evaluation of the Effect of Radiofrequency Denervation
on Quality of Life of Patients with Facet Joint Syndrome
by Oswestry Disability Index Score and Visual Analogue
Scale Score / *Gündoğdu Z., Öterkuş M., Karatepe Ü.* page 278

The Effects of Hyperemesis Gravidarum on the Oral
Glucose Tolerance Test Values and Gestational Diabetes /
Bayraktar B., Balıkoğlu M., Bayraktar M. G., Kanmaz A. G. page 285

Case Reports

Supine Percutaneous Nephrolithotomy in a Patient
with Solitary Lung: A Case Report and Literature Review /
*Danacioğlu Y. O., Arıkan Y., Akkaş F., Şam E.,
Özlı D. N., Emir N. S., Atar F. A.* page 294

Spontaneous Multiple Haematomas in a Patient
with Severe COVID-19 Fully Recovered
with a Conservative Approach / *Alavi-Naini R., Gorgani F.,
Rahmati Z., Pourdehghan S., Keikha M., Farzad Z.* page 300

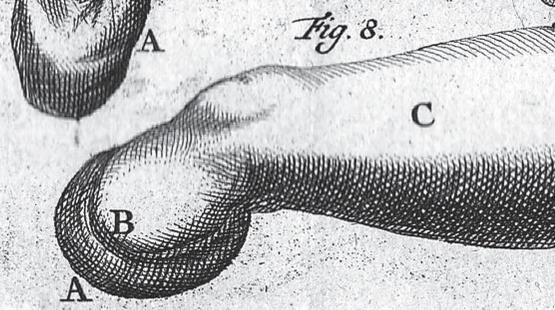
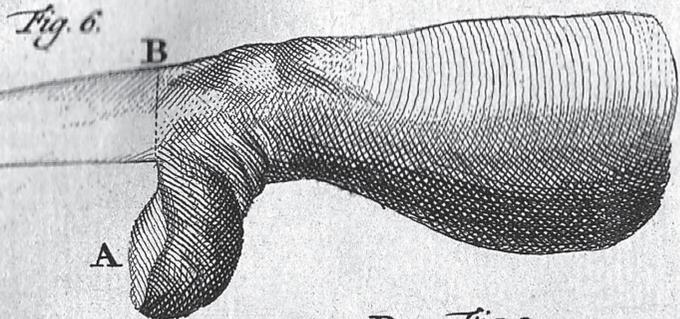
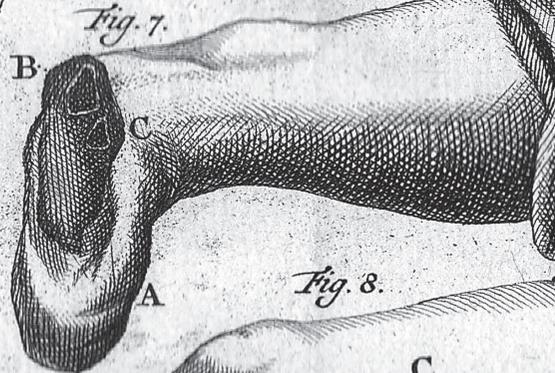
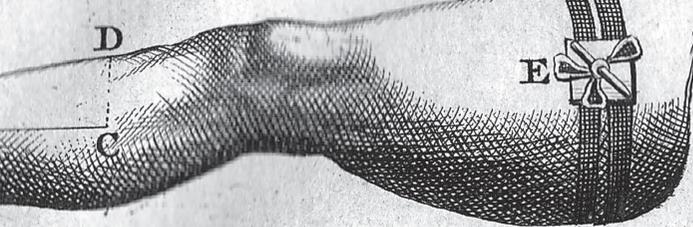
Patella Fracture Identified Using Point-of-care Ultrasound /
Richman M., Kieffer A., Moss R., Dexus D. page 308

Instructions to Authors page 313

Annual Contents page 317

Annual Nominal Index page 321

Annual Referee Index page 323



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Therapeutic Drug Monitoring of Protein Kinase Inhibitors in Breast Cancer Patients

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Key words: Abemaciclib – Everolimus – Lapatinib – Neratinib – Palbociclib – Ribociclib

Abstract: Protein kinase inhibitors (PKIs) represent up-to-date therapeutic approach in breast cancer treatment. Although cancer is a rapidly progressive disease, many substances, including PKIs, are usually used at fixed doses without regard to each patient's individuality. Therapeutic drug monitoring (TDM) is a tool that allows individualization of therapy based on drug plasma levels. For TDM conduct, exposure-response relationships of drug substances are required. The pharmacokinetic data and exposure-response evidence supporting the use of TDM for 6 PKIs used in breast cancer treatment, one of the most common female tumour diseases, are discussed in this review.

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Introduction

Breast cancer is considered the most common female cancer disease worldwide (Sancho-Garnier and Colonna, 2019). It is also the most frequent cause of cancer-related deaths in women in almost all countries except the most economically developed ones, where lung cancer holds the first place (Sancho-Garnier and Colonna, 2019). One of the recently introduced approaches in breast cancer treatment is the inactivation of protein (tyrosine or serine/threonine) kinases. Protein kinase inhibitors (PKIs) are usually used at a fixed dose with no focus on dose individualization. This one-size fits to all strategy could lead in individual patients to suboptimal anticancer effect (underdosing) or to the development of toxicity (overdosing) as the inter-individual variability in pharmacokinetics is very high (Gougis et al., 2019). However, there are no biomarkers for efficacy prediction for any of the 6 PKIs (Table 1) available for the breast cancer therapy. The treatment effect is usually evaluated using radiological assessments every 8–12 weeks, however, the regulation of effective plasma concentration could be beneficial at an early stage of the treatment to stop the progression of the disease as soon as possible (Groenland et al., 2019). Therapeutic drug monitoring (TDM) could be a convenient way for the prediction of treatment response.

TDM directly clarifies the actual drug concentration in serum and allows dosing optimization based on simulated pharmacokinetic parameters of either C_{\max} , C_{trough} , or AUC (area under the curve) derived from a population pharmacokinetic model and adjusted to individual patients' characteristics (Herviou et al., 2016). This approach could improve anticancer treatment efficacy if there was a suitable and predictive pharmacokinetic (PK) parameter. Moreover, PKIs possess a narrow therapeutic window, a significant pharmacokinetic variability and the therapy spans over long time (Groenland et al., 2019). Nevertheless, the exposure-response relationships are not clearly defined for PKIs (Yu et al., 2014). Therefore, the aim of this review is to summarize previously published exposure-response relationships on all six PKIs, which could be used for TDM of PKIs to personalize the treatment in the future.

Literature search and evidence level appraisal

PubMed and Web of Science databases have been searched till February 2021. The key words used for the searches were TDM, therapeutic drug monitoring, pharmacokinetics, and pharmacokinetic target plus tyrosine kinase inhibitor (TKI), PKI, or names of each of 6 PKIs. A total of 1,264 reports have been found using these criteria, which were subsequently screened for the relevance to the aim of this review. There were 5, 11, 6, 4, 6, and 3 relevant publications found for abemaciclib, everolimus, lapatinib, neratinib, palbociclib, and ribociclib, respectively.

Evidence level evaluation derived from Verheijen et al. (2017) was used to characterize the significance of a pharmacokinetic parameter for potential utilization in TDM. Evidence level I, II, and III was used if prospective studies have been already

Table 1 – PKIs used in breast cancer therapy (source: SmPCs, www.ema.europa.eu)

PKIs	Mechanism of action	Dosing
Abemaciclib	CDK 4/6 inhibitor	150 mg Q12H
Everolimus	mTOR inhibitor	10 mg Q24H
Lapatinib	EGFR/HER2 inhibitor	1250 mg Q24H
Neratinib	EGFR/HER2 inhibitor	240 mg Q24H
Palbociclib	CDK 4/6 inhibitor	125 mg Q24H
Ribociclib	CDK 4/6 inhibitor	600 mg Q24H

PKIs – protein kinase inhibitors

performed, if at least two studies showed similar pharmacokinetic values potentially useful for TDM and prospective studies conducting to confirm these values are required in the future, and if pharmacokinetic values came from one study only or from more highly inconsistent studies, respectively.

Pharmacokinetics of PKIs

Since knowledge of pharmacokinetics is essential for the right implementation of TDM, we include a brief pharmacokinetic characteristics of individual PKIs. The basic pharmacokinetic parameters are then summarized in Table 2.

Abemaciclib

Median T_{max} and $t_{1/2}$ ranged from 4 to 6 h and 17.4 to 38.1 h, respectively. When patients with solid tumours were treated with 150 mg twice daily, steady-state AUC_{0-24} reached 4,280 ng×h/ml, and the mean steady-state C_{max} was 249 ng/ml

Table 2 – Basic pharmacokinetic parameters of PKIs

	Half-life (h)	Steady-state C_{max} (ng/ml)	T_{max} (h)	Steady-state AUC (ng×h/ml)	References
Abemaciclib	17.4–38.1	249	4–6	4280	Patnaik et al. (2016)
Everolimus	30.0	61.0	0.5–2.5	514	Gombos et al. (2015)
Lapatinib	24.0	2470	3.0	31900	Chu et al. (2008)
Neratinib	14.0	74.0	4.0	939	Kourie et al. (2016)
Palbociclib	25.9	97.4	5.5	1733	Flaherty et al. (2012)
Ribociclib	32.6	2100	1–5	28200	Infante et al. (2016), Curigliano et al. (2017)

PKIs – protein kinase inhibitors; AUC – area under the curve

(Patnaik et al., 2016). The absorption of abemaciclib was not affected by food intake (Thill and Schmidt, 2018).

Everolimus

The absorption of everolimus was rapid with T_{max} from 0.5 to 2.5 h and the half-life was about 30 h. After 10 mg per day dosing in patients, C_{max} and AUC were 61 ± 17 ng/ml and 514 ± 231 ng×h/ml, respectively (Gombos et al., 2015). High-fat meal reduced C_{max} and AUC by an average of 60% and 16% when compared with treatment under fasting conditions (Falkowski and Woillard, 2019).

Lapatinib

The maximum plasma concentration of lapatinib was reached from 3 to 4 h after the administration and its $t_{1/2}$ was 24 h. Steady-state C_{max} and AUC reached 2.47 µg/ml and 31.9 µg×h/ml, respectively (Chu et al., 2008). There was the only active metabolite GW690006 reported responsible for the inhibition of EGFR (van Erp et al., 2009).

Extreme variability in AUC (6-fold) was observed in patients treated with 1,200–1,500 mg lapatinib (Klumpen et al., 2011). In comparison with fasting state, AUC and C_{max} reached 3.0-fold and 3.2-fold higher values when lapatinib was administered with low-fat breakfast (Burriss et al., 2009). Thus, lapatinib should be taken on an empty stomach (Stein and Mann, 2016).

Neratinib

After a therapeutic dose of 240 mg per day given with food, the mean T_{max} was observed after 4 h and the average $t_{1/2}$ was approximately 14 h. Mean C_{max} of 74 ng/ml and mean AUC_{0-24} of 939 ng×h/ml were observed after 3 weeks of treatment (Kourie et al., 2016).

Palbociclib

C_{max} of 97.4 ng/ml (CV = 41%) (CV – coefficient of variation) was achieved with T_{max} of 5.5 h (2.0–9.8) on day 21 of the treatment with 125 mg once daily. AUC_{0-24} was 1,733 ng×h/ml (CV = 42%) and $t_{1/2}$ was 25.9 h (Flaherty et al., 2012). The reduction of palbociclib levels was observed in fasting conditions, thus palbociclib should be taken with food (Thill and Schmidt, 2018).

Ribociclib

Ribociclib was absorbed with median T_{max} ranging from 1 to 5 h in patients treated with 600 mg per day following a schedule with 3 weeks on and 1 week off treatment. The mean effective half-life was 32.6 h (Infante et al., 2016). The average C_{max} on day 18 was 2,100 ng/ml (CV = 59.3%) and AUC_{0-24} 28,200 ng×h/ml (CV = 64.7%) (Curigliano et al., 2017). The main active metabolite LEQ803 levels correlated with that of ribociclib (Infante et al., 2016). Similarly to abemaciclib, there was no food effect on ribociclib levels (Thill and Schmidt, 2018).

Therapeutic drug monitoring of PKIs

Consistent and defined relationships between exposure and response of each drug are necessary for TDM (Groenland et al., 2019). TDM of PKIs has not become routine as the data on the exposure-response relationships and clinical benefits are insufficient, yet (Cardoso et al., 2020). Prospective clinical studies have already shown promising exposure-response relationships in case of everolimus (Groenland et al., 2019). For the other TKIs, for which pharmacokinetic targets have not been directly established, it is estimated that they reach approximately 82% of the mean population exposure observed in patients treated with approved effective doses in clinical trials (Verheijen et al., 2017). This estimate is derived from TKIs with defined PK target for other therapeutic indications.

The steady-state trough concentration (C_{trough}) may be considered as a surrogate for systemic exposure. Thus, blood sampling should be performed just before the administration of the next dose, which means 12 hours post-dose in a twice-daily regimen and 24 hours post-dose in a once-daily regimen (Gao et al., 2012; Josephs et al., 2013). However, if blood sampling is not performed on time of C_{trough} , in outpatients, PK extrapolation to trough level is needed. It is also important to realize that the time for the first exposure measurement differs among all agents depending on their half-lives as a steady-state is achieved after five $t_{1/2}$ (Cardoso et al., 2020).

Abemaciclib

In preclinical PK/PD analysis, C_{trough} threshold for the efficacy of 200 ng/ml was determined in mice bearing human tumour xenografts. This threshold is consistent with C_{trough} in breast cancer patients treated with efficacious doses of abemaciclib (Tate et al., 2014, 2018).

Consistent data were observed in 5 Japanese patients suffering from advanced solid cancers treated with 200 mg twice daily, in whom mean C_{trough} at steady-state reached 210 ng/ml (CV = 89%). However, in other study group, in which 2 patients were treated with 100 mg twice daily, and another 2 patients with 150 mg twice daily, the C_{trough} in steady state ranged from 102.65 to 1,176.16 ng/ml (Fujiwara et al., 2016). Neutropenia represented the most common adverse event developed in 83.3% of Chinese patients (n=10), followed by diarrhea, leukopenia, and decreased appetite in 75% of the patients (n=9) in phase I abemaciclib study. The mean steady-state C_{trough} of 202 ng/ml (CV = 72%) was observed in 7 patients suffering from tumour diseases, including breast cancer, treated with a standard dose of 150 mg twice daily (Zhang et al., 2021). However, it appears that neutropenia is related to C_{max} of abemaciclib and its metabolites (Groenland et al., 2020).

No relationship between abemaciclib adverse event of a change in QT interval and plasma abemaciclib concentration was found in Japanese patients (Fujiwara et al., 2016).

Groenland et al. (2020) proposed median C_{trough} values of 169 and 197 ng/ml when treated with 150 and 200 mg, respectively, as a promising target for abemaciclib TDM.

The trough level around 200 ng/ml seems to be a promising TDM target. However, more prospective clinical trials are necessary as no robust data on the exposure-response relationship were described.

Everolimus

The strategy of TDM of everolimus has already been established in pediatric oncology and transplantation medicine. In pediatric patients with oncological diagnoses, C_{trough} within 5–15 ng/ml was described as the pharmacokinetic target (Verheijen et al., 2018). In transplantology, a higher number of occurrence of acute rejection was observed when C_{trough} was lower than 3 ng/ml (Kirchner et al., 2004). C_{trough} within 3–8 ng/ml should be targeted when treated with everolimus combined with other immunosuppressants, while 6–10 ng/ml is the range of C_{trough} for everolimus used in monotherapy (Shipkova et al., 2016). The relationship between everolimus exposure and occurrence of adverse effects were also explored in order to define the upper limit of everolimus therapeutic range. While frequency of thrombocytopenia and metabolic disorders increase with increasing everolimus C_{trough} , incidence of leucopenia were relatively constant in the range of everolimus C_{trough} of 1–15 ng/ml (Kovarik et al., 2002; Kirchner et al., 2004).

TDM is not usually applied for everolimus in adult cancer treatment except for tuberous sclerosis complex associated subependymal giant cell astrocytoma and tuberous sclerosis complex-associated partial-onset seizures in which treatment concentrations between 5–15 ng/ml are recommended in the USA (Strobbe et al., 2020). When compared with patients with C_{trough} less than 10 ng/ml, median progression-free survival (PFS) was numerically higher in patients with pancreatic neuroendocrine tumours or renal cell carcinoma with C_{trough} of 10–30 ng/ml (Ravaud et al., 2014). Threshold of 14.1 ng/ml was proposed for the treatment of metastatic renal cell carcinoma as the PFS was 13.3 months in patients achieving this level, while 3.9 months less if lower exposure was measured (Thiery-Vuillemin et al., 2014). Proposed range of 8.2–18.0 ng/ml has been proposed in another study in Japanese patients suffering from renal cell carcinoma. The dose reduction or treatment discontinuation took place when the median everolimus concentration reached 18.0 ng/ml, while patients with dose maintenance had a mean blood concentration of 8.2 ng/ml (Takasaki et al., 2019).

For the breast, kidney, and neuroendocrine cancer treatment with everolimus, C_{trough} between 11.9 and 26.3 ng/ml was proposed. A 4-fold higher risk of toxicity was observed when C_{trough} reached 26.3 ng/ml while a 3-fold higher risk of disease progression was associated with C_{trough} lower than 11.9 ng/ml (Deppenweiler et al., 2017). C_{trough} higher than 19.2 ng/ml was associated with clinically relevant toxicity. The geometric mean C_{trough} was 12.6 ng/ml, but the median PFS was not significantly

different between patients with C_{trough} higher or lower than 12.6 ng/ml (Willemsen et al., 2018). A review of Falkowski and Woillard (2019) based on studies involving exposure-effect relationships for everolimus in oncology considers C_{trough} higher than 20 ng/ml to be a threshold connected with increased risk of overall severe toxicity. Verheijen et al. (2017) described C_{trough} of 13.2 ng/ml as average everolimus exposure and recommended C_{trough} higher than 10 ng/ml as a promising TDM target.

At least some proportion of adverse events such as stomatitis are probably related to the C_{max} . In patients with breast, renal and neuroendocrine tumours switching from once-daily 10 mg regimen to twice-daily 5 mg regimen led to a reduction of 32.7% (21.2 ng/ml) in C_{max} ($p=0.013$) with no negative impact on C_{trough} as an only modest increase in C_{trough} was observed (9.6 [CV = 35.0%] and 13.7 [53.9%] ng/ml when treated with 10 mg once daily and 5 mg twice daily, $p=0.018$). As expected, both AUC and T_{max} maintained with no statistically significant changes ($p=0.70$ and 0.95, respectively) (Verheijen et al., 2018).

Based on available data, the C_{trough} between 10 and 20 ng/ml seems to be a promising TDM target for everolimus in breast cancer treatment. The specific attribute of everolimus is high incorporation into erythrocytes. Therefore, the whole blood should be used for everolimus quantification instead of plasma (Shipkova et al., 2016).

Lapatinib

Large PK variability (6.2-fold for C_{trough} , 2.5-fold for C_{max} , and 6-fold for AUC) was observed in patients treated with 1,200–1,500 mg of lapatinib. This variability could be a reason for the known variation in the anti-cancer effect suggesting possible advantage of TDM in lapatinib treated patients (Klumpen et al., 2011). Neither frequency of diarrhea nor rash as the most prominent adverse events showed apparent relationship to lapatinib serum concentration (Burriss et al., 2005). The diarrhea could be caused by unabsorbed lapatinib, therefore the better correlation is with dose (Klumpen et al., 2011).

The C_{trough} of 480 ± 310 ng/ml was observed in patients treated with 1,200 mg once daily for two weeks (Josephs et al., 2013). In another study, C_{trough} reached the range of 300–600 ng/ml in the majority of responders treated with median dose of 900 mg for metastatic solid tumours. However, only 4 of 67 patients treated for breast cancer showed partial responses (Burriss et al., 2005). Yu et al. (2014) proposed the mean C_{trough} target in steady-state of around 780 ng/ml. This target for the TDM conducting cannot be, however, recommended yet (Yu et al., 2014).

In the study with 21 breast cancer women treated with a combination of 1,250 mg of lapatinib and capecitabine for at least 29 days, the median lapatinib C_{trough} levels reached 5,090 ng/ml. These high values were probably caused by hepatic impairment, drug interactions, or non-compliance with fasting conditions. Despite the high lapatinib levels, no severe toxicity was observed, except for a woman of small stature and low weight with markedly higher levels of 11,250 ng/ml possibly

causing hyperbilirubinemia (Cizkova et al., 2012). Similarly, high levels were observed in patients treated using an intermittent dose-escalation schedule with high doses of lapatinib up to 7,000 mg per day in breast cancer women. Mean concentration in patients who respond to the lapatinib therapy reached 5,727 ng/ml while the mean concentration of non-responders was 2,174 ng/ml. Clinically significant toxicities were noticed in $\geq 10\%$ of patients ($n=40$) and the most common adverse event was diarrhea. Lapatinib treatment led to the resolution of liver metastasis after 2 months, a 63% reduction in a lung metastasis after 17 months, the complete response in bulky mediastinal metastases after 1 year in 3 patients whose lapatinib serum levels exceeded 10,000 ng/ml (Chien et al., 2014).

Due to lacking exposure-response data and significant differences in C_{trough} values in various studies, a specific pharmacokinetic target cannot be established for lapatinib treatment.

Neratinib

As neratinib blocks its target irreversibly, a lower efficacy threshold than the mean could be expected. Due to its irreversible covalent binding, the effect endures even after its elimination from the systemic circulation (Groenland et al., 2019).

In non-clinical mice studies, the exposure of 431 ng \times h/ml was obtained after minimum efficacious dose. In a clinical study the steady-state exposure in 8 partial responders with metastatic breast cancer was about 2.2-fold higher in comparison with the mice exposure (Wong et al., 2009).

Neratinib concentration ≥ 28 ng/ml provided inhibition of autophosphorylation of ErbB2 in ErbB2-overexpressing BT474 cells in preclinical studies. Mean steady-state through concentrations measured in each of 5 study months exceeded this concentration as they ranged from 52 to 59 ng/ml ($CV \leq 62\%$) in 81 breast cancer patients with or without prior trastuzumab treatment treated with 240 mg of neratinib once daily. In 52 of 59 evaluable patients with target lesion at baseline and a minimum of one follow-up, tumour size was reduced. Manageable diarrhea represents the most common adverse event (Burstein et al., 2010).

The concentration of 53.8 ng/ml was measured in a patient suffering from breast cancer with brain metastases treated with neratinib for 13 cycles after surgery. There was no disease progression for 13 cycles and the patient stayed alive for the next 3 years. The level of 53.8 ng/ml corresponds with the aforementioned range of 52 to 59 ng/ml (Freedman et al., 2020).

There is lack information about neratinib relationship between exposure and response. The target of C_{trough} between 52 to 59 ng/ml could be followed and evaluated in prospective clinical studies.

Palbociclib

Only limited exposure-response data exists. To compare concentrations of palbociclib the mean C_{trough} of 61 ng/ml ($CV = 42\%$) observed in patients with

advanced cancer and healthy subjects could be used according to Verheijen et al. (2017), Groenland et al. (2020).

Steady-state geometric mean palbociclib (used together with letrozole) C_{trough} was higher in Japanese (95.4 ng/ml) and other Asians (90.1 ng/ml) when compared with non-Asians (61.7 ng/ml) suffering from estrogen receptor-positive, HER-2 negative advanced breast cancer. The median PFS among Japanese ($n=46$) was 22.2 months and 24.8 among the overall population ($n=666$) when treated with palbociclib in combination with letrozole (Mukai et al., 2019).

Neutropenia is a familiar adverse event when treated with palbociclib and appears to correlate with increased palbociclib exposure (Verheijen et al., 2017). The maximum percent change in absolute neutrophil count correlated with AUC over dosing interval and C_{max} after a 1-cycle of treatment in a study with Japanese patients suffering from advanced solid tumours (correlation coefficients -0.5292 and -0.4581 , respectively). The PFS ranges of 29 to 223 days or 28 to 280 days were gained in patients treated with 100 or 125 mg of palbociclib, respectively. The PFS range of 31 to ≥ 592 days was gained in patients treated with 125 mg of palbociclib concurrently with letrozole. Mean C_{trough} concentration reached 88.5 ng/ml (CV = 49%) in these patients (Tamura et al., 2016). Previous studies showed significantly prolonged PFS in patients suffering from grade 3 or 4 neutropenia. The longer PFS could be caused by the higher sensitivity of patients to palbociclib. Based on the fact that higher palbociclib levels lead to neutropenia and neutropenia lead to longer PFS, Groenland et al. (2020) find an apparent exposure-response relationship.

When palbociclib combined with letrozole, similar median PFS were observed in each of 4 quantiles based on palbociclib exposure (24.9, 27.7, 25.7, and 24.0 months) while all PFSs were higher than PFS of patients treated only with letrozole (14.5 months). This finding suggests that PFS duration is not associated with palbociclib exposure, and patients with different palbociclib exposures benefit similarly. Analogous research was conducted with palbociclib combined with fulvestrant in which average concentration for median PFS was 78.29 ng/ml. Both lower and higher concentrations than 78.29 led to similar PFS (McShane et al., 2018).

On Day 21 C_{trough} was 47.0 ng/ml (CV = 48%) in 4 patients treated with 125 mg once daily. The efficacy was not among the aims of this study, but none of 37 patients treated with different dosages included in the study met RECIST (response evaluation criteria in solid tumours) guidelines for partial response. The only information about responses in patients treated with 125 mg includes a patient with stable disease for ≥ 10 cycles with a testicular tumour (Flaherty et al., 2012).

It is still necessary to evaluate TDM target values for palbociclib treatment in further prospective studies as there is not enough responsible exposure-response data.

Ribociclib

The relationships between exposure and response have not been established due to the lack of data (Shah et al., 2018).

The steady-state geometric mean C_{trough} of 711 ng/ml (CV = 72.9%) was detected in 36 cancer patients treated with 600 mg ribociclib (Samant et al., 2018). However, there is no information about efficacy.

The asymptomatic prolongation of QT interval is a treatment-related adverse event and is associated with C_{max} kinetics. The correlation between neutropenia and thrombocytopenia with exposure was also observed (Infante et al., 2016). Mean QT interval prolongation of 22.87 ms was related to the mean steady-state C_{max} of 2,237 ng/ml (Groenland et al., 2020).

As same as in abemaciclib and palbociclib, higher ribociclib levels are associated with neutropenia (Groenland et al., 2020).

The only available value to verify in further studies is average C_{trough} of 711 ng/ml. Nevertheless, no data on responses in the patients with plasma concentration of 711 ng/ml are available.

Discussion and Conclusion

Using TDM in oncology could help to obtain adequate exposure as soon as possible and thus improve the treatment outcomes (Groenland et al., 2019), however, TDM conducting of PKIs used in the breast cancer treatment is still not a part of routine patient care (Cardoso et al., 2020).

Except for everolimus for which the proposed C_{trough} of 10 ng/ml is a promising target for TDM conduct, the TDM target for the other 5 TKIs has not been established yet. Provisionally, average C_{trough} of responders could be used until special targets become available. However, in many cases there is limited response

Table 3 – C_{trough} proposed as a PK target of PKIs used in breast cancer treatment

	Suggested target C_{trough} (ng/ml)	Evidence level	References
Abemaciclib	200–210	II	Fujiwara et al. (2016), Tate et al. (2018)
Everolimus*	12–19	I	Deppenweiler et al. (2017), Willemsen et al. (2018)
Lapatinib	>600	III	Josephs et al. (2013)
Neratinib	52–59	II	Burstein et al. (2010)
Palbociclib	>62	II	Mukai et al. (2019)
Ribociclib	711	III	Samant et al. (2018)

*In everolimus, target C_{trough} of 10–20 ng/ml is proposed. Everolimus C_{trough} > 10 ng/ml is associated with increased PFS, while C_{trough} > 20 ng/ml is associated with risk of overall severe toxicity. PK – pharmacokinetic; PKIs – protein kinase inhibitors; PFS – progression-free survival

data when achieving the mean C_{trough} . Table 3 shows recently available data on average C_{trough} and everolimus proposed targets for breast cancer therapy. Nevertheless, it is necessary to conduct more prospective studies on feasibility, and utilization of TDM of PKIs to confirm its benefits. Thus, this review is not considered a manual for targeting mentioned concentrations in TDM of PKIs.

Although exposure-response relationships and clear proof of the clinical benefit of TDM of PKIs are absent, these data could help to manage patients with predictive factors for pharmacological failure (Gougis et al., 2019) or patients with unexpected adverse events, or in cases with unsatisfactory efficacy, potential drug-drug interactions, or vulnerable patient populations (Groenland et al., 2019; Cardoso et al., 2020).

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Short Review of Liposteroid: A Novel Targeted Glucocorticoid Preparation for Treatment of Autoimmune and Inflammatory Diseases

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Abstract: This paper briefly reviews the safety and efficacy of liposteroid in different inflammatory and non-inflammatory diseases. Corticosteroids (CS) are the first-line therapy in many inflammatory and autoimmune disorders. Although highly efficacious, long-term use of CS is limited due to the occurrence of significant side effects. Liposteroid, which is a liposomal formulation of dexamethasone palmitate, possess more potent anti-inflammatory and immunosuppressive properties compared to dexamethasone sodium phosphate. These two formulations have markedly different lipid solubility, resulting in different pharmacokinetic and pharmacodynamic properties. Liposteroid has been used with success in patients with rheumatoid arthritis, macrophage activation syndrome, and idiopathic pulmonary hemosiderosis. In addition, liposteroid has been used in some non-inflammatory diseases. Moreover, we conceive that liposteroid may have a beneficial effect in patients, who are critically ill due to COVID-19, and suffer from the macrophage activation syndrome.

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Introduction

Glucocorticosteroids alias corticosteroids (CS) is a class of potent anti-inflammatory and immunosuppressive medications used for treatment of many inflammatory and autoimmune diseases in clinical practice. CS exert their action by inhibiting transcription of proinflammatory genes and altering post-translational modifications of the cytokines, causing reduced secretion of cytokines from the cells (Tobler et al., 1992). Moreover, CS also decrease the production of arachidonic acid metabolites (Newton, 2000).

Dexamethasone is a potent CS with a long half-life. The duration of action ranges between 36 to 72 hours (Shefrin and Goldman, 2009). With equivalent systemic dosing, dexamethasone is 30 times more potent compared to hydrocortisone, regarding its efficacy as an anti-inflammatory agent. Similarly, dexamethasone is 6 times more potent than prednisone or prednisolone, which are the most commonly used systemic CS (Furst and Saag, 2020). Although highly effective, long-term CS therapy is associated with a significant risk of adverse effects, including the propensity of developing infections, metabolic changes (diabetes mellitus, hypertension, obesity) and bone abnormalities (osteoporosis), growth retardation in children, cataract formation, cushingoid appearance, and suppression of the hypothalamic-pituitary axis.

One potential method to reduce CS mediated side effects is the delivery of the necessary quantity of medication to the “site of interest”, i.e., “targeted drug therapy”. Such a strategy will result in a higher concentration of CS in the targeted inflammatory cells and tissues, and a lower systemic dose delivery to “non-target” tissues. In addition, increased potency compared to traditional drug preparations may further enhance the effect and decrease the necessity for a high CS dosing and reduce side effects. To this end, liposteroid represents an attractive and viable alternative to traditional CS therapy (Vishvakrama and Sharma, 2014).

What is liposteroid?

Liposteroid is the liposomal formulation of dexamethasone-21-palmitate (Yokoyama et al., 1985). The liposome vesicles are spherical and composed of a phospholipid bilayer. The lipid bilayer can be uni- or multi-lamellar (Benameur et al., 1993). The specific drug molecule is carried within the hydrophilic center of the liposome vesicle (Figure 1). The average liposomal sphere diameter varies between 0.1 and 0.3 μm , no vesicle being larger than 1 μm (Yokoyama and Watanabe, 1996). Liposteroid was manufactured by Dr. Y. Mizushima in Japan in 1981 and has been used in clinical practice since 1985 (Mizushima et al., 1982). Liposteroid has not yet been approved by the Food and Drug Administration (FDA) in the United States or the European medicines agency (EMA) to treat chronic inflammatory diseases. The medication is not currently manufactured in the United States. Liposteroid is manufactured and marketed as Limethason[®] in Japan for systemic administration and Lipotalon[®]

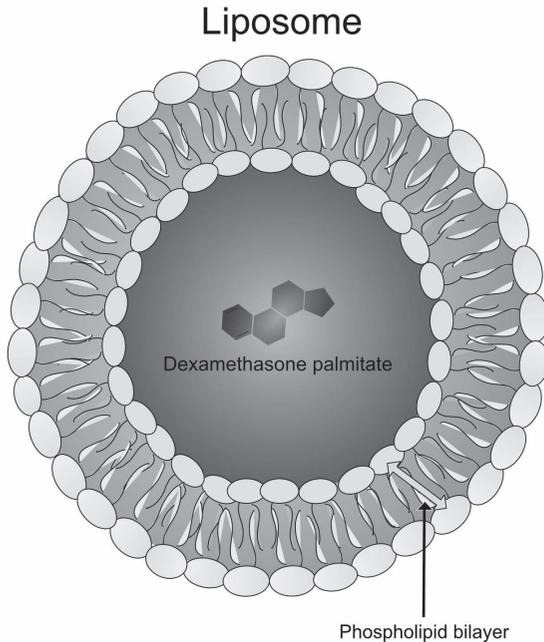


Figure 1 – Structure of the liposteroid.
The hydrophilic dexamethasone palmitate is surrounded by a phospholipid bilayer.

in Germany for topical application. Liposomal preparations of other CS are also available (Schiffelers et al., 2006).

Pharmacokinetic and pharmacodynamic properties

Compared to the conventional parenteral hydrophilic formulation of dexamethasone (dexamethasone sodium phosphate – DSP), liposteroid is much more lipophilic. Consequently, there is a significant difference in the pharmacokinetic properties between liposteroid and DSP (Table 1). Following intravenous injection/infusion, some of the liposomes will undergo partial or total degradation of the lipid bilayer due to hydrolysis by esterases (Gregoriadis et al., 1984), and dexamethasone palmitate is then released into the plasma (Yokoyama and Watanabe, 1996). The intact liposomes are taken up by various cells, either by fusion with the cell membrane or by phagocytosis (Vishvakrama and Sharma, 2014). In phagocytic cells, the liposomes are phagocytosed and the phospholipid wall is degraded by lysozymes, thereby releasing the active drug within the cell (Vishvakrama and Sharma, 2014). The fraction of administered liposomes, which undergo degradation in the blood is dependent on the composition of their lipid structure and the size of the liposome vesicles, i.e., the larger the size, the lower the plasma degradation and the higher the fraction of liposomes being phagocytosed and incorporated into the target cells (Gregoriadis et al., 1984).

Table 1 – Comparison between dexamethasone sodium and liposomal dexamethasone palmitate (liposteroid)

	Dexamethasone sodium phosphate	Dexamethasone palmitate
Preparation	conventional preparation for intravenous and intramuscular administration	liposomal preparation = liposteroid
Plasma concentration following intravenous dose	low	high
Alpha half life due to drug redistribution	0.14 hours	0.32 hours
Elimination half life	5.48 hours	2.17 hours
Tissue concentrations		
Skeletal muscle	high	low
Liver, kidney, lung	similar	similar
Spleen	low	high
Inflamed tissue	low	high
ED ₅₀	0.45 mg/kg	0.08 mg/kg
Potency		5.6 times more potent

ED₅₀ – median effective dose to achieve a specific effect in 50% of the population

Following intravenous administration of liposteroid, the plasma concentration of free dexamethasone palmitate is actually higher than after administration of DSP in equipotent doses, indicating some liposome degradation in the blood. The maximal plasma concentration of dexamethasone palmitate is achieved approximately 1.5 hours after liposteroid administration (Li et al., 1988). The tissue distribution and distribution half-life (alpha half-life) vary markedly between these preparations. Once administered, liposteroid is taken up by phagocytic cells including macrophages in the reticuloendothelial system, both as intact liposomes and at variable stages of degradation (Gregoriadis et al., 1984). The rate of uptake is approximately 8 times faster than that of free dexamethasone palmitate and DSP (Yokoyama et al., 1985; Wakiguchi and Ohga, 2016). Therefore, liposteroid achieves a higher concentration in the spleen compared to DSP (Mizushima et al., 1982). The other organs with high liposteroid deposition are the liver and lungs (Yokoyama and Watanabe, 1996). In contrast, due to its hydrophilic nature, DSP demonstrates a higher concentration in skeletal muscle (Yokoyama et al., 1985). The liver is the primary site of metabolism and degradation of dexamethasone palmitate. After being excreted in the bile, dexamethasone palmitate enters the enterohepatic circulation. Within 48 hours, 60% of dexamethasone is cleared renally, whereas 40% is excreted via the fecal route (Yokoyama and Watanabe, 1996). The elimination or beta half-life also varies

between DSP and liposteroid. In humans, the elimination half-life of DSP is 5.48 hours compared to 2.17 hours for liposteroid (Yokoyama and Watanabe, 1996).

Due to its high lipid solubility and predilection for phagocytic and other inflammatory cells, liposteroid achieves a two-fold higher concentration in inflamed tissues (Yokoyama et al., 1985). The anti-inflammatory effect of liposteroid is 5–6 times more potent than DSP (Mizushima et al., 1982). Moreover, liposteroid exerts a more potent inhibitory effect than DSP on the proinflammatory functions of the macrophages, such as receptor-mediated phagocytosis, production of superoxide, lipid peroxidation, and chemotaxis (Yokoyama et al., 1985; Yokoyama and Watanabe, 1996). In experimental studies, receptor-mediated phagocytosis by macrophages was suppressed by 80% with liposteroid at a concentration of 0.03 mg/ml compared to a 30% inhibition with DSP at a 10-fold higher concentration of 0.3 mg/ml. Similarly, the superoxide production was reduced by 75% by liposteroid at a concentration of 0.03 mg/ml (Yokoyama and Watanabe, 1996). Based on animal studies, the ED₅₀ (median effective dose to achieve a specific effect in 50% of the population) for liposteroid was 0.27 mg/kg and 0.072 to 0.15 mg/kg to prevent edema and granuloma formation, respectively (Yokoyama and Watanabe, 1996).

As liposteroid is distributed predominantly in cells in the reticuloendothelial system, the suppression of the hypothalamic-pituitary axis is lower than conventional steroid formulations. In animal studies, the level of dexamethasone in the pituitary was significantly lower with liposteroid compared to DSP (Mizushima et al., 1982). Likewise, there appear to be fewer metabolic side effects with liposteroid than with DSP (Schiffelers et al., 2006).

Liposteroid in autoimmune and inflammatory diseases

Liposteroid has been utilized for several inflammatory and noninflammatory conditions. These autoimmune and inflammatory diseases include rheumatoid arthritis (RA), graft versus host disease (GVHD), hemophagocytic lymphohistiocytosis (HLH) or macrophage activation syndrome (MAS), and idiopathic pulmonary hemosiderosis (IPH). In addition, liposteroid has been used in patients with infantile spasms or refractory seizures and for vascular protection during intraarterial chemotherapy.

Rheumatoid arthritis

Rheumatoid arthritis (RA) is an autoimmune systemic inflammatory disorder characterized by symmetric destructive polyarthritis. The role of liposteroid was studied early in patients with RA (Mizushima et al., 1983; Hoshi et al., 1985). In a multicenter, double-blind comparative trial of 138 patients with RA, Hoshi et al. (1985) reported a significantly higher rate of symptomatic improvement and lower frequency of adverse effects with intravenous/intramuscular liposteroid (2.5 mg dexamethasone) given every other week, compared to DSP. The study was conducted over a period of eight weeks. Unfortunately, no subsequent trials have been performed.

Macrophage activation syndrome/hemophagocytic lymphohistiocytosis

Macrophage activation syndrome (MAS) or hemophagocytic lymphohistiocytosis (HLH) is a life-threatening condition associated with profound immunologic activation, i.e., cytokine storm, tissue destruction, and multi-system dysfunction. HLH carries a high mortality rate. One of the primary cells involved in the pathogenesis of HLH is the macrophage. The absence of normal downregulation of macrophage activity plays a critical role in the pathogenesis of HLH (Filipovich et al., 2010). As liposteroid is a more effective inhibitor of proinflammatory macrophage activity, researchers have used liposteroid with success in patients with HLH who demonstrated relative refractoriness to conventional CS therapy. Funauchi et al. (2003) reported a case of HLH in a patient with systemic lupus erythematosus where the patient initially improved on intravenous methylprednisolone. However, the cytopenia and ferritinemia were refractory to traditional CS therapy, but normalized following liposteroid therapy (Funauchi et al., 2003). Kobayashi et al. (2007) reported a pediatric patient with familial HLH with perforin deficiency, who was managed with liposteroid prior to a successful bone marrow transplantation. MAS secondary to juvenile dermatomyositis has also been treated successfully with liposteroid (Wakiguchi et al., 2015).

Graft versus host disease

Graft versus host disease (GVHD) is often occurs after allogeneic stem cell transplant. Infiltration of the affected tissue by macrophages is thought to be refractory to therapy and carry a poor prognosis (Nishiwaki et al., 2009). In an animal model of GVHD, Nishiwaki et al. (2014) demonstrated that liposteroid was effective against activated macrophages infiltrating the skin, whereas DSP was not. GVHD refractory to high dose systemic CS has shown improvement with liposteroid therapy (Kurosawa et al., 2020).

Idiopathic pulmonary hemosiderosis

Idiopathic pulmonary hemosiderosis (IPH) is a rare disease characterized by recurrent episodes of diffuse alveolar hemorrhage (DAH) without any known etiology (Saha, 2020; Saha and Chong, 2021). IPH is more prevalent among children than adults (Chen et al., 2017). The latest evidence point towards autoimmune pathogenesis with a genetic predisposition (Saha, 2021). CS represents the first line of therapy both during the acute phase for remission induction and subsequently for maintenance of remission (Saha and Milman, 2021). A minority of patients are refractory to CS and require second-line immunosuppressive medications, such as azathioprine or cyclophosphamide, to achieve disease control (Saha and Milman, 2021). Unfortunately, these medications are associated with an increased risk of infections and malignancies.

Liposteroid has been used successfully in patients with IPH refractory to high dose conventional CS therapy (Sakurai et al., 1999; Doi et al., 2013; Sakamoto et al.,

2018; Tobai et al., 2020). Typically, liposteroid is infused for three successive days at doses ranging from 0.06 to 0.1 mg/kg body weight/day in order to induce remission. The subsequent maintenance dosing is usually started one week after the last induction dose, and subsequently, the interval between infusions is gradually increased, provided the bleeding remains under control. The maximal interval between maintenance doses is four weeks. Doi et al. (2013) reported 9 pediatric patients treated with liposteroid, with a median follow-up of 11 years; 3/9 patients were cured, and another three patients obtained long-term remission. Importantly, all patients survived during the observation period (Doi et al., 2013). This finding is crucial as pediatric patients with IPH have been reported to have a median survival of 2.5 years in previous studies (Ohga et al., 1995).

Other inflammatory diseases

Similar efficacy has been reported in patients with other inflammatory and autoimmune diseases, such as inflammatory myopathy, immune thrombocytopenia (idiopathic thrombocytopenic purpura), and gouty arthritis (Shimizu, 1996; Sakurai et al., 1999; Wakiguchi and Ohga, 2016; Wakiguchi, 2017). Table 2 summarizes the use of liposteroid in autoimmune and inflammatory disorders.

Use of liposteroid for noninflammatory disorders

Prevention of hepatic artery stenosis

Liposteroid also possesses protective effects on the vascular endothelium (Suzuki et al., 1992). Sadahiro et al. (2000) reported an exciting application of liposteroid therapy. The authors utilized liposteroid for the prevention of hepatic artery stenosis due to hepatic arterial infusion of chemotherapeutic drugs for liver metastasis in patients with colorectal cancer (Sadahiro et al., 2000). In their study, when liposteroid was simultaneously infused with 5-fluorouracil, none of the 12 patients developed hepatic artery stenosis. In contrast, 67% of patients in the control arm developed hepatic artery stenosis, defined as $\geq 50\%$ narrowing of the artery. Liposteroid contained 4 mg of dexamethasone palmitate, was infused during each treatment session. For the comparison of efficacy, the reported incidence of hepatic artery stenosis due to hepatic arterial chemo infusion varies between 10–40% (Oberfield et al., 1979).

Infantile spasms and refractory seizures

“West syndrome” is a form of generalized childhood epilepsy characterized by refractory daily seizures and mental retardation. Although the exact mechanism is unknown, adrenocorticotrophic hormone (ACTH) and CS represent first-line agents in the treatment of this disease. Liposteroid therapy has shown improved outcomes and fewer side effects compared to ACTH in several studies of infantile spasms and refractory epilepsy (Yamamoto et al., 1998, 2007; Yoshikawa et al., 2000).

Table 2 – Outcomes in patients treated with liposteroid for inflammatory and non-inflammatory diseases

Disease	Type of study	Patient population	Liposteroid dose	Outcome	References
Rheumatoid arthritis	double blind, prospective trial	adult	2.5 mg IV or IM every 2 weeks	Tendency to higher rate of improvement compared to DSP. Lower frequency of side effects with liposteroid.	Mizushima et al. (1983), Hoshi et al. (1985)
Hemophagocytic lymphohistiocytosis/macrophage activation syndrome	case reports	pediatric	2.5 mg IV daily for 2 weeks, followed by 2.5 mg IV every other day for 2 weeks 7.5 mg/m ² /day for 3 days followed by 3.75 mg/m ² /day for 4 days	Decrease in pancytopenia, serum lactate dehydrogenase and ferritin. Marked regression of systemic symptoms and hepatosplenomegaly.	Funauchi et al. (2003), Kobayashi et al. (2007), Filipovich et al. (2010), Wakiguchi et al. (2015)
Graft versus host disease	case report	adult	10 mg/day three times a week gradually increased to 10 mg/day	Regression of pericardial effusion, ascites, and generalized edema. Decrease in serum ferritin and soluble interleukin 2 receptor.	Nishiwaki et al. (2014), Kurosawa et al. (2020)
Idiopathic pulmonary hemosiderosis	case reports and patient series	pediatric	0.06–0.08 mg/kg/day IV for 3 days, followed by gradual increase in dosing intervals up to 4 weeks	Induction of remission and maintenance therapy.	Sakurai et al. (1999), Doi et al. (2013), Sakamoto et al. (2018), Tobai et al. (2020)

DSP – dexamethasone sodium phosphate; IV – intravenous infusion; IM – intramuscular

Different dosing regimens have been used without any significant adverse reactions (Yamamoto et al., 1998, 2007).

Adverse effect of liposteroid therapy

Liposteroid therapy is generally well tolerated. The incidence of acute toxicity is very low. Sakamoto et al. (2018) reported the development of restlessness, irritability, hypertension, and altered mental status secondary to the development of posterior reversible encephalopathy in a 2-year-old girl after the first dose of liposteroid. The authors also reported a systemic inflammatory syndrome due to the palmitate component of the liposteroid. However, the dose used in this child (0.8 mg/kg body weight/day) was erroneously 10 times higher than the normal standard dose (Doi et al., 2013, 2015). There are no reports of acute systemic toxicity from liposteroid infusion in standard dosing regimens.

There is more concern about possible adverse effects in patients receiving long-term CS therapy. Doi et al. (2013) reported no cases of obesity, hypertension, cushingoid appearance, metabolic- or bone abnormalities in children receiving liposteroid for 2.3–15.6 years. All children had body heights between the 80th to 85th percentiles for normal children, so it is possible that there may be a slight growth retardation.

What is the importance of liposteroid?

Glucocorticoids are the mainstay of therapy for many inflammatory and autoimmune diseases. Despite their usefulness, clinicians are wary of prolonged CS therapy due to the risk of adverse effects. Liposteroid is a unique targeted drug delivery formulation of systemic CS that is more potent and reaches higher concentrations at the sites of inflammation than conventional CS, thereby enabling the clinician to use a lower total systemic dose. This may translate into reduced adverse events while ensuring better outcomes and patient compliance. Although not available throughout the world, the data from Japan is intriguing regarding the safety and efficacy of liposteroid for a multitude of conditions. Large-scale prospective, controlled studies will be necessary to define the role of liposteroid in clinical medicine.

Potential use in COVID-19

Since the beginning of the coronavirus disease-19 (COVID-19) pandemic due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), researchers have been trying to find medications, which are effective in the treatment of both mild and severe disease (Saha et al., 2020). COVID-19 is associated with a significant inflammatory response, and treatment with low-dose dexamethasone has been shown to improve survival among critically ill patients with presumed MAS (RECOVERY Collaborative Group et al., 2021). Consequently, dexamethasone or an equivalent dose of other CS is currently standard of practice throughout the World in these patients. As liposteroid, by targeting the macrophages, has a more potent

anti-inflammatory effect than DSP, it is conceivable that liposteroid could provide a higher beneficial effect for patients with severe COVID-19 pneumonia than DSP. Although this issue so far has not been given attention in the COVID-19 pandemic, we suggest that this hypothesis requires further clinical investigations.

Conclusion

Liposteroid is a liposomal preparation of dexamethasone palmitate with significantly higher potency and anti-inflammatory properties compared to free dexamethasone. Liposteroid accumulates predominantly in phagocytic cells in the reticuloendothelial system and achieves a much higher concentration in inflammatory tissues than DSP. It also provides more effective inhibition of proinflammatory macrophage activity. Although positive outcomes have been reported in most trials with liposteroid, the actual number of trials are limited. This is likely due to the unfamiliarity of this preparation among clinicians as the medication is not available worldwide. Given the potential efficacy and the possibility of reduced adverse effects, further studies are necessary to define the role of this compound in clinical medicine.

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Evaluating the Effect of Conservative Therapy in Patients with Wilkes Stage III Temporomandibular Joint Derangement

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Abstract: The authors evaluated effects of physiotherapy in patients experiencing Wilkes III temporomandibular joint (TMJ) derangement with clinically limited joint mobility, but no pain. The group consisted of 31 patients with unilateral temporomandibular joint involvement, 3 men and 28 women (average age was 30.93, ranging from age 12 to 61). None of the patients in the group had experienced any previous TMJ therapy. The patients underwent conservative therapy in the form of home exercise (mobilisation and isometric exercises) as the first step in treatment. The authors evaluated the improvement in jaw movement (maximal interincisal opening – MIO) and the patients' subjective assessments of their condition. Disc position before and after two months of exercise was also evaluated using ultrasound examination. The average MIO value in patients before starting the exercises was 33.5 mm, and after two months of exercises, 42.4 mm. Subjective assessment by patients: 26 patients (83%) described their condition as completely satisfactory, not requiring further therapy. Of these patients, ultrasound examination showed 10 patients with complete disc reduction, 9 patients with a change in disc displacement with reduction, and 7 patients with a continuing (unchanged) state of disc displacement. Results of our study show the effect of conservative therapy in patients with painless TMJ due to disc displacement (WIII). Effect of home exercises which were easy to perform, simple and acceptable to the patient were demonstrated.

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Introduction

Wilkes stage III (WIII) is a term for an intra-articular disorder of the temporomandibular joint (TMJ) which clinically manifests as limited jaw mobility, blocked jaw movement, frequent pain, joint tenderness and headache. WIII is characterised by disc displacement without reduction and thinning-deformation of the disc. Degenerative changes in the head of the joint and socket are not present (Wilkes, 1989). Treatment of WIII is usually conservative (non-surgical). If conservative treatment fails, minimally invasive procedures (arthrocentesis) or surgery (arthroscopic lavage and lysis, arthroscopic surgery, open surgery) are necessary. (Tenenbaum et al., 1999; Okeson, 2008; Machoň, 2017).

Physiotherapy is an integral part of conservative therapy for temporomandibular joint disorders (TMD), as is the use of occlusal splints or drug therapy. In the case of disc displacement without reduction, the main treatment option is physiotherapy with manual manipulation, especially in acute cases, and muscle massage, relaxation (in the presence of muscle spasm), muscle exercises (passive muscle stretching, assisted muscle stretching, resistance exercises) (Okeson, 2008).

The aim of the study was to evaluate the effect of physiotherapy on maximum opening of the mouth in patients with unilateral, painless WIII, who had not yet undergone any therapy. Another goal was to assess how many patients subjectively regarded their condition as satisfactory, not requiring further care after physiotherapy, and to assess disc position in these patients to see whether any change had occurred since the commencement of exercises. Another aim was to evaluate whether the average age of patients and average duration of the patient's symptoms contributed to any improvement in disc position.

Material and Methods

The primary treatment protocol for patients with WIII at the authors' workplace consists of educating the patient. The next step varies depending on the presence of pain. Patients who experience WIII without pain begin the next step in treatment with physiotherapy. If their condition does not improve within two months, the use of an occlusal splint follows, and physiotherapy is continued. In patients who experience WIII with pain present, treatment begins with the use of analgesics (NSAIDs), muscle relaxants and the application of thermotherapy. If pain reduces within 10 days, the patient begins physiotherapy. In the opposite case, arthrocentesis is indicated (Machoň, 2017).

Physiotherapy takes place in the form of home exercise, which consists of two types:

- 1) Extending the jaw forward (into protrusion), then opening the mouth and biting down (repeat three times, at least three times a day) (Figures 1–3);
- 2) Supporting the jaw with the palms, then attempting to open the mouth for 10 seconds, pushing against the palm. Relaxing the palm after 10 seconds and slowly opening the mouth (repeat three times, at least three times a day) (Figures 4 and 5).



Figures 1–3 – Extending the jaw forward (into protrusion), then opening the mouth and biting down.

In addition to a clinical examination, all patients at the authors' workplace undergo an ultrasound examination of the joint (Mindray DP-50, 7.5 MHz, Shenzhen Mindray Bio-medical Electronics) to determine a precise diagnosis. This examination is also performed on all patients six weeks after the commencement of exercise. This treatment protocol was also applied to the patients evaluated in the study.



Figures 4 and 5 – Supporting the jaw with the palms, then attempting to open the mouth for 10 seconds, pushing against the palm. Relaxing the palm after 10 seconds and slowly opening the mouth.

Criteria for the selection of patients for the evaluation study:

Patients diagnosed with unilateral disc displacement without reduction, where patients experience limited mobility of the affected joint, although without any pain present. In addition, no patients have any systemic diseases (autoimmune, endocrinological, osteological). Patients who had already received some form of therapy were not included in the study. The study also excluded patients with palpable pain of the masticatory muscles, with the presence of muscle spasms, and patients who had been treated or were currently receiving physiotherapy treatment for problems associated with their neck muscles or cervical spine.

The authors examined 175 patients with blocked jaw movement due to disc displacement (WIII); however, only 31 had a unilateral, painless disorder which satisfied the study criteria, i.e. 3 men and 28 women (average age was 30.93, ranging from age 12 to 61).

Evaluation of the effect of exercise:

Maximum interincisal opening (MIO in millimetres), symmetry of movement and the presence of potential acoustic phenomena were noted in patients before the commencement of therapy.

If no deterioration in the condition was observed, the first follow-up examination was conducted two months after the commencement of treatment with home exercise, during which:

- a) MIO, symmetry of jaw movement, the presence of acoustic phenomena and the presence of any pain were clinically evaluated;
- b) Patients were asked for their subjective view whether they felt an improvement in their condition, whether the state of their TMJ was such that it did not require further treatment, or conversely, whether it required the continuation of therapy.

Another factor was the evaluation of ultrasound findings, i.e. the position of the disc in patients before and two months after the commencement of exercises.

Statistical evaluation was applied to assess groups of patients who exhibited:

- Displaced disc reduction
- A change in disc displacement with reduction

following exercise, or who showed no change in disc position. Student's *t*-test was applied for evaluation and compared the age of patients and duration of symptoms. Statistically significant differences were set at $p < 0.05$.

Results

Evaluation of patients before the commencement of home physiotherapy:

The average MIO value was 33.5 mm, with jaw movement deviating to the affected side in all cases, while acoustic phenomena and pain were not recorded in any case. Ultrasound examination of all patients showed anterior disc displacement. The average duration of blocked movement before the commencement of treatment was 4.15 months (1–12 months).

During the two months of home exercise, no patient experienced a deterioration in condition which required monitoring sooner than two months after the commencement of therapy.

The average MIO value was 42.4 mm. Improvement in opening of the mouth occurred in 25 patients, with an average improvement in movement of 9 mm (3–23 mm).

In 10 patients (32%), lower jaw movement showed symmetry; 9 patients (29%) recorded movement of the jaw with deflection to the side of the joint with disc displacement, while in 12 patients (39%), movement with deviation to the affected side persisted.

Pain was not reported by any patient, and acoustic phenomena (clicking) were observed in 9 patients during jaw movement.

Patients' subjective assessments: 26 patients (83%) described their condition as completely satisfactory, not requiring further therapy. According to ultrasound examination, 10 of these patients experienced complete disc reduction (38% – the average age was 28.9, with an average duration of symptoms of 2.3 months). In 9 patients, a change in the state of disc displacement with reduction occurred (34% – the average age was 32.7, with an average duration of symptoms of 2.1 months). Permanent disc displacement persisted in 7 patients (22% – the average age was 31.25, with an average duration of symptoms of 6.1 months).

Statistical evaluation did not show a statistically significant difference between the groups with complete disc reduction, disc displacement with reduction or persistent disc displacement without reduction following therapy in terms of the patients' average age (P-value = 0.29) and the duration of symptoms (P-value = 0.4068).

Five patients subjectively assessed their condition as unsatisfactory, requiring further treatment – these were all patients with persistent disc displacement without reduction according to the ultrasound examination.

Discussion

Conservative therapy for patients diagnosed with WIII is the basic treatment method and produces results comparable to mini-invasive and surgical therapy (Schiffman et al., 2007, 2014). Given that conservative therapy methods relating to joint structures are reversible, with minimal risk of structural damage, they are always the first treatment method selected (Randolph et al., 1990, Okeson, 2008). The goal of conservative therapy is to reduce pain (use of nonsteroidal anti-inflammatory drugs, soft food diet, application of heat) and subsequently improve opening of the mouth through physiotherapy and joint mobilisation (Nicolakis et al., 2001; Okeson, 2008; Machoň, 2017).

A basic step in physiotherapy in patients who experience WIII is manual mobilisation (MM), a manual disc reduction technique recommended by many authors as a first therapeutic step (Foster et al., 2000; Okeson, 2008; Miernik and Więckiewicz, 2015). Therefore, for successful MM, it is ideal if the condition is the patient's first episode of blocked joint movement and that the duration of symptoms has been less than one week (Okeson, 2008). Another factor for the success of therapy is the state of disc displacement. Changes and deformations reduce the success of MM (Kurita et al., 1999; Foster et al., 2000). For greater therapeutic effect, MM should be performed under general anaesthesia using central myorelaxation; however, this places greater stress on the patient (Kurita et al., 1999; Foster et al., 2000). The authors did not perform MM, mainly because most patients consult the authors' workplace after experiencing several weeks of symptoms (the average duration of blocked jaw movement in the study was 3.5 months).

In addition to joint mobilisation, physiotherapy also focuses on the involvement of masticatory muscles and the treatment of muscle co-contraction and muscle pain (Okeson, 2008). In the authors' work, the treatment of patients with painless WIII only focused on exercises which led to joint mobilisation; patients with evident muscle pain were not included in the study.

A number of exercise protocols are mentioned in the literature for patients with TMD. The Rocabado 6×6 programme is often mentioned (Rocabado and Iglarsh, 1991) (rest position of the tongue, control of TMJ rotation, rhythmic stabilisation technique, axial extension of the neck, shoulder posture, stabilised head flexion): these six exercises are performed six times a day. Kraus (1988) presents exercises in three parts. The first includes the rest position of the tongue, the relative position

of the jaw, diaphragmatic breathing, palpation and strength training. The second part focuses on neuromuscular control of mandibular movement. The third part includes isometric exercises. Yoshida et al. (2011, 2013) recommend exercises in two stages for patients with WIII; the first stage of the exercise programme consists of active movements repeated for 10 minutes, i.e. lateral movement towards to the right and left, protrusion and opening of the mouth. The second stage consists of passive exercises, i.e. opening the mouth with the fingers. Both stages are repeated at least eight times per day.

The authors are convinced that exercises performed by the patient at home are especially important for successful physiotherapy (Yoshida et al., 2011, 2013; Shafferr et al., 2014). Physiotherapy performed under repeated supervision by a therapist or physician can be limiting for many patients in terms of time. Another factor contributing to success is the simplicity of the exercises and their ease of performance (Yoshida et al., 2011, 2013; Shaffer et al., 2014). Therefore, the authors of the study recommend only two types of exercises for patients: mobilisation exercises (where the patient moves their jaw into protrusion, opening the mouth) and isometric exercises. The authors believe that a greater number of exercises becomes a less attractive option due to the time required to perform the exercises for some patients and the routine being less clear and comprehensible to others. Fewer exercises are easier for the patient to master to achieve regular and correct performance.

In addition to the performance of physiotherapy, good communication between the physician and patient, thorough instruction and patient motivation are also important in treatment. The physician's initial consultation with the patient should include a careful explanation of the patient's problem, the possible causes and treatment options (Randolph et al., 1990). The authors emphasise the need for thorough instruction and practice of the exercises.

The results of the authors' study show that 83% of patients subjectively viewed the therapy as effective and were satisfied with their condition after two months, characterising it as requiring no further therapy. Objective evaluation of jaw movement showed an improvement in opening of the mouth in 80% of patients, with an average improvement in movement of 9 mm (3–23 mm). These results are comparable to the work of other authors (Nicolakis et al., 2001; Shiffman et al., 2007, 2014).

Ultrasound examination showed an objective improvement in condition in 19 patients (61%) after exercise: in 10 cases, complete disc reduction occurred (32%), and in 9 cases, disc displacement with reduction when opening the mouth was seen (29%). Improved disc mobility was seen in patients with an average duration of symptoms of 2.2 months, while in patients where disc mobility did not improve, the average duration of symptoms was 6.1 months. This may confirm the fact that conservative therapy and physiotherapy are more effective in patients with acute symptoms (Randolph et al., 1990; Miernik and Więckiewicz, 2015). However,

this was not verified by the statistical evaluation in the authors' study. Furthermore, spontaneous adjustment of disc position must not be disregarded in the evaluation of the effect of therapy (Sato et al., 1997; Shiffman et al., 2014).

The authors' study has several disadvantages. This is a simple evaluation of therapy without a comparison group; therefore, the placebo effect of these exercises cannot be clearly assessed. Another negative aspect is the low number of patients (31 patients), which was affected by the conditions for the inclusion of patients in the study. The third negative factor is the evaluation of disc position using ultrasound examination alone, whereas much greater accuracy is achieved with magnetic resonance imaging (Almeida et al., 2019). On the other hand, ultrasound examination is readily available (waiting time for magnetic resonance imaging of the TMJ is up to 6 weeks at the authors' workplace) and may be performed immediately, with a clear advantage from an economic perspective.

Conclusion

Results of our study show the effect of conservative therapy in patients with painless blocked movement of the TMJ due to disc displacement (WIII). The authors demonstrated the effect of simple, easy to perform home exercises which were acceptable to the patient. However, the integral part of the success of treatment is the patient's motivation and instruction, and, of course, the effect of spontaneous disc adjustment.

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Evaluation of the Effect of Radiofrequency Denervation on Quality of Life of Patients with Facet Joint Syndrome by Oswestry Disability Index Score and Visual Analogue Scale Score

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Abstract: In this study, we aimed to investigate the effect of radiofrequency denervation procedure on pain and quality of life of patients with facet joint syndrome. Forty-seven patients who were admitted to our hospital with low back pain and diagnosed with facet joint syndrome between January 2018 and December 2018 were included in our study. The patients underwent denervation with radiofrequency under fluoroscopy in a sterile operating room condition. The pre-procedure and 6th month follow-up VAS (visual analogue scale) and ODI (Oswestry disability index) scores of the patients were recorded. When the demographic data of the patients were analysed, the mean age of the patients was found to be 52. Of the patients, 61.7% were female. In the evaluation of VAS and ODI scores, which we used to measure the efficiency of the procedure, the 6th month values were found to be statistically lower than the pre-procedure values ($p < 0.05$). The first treatment for

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facet joint syndrome is bed rest and medical treatment. Resistant cases also benefit from physical therapy and intra-articular steroid injection. In patients unresponsive to these treatments, denervation with radiofrequency appears to be an effective method. At least two levels must be performed for the procedure to be successful. Studies have shown that pain decreases in the long term (6–12 months) and quality of life increases. We also obtained similar results in our studies. In conclusion, we think that RF (radiofrequency) can be used as an effective method in cases where other treatments fail.

Introduction

It is possible to define chronic pain as a condition that is resistant to administered treatment regimens, requires long-term treatment, and affects the quality of life of individuals in all fields. This constant pain restricts the simplest movements of individuals and causes difficulties in both work and daily life. This leads to anxiety and depression. Most of these pains are low back and leg pain. Although the most common cause is lumbar disc herniation, studies have shown that 15–40% of low back pain is caused by facet joint pain (Al-Najjim et al., 2017). The pain originates from the median branch of the spinal dorsal ramus (McCormick et al., 2014; Al-Najjim et al., 2017). Medical treatment (analgesics, anti-inflammatory drugs, muscle relaxants and antidepressants, etc.) and bed rest are given as treatment. If pain persists, physical therapy and/or surgical therapy is another treatment option. In treatment-resistant persistent cases, invasive procedures such as radiofrequency (RF), steroid and/or local anesthesia can be used for the treatment (Bogduk, 2005).

Facet joint denervation with radiofrequency is used as a treatment option in resistant cases (Schwarzer et al., 1994). It was first used in 1973 by Dr. Shealy. Radiofrequency denervation aims to prevent the transmission of nonspecific stimuli by damaging the nerve that transmits pain. If the local anesthetic injection temporarily relieves the pain, RF will be beneficial. With radiofrequency, a clinical improvement is observed in pain lasting 6–12 months (Shabat et al., 2013). Today, quite successful results can be obtained with the development of radiological imaging examinations.

Material and Methods

In this retrospective clinical study, 47 patients between the ages of 18–75 who were diagnosed with facet syndrome and underwent facet denervation among the patients who were admitted to the Algology Outpatient Clinic of Elazig Fethi Sekin City Hospital between January 2018 and December 2018 after the ethics committee approval was obtained. The sample size was calculated with reference to previous studies. Alpha error of 0.05 was accepted as beta error 0.8, and the minimum sample size was calculated as 44 patients. Firat University non-invasive studies were approved by the ethics committee dated 14.01.2021 and numbered 2021/01-28.

Patients requiring surgical treatment, those who were pregnant or were suspected pregnancy, patients younger than 18 years of age, patients with coagulation disorder, patients with local or systemic infectious disease were excluded from the study.

Patients who were scheduled for denervation procedure with RF due to lumbar facet joint syndrome were transferred to the operating room. After the diagnostic block was performed with local anesthetic (1 cc, 2% lidocaine) under fluoroscopy, the patients who benefited from the block 50% or more underwent denervation with RF. All patients underwent denervation procedure with conventional RF under fluoroscopy using a 17 G C-RFA electrode (Lumbar Cool [R] Cooled Radiofrequency Kit, Kimberly-Clark, LLC, Roswell, GA) for 90 seconds at 80 degrees by finding the target nerve at L1-5 levels. The patients were discharged with recommendations (not using cars and tools requiring manual skills for 24 hours, etc.) after the observation in the ward for a few hours after the procedure.

Age, gender, trauma history (present-absent), previous treatments received (medication, physical therapy, radiofrequency treatment), pre-treatment visual analogue scale (VAS) scores and Oswestry disability index (ODI) were recorded. The VAS and ODI scores of the patients were recorded again in the 6th month after the procedure in order to evaluate the success of the procedure.

Statistical analysis

Number (n) and percentage (%) values were used to show the distribution of individuals and demographic information such as gender, hypertension and diabetes. The normality distribution of continuous variables such as age, height, weight, pre-VAS score, post-VAS score, pre-ODI score, post-ODI score in the study were evaluated graphically by the Shapiro-Wilks test. The median (IR – interquartile range) values were used to show descriptive statistics. Additionally, mean \pm standard deviation values were used for descriptive statistics. The paired sample paired two-sample *t*-test (*t*) was used to compare pre-ODI score and post-ODI score values. In addition, the Wilcoxon signed-rank test was used to compare pre-VAS score and post-VAS score values. The Wilcoxon signed-rank test (*Z*) was used to compare the pre- and post-values of the ODI score sub-dimensions (pain intensity, personal care, lifting, etc.). IBM SPSS Statistics Version 21.0 (IBM Corp. Released 2012; IBM SPSS Statistics for Windows, Version 21.0, Armonk, NY) and MS-Excel 2007 software were used for statistical analysis and calculations. The level of statistical significance was accepted as $p < 0.05$.

Results

Of the individuals participating in the study, 38.3% ($n=18$) were male and 61.7% ($n=29$) were female. The mean age of the individuals was determined as 52.16 ± 12.67 years. In addition, it was determined that the mean height of the individuals was 164.77 ± 9.38 cm and the mean weight was 75.43 ± 13.89 kg (Table 1).

Table 1 – Descriptive statistics

	Mean ± SD	Median (IR)
Age	52.16 ± 12.67	55.0 (16.0)
Height	164.77 ± 9.38	165.0 (14.0)
Weight	75.43 ± 13.89	73.0 (23.0)
pre-VAS	7.04 ± 1.30	7.0 (2.0)
post-VAS	3.78 ± 0.92	4.0 (1.0)
pre-ODI	46.24 ± 17.54	46.0 (22.0)
post-ODI	21.56 ± 7.35	22.0 (11.0)

VAS – visual analogue scale; ODI – Oswestry disability index; SD – standard deviation; IR – interquartile range

Table 2 – Comparison of pre- and post-procedure VAS values

pre-VAS	post-VAS	Test statistics	
Median (IR)	Median (IR)	Z	p
7.0 (2.0)	4.0 (1.0)	5.974	<0.001

VAS – visual analogue scale; IR – interquartile range; Z – Wilcoxon signed-rank test statistics

Table 3 – Comparison of pre- and post-procedure ODI values

pre-ODI	post-ODI	Test statistics	
Mean ± SD	Mean ± SD	t	p
46.24 ± 17.54	21.56 ± 7.35	13.294	<0.001

ODI – Oswestry disability index; SD – standard deviation; t – paired two-sample t-test

It was found that the individuals showed a statistically significant difference in the comparison of the pre-procedure VAS values and post-procedure VAS values ($Z = 5.974$; $p < 0.001$). It was determined that the median pre-procedure VAS value was higher than the median post-procedure VAS value (Table 2).

A statistically significant difference was found in the comparison of the pre-procedure ODI values and the post-procedure ODI values ($t = 13.294$; $p < 0.001$). It was found that the mean pre-procedure ODI values of the individuals were higher than the mean post-procedure ODI values (Table 3).

A statistically significant difference was found in the comparison of the pre- and post-pain intensity values of the individuals participating in the study ($Z = 5.809$, $p < 0.001$). The pre-procedure median value of the pain intensity of the individuals was determined as 3.0 (IR = 1.0) and the post-procedure median value was 1.0 (IR = 0.0) (Table 4). The comparison of other parameters is summarized in Table 4.

Table 4 – Comparison of pre- and post-values of the parameters

	Pre-median (IR)	Post-median (IR)	Test statistics	
			Z	p
Pain intensity	3.0 (1.0)	1.0 (0.0)	5.809	<0.001
Personal care	1.0 (2.0)	1.0 (1.0)	3.992	<0.001
Lifting heavy	3.0 (4.0)	1.0 (1.0)	5.010	<0.001
Walking	3.0 (1.0)	1.0 (0.0)	5.566	<0.001
Sitting	3.0 (2.0)	1.0 (0.0)	5.311	<0.001
Standing up	3.0 (2.0)	1.0 (1.0)	5.737	<0.001
Sleep	2.0 (3.0)	1.0 (1.0)	4.755	<0.001
Sexual life	1.0 (1.0)	1.0 (1.0)	2.658	0.008
Social life	1.0 (3.0)	1.0 (0.0)	4.336	<0.001
Travel	2.0 (2.0)	1.0 (0.0)	5.261	<0.001

IR – interquartile range; Z – Wilcoxon signed-rank test statistics

Discussion

The facet joints in the lumbar region have an important role in the movement and stabilization of the spine (Hägg and Wallner, 1990; Acarkan et al., 2019). They also play an important role in carrying body weight (Beyazova and Gökçe Kutsal, 2000). The fibers of the medial branch of the posterior primary ramus and the dorsal branch of the sinovertebral nerve provide innervation of the facet joints. The pain originates from the medial branch located at the same level and the medial branch originating from the upper segment. It is pain in the form of back pain may radiate to the side of groin, thigh or knee.

Lumbar facet syndrome occurs as back pain or sciatic pain due to facet joint degeneration due to aging, traumatic, etc. (Maas et al., 2015). Patients present with pain that increases with movement (bending back and side). Pain spreads to regions such as hips, thighs and knees. There is pain with palpation of the facet joint. Patients complain of a blunt pain. Hypertrophy of the facet joints, synovial cysts and irregularities in the joint surfaces can be visualized radiologically. In the examination, the straight leg raise test is negative. Diagnostic blocks the facet joints and nerves that innervate these joints with local anesthetics make a diagnosis; however, this is not a 100% reliable method (Cohen and Raja, 2007). The first-line treatment is bed rest and medication (non-steroidal anti-inflammatory drugs – NSAIDs, myorelaxants, antidepressants, opioids, etc.). Physical therapy is added to the treatment in unresponsive patients. Cases resistant to conservative treatment benefit from the injections of local anesthetic and steroid into the facet joint (Cohen and Raja, 2007; Çırak and Çağlar Okur, 2020). Denervation is performed with RF in cases that do not respond to current treatments. At least two levels of denervation should be performed, since the facet joints are innervated from the medial branches at the same level and the upper one. The effectiveness of surgery in facet joint syndrome is controversial (Manchikanti et al., 2000).

There are two different types of RF, namely conventional RF used for procedures such as facet joint denervation, and pulsed RF used for conditions such as chronic neuropathy and peripheral neuropathies. In conventional practice, heat ablation is provided by stimulation with continuous heat dissipation from a needle catheter (Cohen and Raja, 2007; Vatansever et al., 2008). Before the procedure, the medial branches of the facet joint should be locally anesthetized under fluoroscopy and under sterile conditions and it should be observed that more than 50% relief is achieved in pain. This procedure is diagnostic. After this procedure, conventional RF is performed at 80 °C for 60–120 seconds. In our study, we completed the denervation procedure by applying RF at 80 °C for 90 seconds.

Tekin et al. (2007) compared the efficacy of pulsed RF and conventional RF methods in chronic facet joint pain and evaluated patients' VAS and IR values before the procedure, 6 months and 1 year after the procedure. As a result, they reported that both pulsed RF and conventional RF methods were effective in reducing pain and could be an alternative method in treatment. However, they concluded that conventional RF was more effective than pulsed RF, and the number of patients not using analgesics and patient satisfaction were higher in conventional RF (Tekin et al., 2007).

Studies have shown that patients' back pain increases from the age of 35 and this increase continues until the age of 50s (Nagi, 1976). The reason for this increase can be attributed to the fact that patients are more physically active and therefore more exposed to factors such as trauma. In our study, we found the mean age of the patients as 52.

Studies have found that low back pain is more common in housewives (Stranjalis et al., 2004). Similarly, the study by Nagi (1976) found that females had more back pain than males. Similarly, we found that it was more common in females (61.7%). This difference can be explained by the fact that women are more susceptible to trauma, they do more housework, express their existing complaints more and by hormonal changes due to menstruation.

Studies have shown long-term (6–12 months) improvement in patients after denervation with RF. In a meta-analysis studies conducted by Lee et al. (2017), VAS values were found to be significantly better in the RF group at 12-month follow-up compared to the control group. Similarly, in another cohort study performed, significant improvements were observed in patients at 12 months in denervation with RF (Dreyfuss et al., 2000).

In our study, we examined the VAS and ODI scores to evaluate the effectiveness of the treatment and the effect of the procedure on the quality of life. We found a significant decrease in VAS values at the post-procedure 6-month follow-ups. In the analysis of the ODI score values, in which the patients' deteriorated quality of life (sleep, social life, walking, etc.) by pain was evaluated, it was found that there was a significant increase in the quality of life due to the post-procedure decrease in pain.

Conclusion

We think that in cases resistant to other treatment options, denervation with RF provides significant relief in the pain levels of the patients and increases the quality of life.

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The Effects of Hyperemesis Gravidarum on the Oral Glucose Tolerance Test Values and Gestational Diabetes

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Key words: Hyperemesis gravidarum – Gestational diabetes – Oral glucose tolerance test – Pregnancy complications – Pregnancy outcome – Fetal macrosomia

Abstract: This study is aimed at determination whether pregnant women who develop hyperemesis gravidarum in the first trimester have a tendency to develop gestational diabetes mellitus (GDM). It is also aimed at identification of effects of hyperemesis gravidarum and GDM on prenatal and neonatal status in case they were detected together. Hyperemesis gravidarum diagnose was based on the following signs and symptoms. To diagnose GDM, first trimester fasting blood glucose measurement and subsequent blood glucose monitoring and 75-g oral glucose tolerance test (OGTT) were performed in the second trimester. A total of 949 singleton pregnant women (95 with and 852 without hyperemesis gravidarum) who met our criteria were included in the study. In the first trimester, plasma blood glucose and positive GDM screening were found to be significantly higher in the hyperemesis gravidarum group compared to the control group ($p=0.042$ and $p<0.001$, respectively). However, actual GDM cases were similar between both groups. The positive predictive value was significantly lower in the hyperemesis gravidarum group (28.5% vs. 72.7%, $p=0.003$). In the second trimester, the prevalence of GDM was 6.6% in the hyperemesis gravidarum group and 7.3% in the control group, with no significant difference ($p=0.218$) between-groups. In this study, hyperemesis gravidarum was found to cause changes in maternal metabolism in the first trimester of pregnancy due to limited calorie intake and fasting; in the presence of hyperemesis gravidarum, it should be known that the positive predictive value of first trimester gestational diabetes screening may decrease and the diagnosis of pseudo-GDM may increase.

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Introduction

Nausea often refers to an uneasy sensation including an urge to vomit; vomiting can be defined as the oral excretion of stomach and duodenum contents due to the contraction of the diaphragm and other abdominal muscles (Golembiewski et al., 2005). Although vomiting is frequently preceded by nausea, it may occur without nausea or with persistent nausea (Golembiewski et al., 2005).

Nausea and vomiting are common complaints in 50–80% of pregnant women, negatively impacting their family, social, and work life (Matthews et al., 2010). Symptoms usually begin at 2–4 weeks after the last menstrual period; they peak at 9–16 weeks and disappear until 22 weeks of gestation at the latest (Lacroix et al., 2000).

Hyperemesis gravidarum is a pregnancy complication characterized by vomiting, malnutrition due to excessive vomiting, ketonemia-ketonuria, electrolyte imbalance, and, ultimately, loss of >5% of body weight (Pollack and ACOG Committee on Practice Bulletins-Gynecology, 2003), with its frequency ranging from 0.3% to 3% (Matthews et al., 2010). Persistent symptoms continue during pregnancy in 10% of pregnant women, although they usually disappear around 22 weeks (Lacroix et al., 2000). Although spontaneous recovery is frequently observed, dehydration and ketonemia may lead to electrolyte and acid-base imbalance, which could eventually lead to hepatic and renal failure (Fairweather, 1968). The etiopathogenesis of hyperemesis gravidarum remains to be fully elucidated; however, it is associated with a number of factors such as pregnancy hormones (human chorionic gonadotropin, estradiol, progesterone), hyperthyroidism, upper gastrointestinal dysmotility, immune system dysfunction, nutritional disorders, helicobacter pylori infection, and psychological factors that may exacerbate the situation (Pollack and ACOG Committee on Practice Bulletins-Gynecology, 2003). The American College of Obstetricians and Gynecologists (ACOG) recommends early intervention to prevent the progression of nausea and vomiting during pregnancy to hyperemesis gravidarum, which negatively affects a women's family, social, and business life (Pollack and ACOG Committee on Practice Bulletins-Gynecology, 2003).

Gestational diabetes mellitus (GDM) can be defined as glucose intolerance of any degree, which is first diagnosed or first occurs during pregnancy (American Diabetes Association, 2003). Approximately 7% of all pregnancies are complicated by GDM, with this rate varying between 1% and 14% in different populations (American Diabetes Association, 2003). Compared with non-pregnant women, to maintain maternal euglycemia, the amount of insulin secreted from the pancreas due to increased insulin resistance seems to be higher among pregnant women. During pregnancy, insulin resistance is physiologically tolerated by healthy women, whereas those with diabetes mellitus (DM) or those who did not have DM before pregnancy cannot compensate for the insulin resistance; therefore, GDM may occur in them (Creasy et al., 2009).

Due to the maternal metabolism that is impaired because of hyperemesis gravidarum and starvation, ketone formation occurs through fatty acid oxidation. *In vitro* study has shown that long-term fatty acid oxidation and ketone accumulation in the plasma may impair pancreatic B-cell functions and decrease insulin secretion and may increase blood glucose levels (Zhou and Grill, 1995).

Therefore, this study aimed to determine whether pregnant women who develop hyperemesis gravidarum in the first trimester have a tendency to develop GDM and aimed to identify the effects of hyperemesis gravidarum and GDM on prenatal and neonatal status in case they were detected together.

Material and Methods

The study was designed as a retrospective cohort. Pregnant women who were diagnosed with hyperemesis gravidarum between 2016 and 2019, who underwent first trimester fasting glucose measurement and were followed up using a 75-g oral glucose tolerance test (OGTT) were selected as the study group. Pregnant women whose follow-up results could be accessed through the hospital information system, who gave birth at our hospital, and for whom newborn treatment and newborn intensive care follow-ups were provided at our hospital were included in this study. Hyperemesis gravidarum was diagnosed based on the following signs and symptoms: nausea and vomiting combined with ketone in urine made with dipstick test, >5% of body weight loss, or severe nausea and vomiting that could limit fluid intake, even when the other condition were absent (Pollack and ACOG Committee on Practice Bulletins-Gynecology, 2003). Pregnant women aged <18 and >35 years and those with multiple pregnancies; with fetal weight < 500 g; with known type 1 and type 2 DM; with hepatitis, gastroenteritis, pyelonephritis, or urolithiasis; and with missing findings in their records were excluded. Pregnant women without any additional pregnancy complications, whose fasting plasma glucose was measured in the first trimester and who were administered 75-g OGTT and gave birth at our hospital were included as the control group in the study.

In the protocol of our hospital, peripheral blood glucose measurements are made six times a day for pregnant women with fasting plasma glucose of ≥ 92 mg/dl in the first trimester. Based on these measurement values, gestational diabetes is diagnosed. In addition, all pregnant women are administered 75-g OGTT between the 24 and 28 weeks of gestation according to the recommendations of the International Association of Diabetes and Pregnancy Study Groups (IADPSG) (International Association of Diabetes and Pregnancy Study Groups Consensus Panel et al., 2010). To diagnose GDM, values ≥ 92 mg/dl after fasting, 180 mg/dl after the first hour, and 153 mg/dl after the second hour are used during the second 75-g OGTT as accepted by IADPSG (International Association of Diabetes and Pregnancy Study Groups Consensus Panel et al., 2010). Simultaneously, newborns weighing $\geq 4,000$ g were considered to have macrosomia.

Ethics committee approval for this study was obtained from the University of Health Science Tepecik Education and Research Hospital Ethics Committee and informed consent was not necessary due to the retrospective nature of this study.

Statistical analysis

The Statistical Package for the Social Sciences (SPSS) 22.0 version (IBM Corporation, Armonk, New York, US) software package was used for statistical analysis. The normally distributed variables were evaluated using Kolmogorov-Smirnov ($n > 30$) and Shapiro-Wilk ($n < 30$) tests. For parametric variables, student's *t*-test was used and data were presented as mean \pm standard deviation, whereas for non-parametric variables, Mann-Whitney U test was used and data were presented as median \pm (min, max). For categorical variables between the groups, chi-square test was used and odds ratio (95% confidence interval [CI]) was calculated. Results were considered significant at $p < 0.05$.

Results

A total of 947 singleton pregnant women (95 with and 852 without hyperemesis gravidarum) followed up at our hospital between 2016 and 2019 were included in the study. Their demographic information is summarized in Table 1. Although the frequency of nulliparity was higher in the hyperemesis gravidarum group, no significant difference was found between the two groups in terms of age, parity, and fetal gender. Furthermore, no significant difference was found between the groups when body mass index (BMI) was evaluated during the test.

In the first trimester, plasma fasting blood glucose and positive GDM screening were found to be significantly higher in the hyperemesis gravidarum group compared

Table 1 – Demographic features of pregnant women involved in the study

	Hyperemesis gravidarum group (n=95)	Control group (n=852)	P-value
Age (mean \pm SD)	30.6 \pm 6.3	30.6 \pm 6.6	0.855
Parity (n, %)			0.143
Primipara	35 (36.8%)	252 (29.5%)	
Multipara	60 (63.2%)	600 (70.5%)	
Gender (n, %)			0.611
Male	46 (44.7%)	436 (51.9%)	
Female	49 (55.3%)	416 (48.1%)	
BMI during test (mean \pm SD) (kg/m ²)	25.3 \pm 4.2	26.8 \pm 5.7	0.742

BMI – body mass index; SD – standard deviation

Table 2 – Values of fasting plasma glucose among pregnant women and presence of gestational diabetes

	Hyperemesis gravidarum group (n=95)	Control group (n=852)	P-value
Positive GDM screening test (n, %)	14 (15.7%)	44 (5.1%)	<0.001
GDM prevalence (n, %)	4 (4.2%)	32 (3.7%)	0.826
Positive predictive value (%)	28.5	72.7	0.003
Fasting (median, min–max) (mg/dl)	89.6 (60–158)	84.6 (57–153)	0.042

GDM – gestational diabetes mellitus

Table 3 – Values of 75-g oral glucose tolerance test among pregnant women and presence of gestational diabetes

	Hyperemesis gravidarum group (n=91)	Control group (n=820)	P-value
GDM prevalence (n, %)	6 (6.6%)	60 (7.3%)	0.800
Fasting (median, min–max) (mg/dl)	86.9 (59–151)	86 (61–203)	0.888
Hour 1 (median, min–max) (mg/dl)	148.6 (82–328)	145.6 (41–315)	0.749
Hour 2 (median, min–max) (mg/dl)	118.5 (60–313)	114.7 (32–283)	0.563

GDM – gestational diabetes mellitus

to the control group ($p=0.042$ and $p<0.001$, respectively). However, actual GDM cases were similar between the groups. The positive predictive value was significantly lower in the hyperemesis gravidarum group (28.5% vs. 72.7%, $p=0.003$). The findings are summarized in Table 2.

In the second trimester, the prevalence of GDM was 6.6% in the hyperemesis gravidarum group and 7.3% in the control group, with no significant between-group difference ($p=0.218$). Similarly, 75-g OGTT administered after fasting and after the first and second hours showed that there was no significant difference between the hyperemesis gravidarum group and the control group ($p=0.888$, $p=0.749$, and $p=0.563$, respectively). The findings are summarized in Table 3.

The effects of hyperemesis gravidarum as a secondary analysis on the outcomes in pregnant women with GDM are summarized in Table 4. There was no significant difference between the group with hyperemesis gravidarum with GDM and the group with only GDM in terms of birth week and weight. The frequency of macrosomia was similar between the groups. Moreover, the number of newborns with Apgar scores of < 7 in the first and fifth minutes was lower in the hyperemesis gravidarum group, with no significant between-group difference. The need for neonatal intensive care unit (NICU) admission was found to be similar between the two groups.

Table 4 – Delivery outcomes in gestational diabetes mellitus with together hyperemesis gravidarum and the group with only gestational diabetes

	Group with GDM and hyperemesis gravidarum (n=10)	Group with only GDM (n=92)	P-value
Gestational age at delivery (mean ± SD)	38.3 ± 1.5	38.6 ± 2.0sp	0.327
Preterm delivery (n, %)	1 (10%)	12 (13.0%)	0.784
Birth weight (mean ± SD) (g)	3237 ± 587	3309 ± 437	0.724
Macrosomia (n, %)	1 (10%)	20 (21.7%)	0.383
1 minutes Apgar score < 7 (n, %)	1 (10%)	12 (13.0%)	0.784
5 minutes Apgar score < 7 (n, %)	1 (10%)	10 (10.9%)	0.932
NICU admission (n, %)	1 (10%)	10 (10.9%)	0.932

GDM – gestational diabetes mellitus; NICU – neonatal intensive care unit; SD – standard deviation

Discussion

In this study, hyperemesis gravidarum was found to cause changes in maternal metabolism in the first trimester of pregnancy due to limited calorie intake and fasting; however, it did not increase the incidence of GDM.

In a retrospective analysis performed by Ohara et al. (2016), OGTT was performed in the first trimester in pregnant women with hyperemesis gravidarum, and the incidence of screening test positivity found to be higher in hyperemesis gravidarum group. However, similar to our study, the actual prevalence of gestational diabetes was similar between the groups. In addition, first trimester fasting blood glucose level values were compared between the groups in our study and it was found to be significantly higher in the hyperemesis gravidarum group. Hyperemesis gravidarum is a complication, which can be detected in 0.3–3% of pregnant women; it affects calorie intake at varying levels and may cause ketonemia due to fatty acid oxidation (Pollack and ACOG Committee on Practice Bulletins-Gynecology, 2003; Matthews et al., 2010). In the acute period; prolonged fasting, low calorie intake and ketonuria may decrease insulin secretion and increase blood glucose levels; thus, hypothetically it would reasonably increase the incidence of pseudo-GDM in this group of patients (Zhou and Grill, 1995). Also, a stress response caused by vomiting and nausea may contribute to high glycemia in the hyperemesis gravidarum group, especially if present at the time of blood glucose determination.

Both Ohara et al. (2016) and Madendag et al. (2018) investigated the prevalence of GDM in the second trimester. However, similar to us, they found no difference between the groups in terms of GDM in the 75-g OGTT test they performed between 24–28 weeks of gestation. This may be explained by the nature of hyperemesis gravidarum. Majority of pregnant women with hyperemesis gravidarum regain their health at the beginning of the second trimester; however, OGTT is still

performed until the end of the second trimester. Therefore, the incidence of GDM is not directly affected by hyperemesis gravidarum.

In our study, all values obtained for OGTT were found to be higher in the hyperemesis gravidarum group than in the control group, but the difference was not significant. Similarly, Ohara et al. (2016) have reported higher OGTT values in the hyperemesis gravidarum group both in the first and second trimesters. However, while the fasting value was higher in the hyperemesis gravidarum group, the first- and second-hour values were higher in the control group in Madendag et al.'s (2018) study. These different results are attributable to different patient selection criteria.

The secondary purpose of this study was to investigate the outcomes of pregnancies complicated by GDM with hyperemesis gravidarum. Although some studies have shown a relationship among GDM (Hedderson, 2003; Köck et al., 2010; Dorfman et al., 2015), hyperemesis gravidarum (Tierson et al., 1986; Goodwin, 2008; Veenendaal et al., 2011; Peled et al., 2013; Vikanes et al., 2013), and preterm labour, studies on pregnancies complicated by both are limited. We compare the group with hyperemesis gravidarum and GDM with the group with only GDM. The prevalence of preterm birth and gestational age at delivery were lower in the hyperemesis gravidarum group, and macrosomia was more frequent in pregnancies complicated by only GDM, but the results were not significant. Considering the literature suggesting that hyperemesis gravidarum may negatively affect the fetal weight (Bailit, 2005; Dodds et al., 2006; Roseboom et al., 2011; Veenendaal et al., 2011), it can be predicted that hyperemesis gravidarum in association with GDM decreases the incidence of macrosomia. The prevalence of newborns Apgar score of < 7 in the first and fifth minutes and the prevalence of admission to the neonatal intensive care unit (NICU) were lower in the hyperemesis gravidarum group; but results such as other studies were not significant (Roseboom et al., 2011; Vikanes et al., 2013).

Because genetic infrastructure, nutritional habits, and race are known to be associated with DM, our study may be deficient in diversity. Another limitation of the study is the lack of regular weight monitoring. In addition, since sample size in the group with GDM and hyperemesis gravidarum group was relatively small, the reliability of the results in this table may have been affected. As our institute is a high-volume hospital, we aimed to decrease the effect of these limitations on our results by increasing the number of patients, using strict patient selection criteria, and extending the retrospective examination period.

Conclusion

In conclusion, in the presence of hyperemesis gravidarum, it should be known that the positive predictive value of first trimester gestational diabetes screening may decrease and the diagnosis of pseudo-GDM may increase. Although the incidence of actual GDM is not affected by hyperemesis gravidarum, both physicians and patients

need to be more knowledgeable in this regard. Therefore, international, prospective randomized studies are needed on this subject.

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Supine Percutaneous Nephrolithotomy in a Patient with Solitary Lung: A Case Report and Literature Review

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Abstract: Percutaneous nephrolithotomy (PNL) surgeries are performed with different patient positions, anesthesia methods and different-sized access sheaths in order to reduce the complication rates. Supine positioned PNL can be performed safely in the high-risk group patients with comorbidities. Herein, we present a patient who had a past surgical history of right pneumonectomy and underwent a supine PNL procedure under regional anesthesia for a staghorn renal stone in the right kidney.

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Introduction

Percutaneous nephrolithotomy (PNL) is the gold standard treatment method for renal stones larger than 2 cm. It has been made possible to perform this surgery in patients from all age groups by means of the technological developments in the field of endourology (Fernström and Johansson, 1976). Despite these developments, PNL surgeries are performed with different patient positions (i.e. prone, supine, flank), anesthesia methods (regional, general) and different-sized access sheaths in order to reduce the complication rates (Basiri et al., 2010; Nouralizadeh et al., 2013). Thus, with the help of these flexibilities, PNL can be performed safely in the high-risk group patients with comorbidities. Supine PNL which became popular during the last two decades was defined by Valdivia Uría in 1987. It has been shown by subsequent studies that, this position had several advantages when compared with the prone PNL (Proietti et al., 2019). Lesser exposure of the surgeons to radiation, shorter surgical time, rendering simultaneous endoscopic intrarenal surgery possible and most importantly, reduction of the risks associated with anesthesia in high-risk patients who have respiratory compromise are the main advantages of this approach (Curry et al., 2017; Proietti et al., 2019). There are case reports published in the literature regarding supine PNL surgeries performed in nephrolithiasis patients with high anesthesia-related risks (ASA \geq 3) and comorbidities (Manohar et al., 2007). In this report, we are presenting a patient who had a past surgical history of right pneumonectomy and underwent a supine PNL procedure under regional anesthesia for a staghorn renal stone in the right kidney.

Case report

A 58-year-old male patient presented to our outpatient clinic with the complaint of right-sided flank pain. His past medical history was significant for a history of lung cancer for which he underwent right pneumonectomy and received adjuvant chemotherapy in 2013. No cancer recurrence or metastasis was detected during

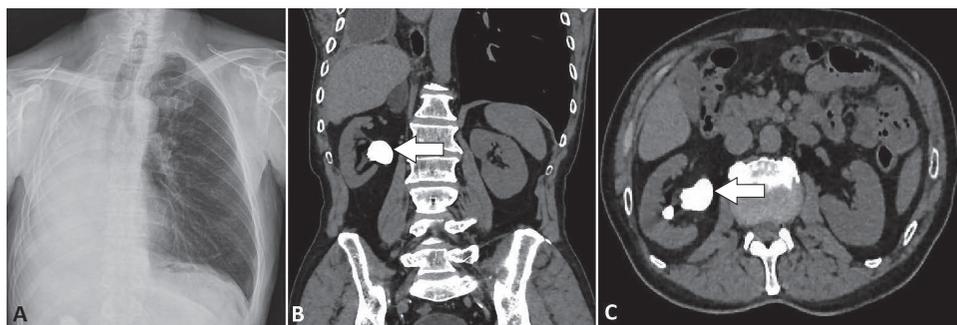


Figure 1 – Preoperative radiological imaging. A) Preoperative chest X-ray of the patient. B) Coronal view of the staghorn calculi filling his right kidney pelvis and lower pole. C) Axial view of the staghorn calculi filling his right kidney pelvis and lower pole.

his 5-year follow-up (Figure 1A). Physical examination, blood biochemistry and urinalysis findings were all unremarkable. Ultrasonography showed a staghorn renal stone and grade 2 pelvicalyceal dilatation in the right kidney. Non-contrast computerized tomography (NCCT) and intravenous urography were performed for more thorough investigation of renal anatomy, localization of the stone and assessment of the renal function. These investigations revealed that both kidneys were functional and there was a 45×40×35 mm staghorn stone in the right renal pelvis (Figure 1B and C). The stone volume was calculated by the formula: $\pi \times 1/6 \times \text{length} \times \text{width} \times \text{height}$, as 315 mm³. The maximum stone density was calculated as 940 Hounsfield unit (HU). Right-sided PNL surgery was planned. Pre-operative workup included pulmonary function tests which revealed a forced expiratory volume in 1 second (FEV1) and a forced vital capacity (FVC) of 25% and 24%, respectively.

An epidural catheter was introduced to the intervertebral space between T12 and L1 by an 18-G needle in order to provide sensitive anesthesia between the segments T6 and S4 (from the level of kidneys to the level of the penile urethra). Adrenalin (1:200,000) and 3 ml of lidocaine were administered. Subsequently, the solution



Figure 2 – The Galdakao-modified Valdivia supine position.

including 5 mg 0.5% bupivacaine and 20 ml of 0.05 mg/ml fentanyl was injected through the epidural catheter and sensitive anesthesia was provided. Anesthesia maintenance was obtained by administration of 10 ml from this solution every hour. Sensitive anesthesia was obtained without motor blockade by means of the selected drug concentration.

Galdakao-modified Valdivia supine position was given to the patient and the right flank was elevated by the help of a surgical gel positioning pad. Posterior axillary line, iliac crest and 12th rib were marked with a pen (Figure 2). A 5-F ureteral catheter was advanced through the right ureteral orifice by means of a 7-F semirigid ureteroscope (Karl Storz[®], Tuttlingen, Germany). An 18-G Chiba needle (Cook Medical, Bloomington, IN, USA) was introduced to the lower pole and a 0.038-inch guidewire (Sensor guidewire, Boston Scientific[®], US) was advanced through the needle under fluoroscopy and ultrasound (Logic3, GE Healthcare, US) guidance. The tract was dilated over the guidewire by a 9-F coaxial. Further dilatation was achieved over the 9-F coaxial by dilators (Amplatz Type Renal Dilators Set, Boston Scientific[®], US) ranging from 16-F to 24-F. Subsequently, a 24-F access sheath (Amplatz sheath, Boston Scientific[®], US) was placed into the tract. A 19-F nephroscope (Karl Storz[®], Tuttlingen, Germany) was introduced through the access sheath. The stone was visualized and subsequently fragmented by a pneumatic lithotripter (EMS, LithoClast Master, Switzerland). Stone fragments were removed by using a stone grasper (Grasping Forceps, Karl Storz[®], Tuttlingen, Germany). No residual stones were identified during fluoroscopic imaging. A 14-F nephrostomy tube was inserted into the renal pelvis after fragmentation of the stones. Duration of surgery and total blood loss were determined as 63 minutes and 130 milliliters, respectively. There were no intraoperative and postoperative complications. The

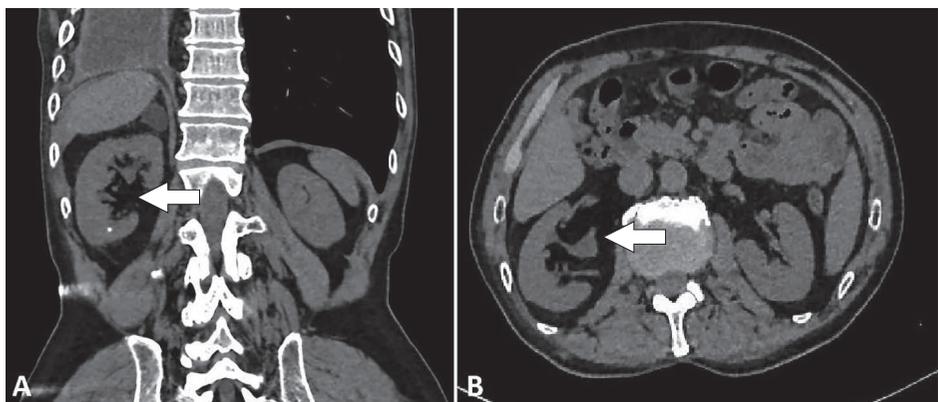


Figure 3 – Postoperative radiological imaging. A) Coronal imaging in non-contrast computed tomography after the operation. No residual stone in the right kidney. B) Axial imaging in non-contrast computed tomography after the operation. No residual stone in the right kidney.

patient was discharged on the 2nd postoperative day following the removal of the nephrostomy tube. The patient did not have any complaints in the first follow-up visit one month after the surgery and the NCCT scan did not reveal any residual stones (Figure 3).

Discussion

Despite the fact that switching from the conventional prone approach to the supine approach did not have any impact on the success rates, supine PNL is still less frequently preferred by the endourologists (Sofer et al., 2017). As a matter of fact, supine PNL has several advantages over prone PNL. Shorter surgical time, less intrarenal pressure increase, less radiation exposure and rendering simultaneous retrograde intrarenal surgery possible for the endourologist represent its surgical advantages. Since there is no need for intraoperative position change, the procedure lasts shorter (Proietti et al., 2019). Easier exposure for respiratory and cardiac interventions, absence of inferior caval vein compression and less risk for thromboembolism with the help of more favourable ventilator parameters constitute the anesthesia-related benefits of this approach (Proietti et al., 2019).

Although PNL is considered as a safe procedure especially inexperienced hands, complications may still occur. Complication rates are similar between supine and prone-positioned PNL procedures (Baard et al., 2014). Furthermore, most of the perioperative complications in the prone PNL are anesthesia-related and pulmonary problems arising from position change can lead to these complications (Kyriazis et al., 2015). Advanced patient age, obesity and the presence of a lung disease are the major risk factors for pulmonary complications. Despite the fact that pain management can be suboptimal; spinal, epidural and intrapleural anesthesia methods can be implemented for patients who have a high risk for surgery (Mehrabi et al., 2013).

To the best of our knowledge, this report is the first in the literature to present a case of supine PNL performed under regional anesthesia in a patient with one lung. In this case, we performed supine PNL under regional anesthesia in order to reduce the risk of anesthesia-related complications since our patient had a history of right pneumonectomy which lowered the functional lung capacity. The supine approach led to lower intrarenal pressure with subsequent less fluid absorption, less perirenal fluid extravasation and cardiac preload while regional anesthesia led to easier patient management. One of the reasons for choosing supine PNL is that it allows general anesthesia to be applied if regional anesthesia is not provided with sufficient anesthesia. General anesthesia was not required in our patient to the end of the operation.

Conclusion

Peri-operative management of high-risk patients is challenging both for the surgeon and anesthesiologist. The surgical approach should be individualized in order to

reduce complication rates. In line with this approach, supine PNL can be preferred to prone PNL in for the patients who have lung disease. Case series are needed to elaborate on the safety profile of this approach in these patients as well as other high-risk patient populations.

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Spontaneous Multiple Haematomas in a Patient with Severe COVID-19 Fully Recovered with a Conservative Approach

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Abstract: A significant number of hospitalized patients with COVID-19 are prone to thromboembolic events including deep vein thrombosis, pulmonary embolism, cerebrovascular accident, and myocardial infarction. However, some COVID-19 patients have a higher risk of bleeding that is associated with an increased risk of mortality. We report a 71-year-old woman who was a confirmed case of COVID-19 admitted for pulmonary involvement and complicated acute renal failure. During hospitalization, she suffered from a sudden onset of severe pain in the lower left abdomen as well as a sudden drop in blood pressure and hemoglobin. Haematomas in the left rectus and obturator internus muscle were observed in abdominal and pelvic computed tomography scan. Signs of haemorrhage were also seen in the anterolateral aspect of the bladder with extension to the paracolic, subdiaphragmatic, perihepatic and, perisplenic spaces. The patient was totally recovered by a conservative approach. Bleeding tendency could be a serious complication, especially, in COVID-19 patients with complicated renal failure that receive heparin prophylaxis.

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Introduction

Patients with severe form of COVID-19 are at risk of systemic coagulopathy which mostly appears as thrombotic events rather than bleeding tendency. High ACE2 expression in the endothelium of blood vessels is responsible for the attachment of SARS-CoV-2 spike protein leading to internal injury inside the vascular wall of blood vessels (Tang et al., 2020). Subsequently, thrombosis can develop in many organs causing pulmonary embolism, deep vein thrombosis, cerebrovascular accident, myocardial infarction, and mesenteric ischemia (Miesbach and Makris, 2020).

Although thrombotic events represent the most common coagulation disorders, few patients with COVID-19 have a higher tendency to bleeding for many reasons including consumption of coagulation factors, thrombocytopenia and administration of anticoagulant (Al-Samkari et al., 2020).

Herein, we describe a confirmed COVID-19 patient with severe bleeding presenting as multiple intramuscular haematomas that fully recovered after a severe critical condition without any interventional and surgical management.

Case report

A 71-year-old woman with a history of hypertension and hypertrophic cardiomyopathy presented to the Emergency Department (ED) complaining of cough, dyspnea, and vomiting, on 14 April 2021. The disease started 12 days before admission with myalgia, fatigue and anorexia followed five days later by nausea, vomiting, dry cough and shortness of breath. She denied sore throat, nasal discharge or obstruction, anosmia and diarrhea during this period of time.

The patient was admitted four days before her recent admission complaining of fever, malaise, cough and mild shortness of breath but she did not receive any medical treatment except oxygen and fluid therapy; and was discharged after two days. Following the progression of dyspnea at home, she was referred to our ED two days later for further evaluation and treatment. She had a long history of hypertension, for which she had been treated with triamterene H, amlodipine and atenolol. The patient had been hospitalized twice for uncontrolled hypertension and heart disease. She did not have any history of chronic kidney injuries, diabetes mellitus or chronic obstructive pulmonary diseases.

On admission, she appeared ill but was alert and responded to all of the questions by herself. Her temperature was 37.5 °C; blood pressure 130/80 mm Hg; heart rate 98 beats/min; and respiratory rate 24/min. Oxygen saturation (SpO₂) was 88–90% while breathing in ambient air and the ratio of arterial oxygen partial pressure to fractional inspired oxygen (PiO₂/FiO₂ ratio) was 270. The most important results of laboratory blood tests taken at the time of admission and subsequently are demonstrated in Table 1. It should be mentioned that her last routine laboratory test was done approximately three years ago with normal results. Real-time polymerase chain reaction analysis of a nasopharyngeal and oropharyngeal swab sample confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection.

Table 1 – Laboratory tests during the hospitalization

Laboratory tests (unit)	14-April	18-April	23-April	24-April	26-April	1-May
White cell count (/μl)	7.500	10.700	19.600	26.500	15.000	5.500
Neutrophil count (%)	85	86	89	94	89	75
Haemoglobin (g/dl)	14	12.80	8.7	6.7	10.7	11.3
Platelet count (/μl)	110000	165000	211000	120000	65000	165000
Blood urea nitrogen (mg/dl)	60	53	46	55	33	23
Creatinine (mg/dl)	2.6	2.3	2.1	2.6	1.7	1.1
Prothrombin time/INR (second)	13(1)	14(1.2)	13(1)	13(1)	13(1)	13(1)
aPTT (second)	30	35	100	110	36	38
Aspartate amino-transferase (IU/l)	12		514		169	42
Alanine amino-transferase (IU/l)	18		838		110	48
Lactate dehydrogenase (IU/l)	393		894		760	220
Fibrinogen (mg/dl)			136			
D-dimer (ng/ml)			720			
Ferritin (ng/ml)	362				922	
ESR (mm/h)	90				58	
C-reactive protein (mg/l)	48		56			21

The reference ranges of laboratory parameters for adults: WBC: 4,500–11,000 per microliter; haemoglobin: 12.0–15.5 grams per deciliter; platelet count: 150,000–400,000 platelets per microliter; blood urea nitrogen: 7–20 mg/dl; creatinine: 0.59–1.04 mg/dl; prothrombin time: 10–13 seconds; international normalized ration (INR): 0.8–1.1; activated partial thromboplastin time: 30–40 seconds; aspartate aminotransferase: 0–35 IU/l; alanine aminotransferase: 19–25 IU/l; lactate dehydrogenase: 140–280 IU/l; fibrinogen: 200–400 mg/dl; D-dimer: <250 ng/ml; ferritin: 12–150 ng/ml; erythrocyte sedimentation rate (ESR): 0–20 millimeters per hour; C-reactive protein: 0–10 mg/l

Four of her children also had been recently tested positive for SARS-CoV-2 and received symptomatic treatment (intrafamilial transmission).

Bilateral peripheral ground-glass opacities were detected in chest computed tomography (CT) scan suggestive of viral interstitial pneumonia. Supplemental oxygen therapy with an orofacial mask was prescribed at the time of admission. We could not administer remdesivir because of the estimated glomerular filtration rate (eGFR) of less than 20 ml/min. Low dose intravenous dexamethasone, ceftriaxone, pantaprazole as well as prophylactic subcutaneous unfractionated heparin were

administered for the patient. Previous anti-hypertensive medications were also prescribed on condition that her blood pressure increased.

The ultrasonography of the kidneys revealed a cortical cyst with a diameter of 9 millimetres in the upper pole of the left kidney and a 4 mm stone in the upper pole of the right kidney. Both kidney sizes were within normal limit with increased parenchymal echogenicity. The result of echocardiography showed left ventricular hypertrophy with an ejection fraction (EF) of 50%. At the end of the first week, she recovered from acute respiratory failure.

On day 9, the patient complained about an acute diffuse abdominal pain with a bulging in her left lower quadrant (LLQ). The abdomen was tender on examination and a firm tender mass was felt on the LLQ. No trauma had occurred and no physiotherapy had been done for the patient. The systolic blood pressure decreased

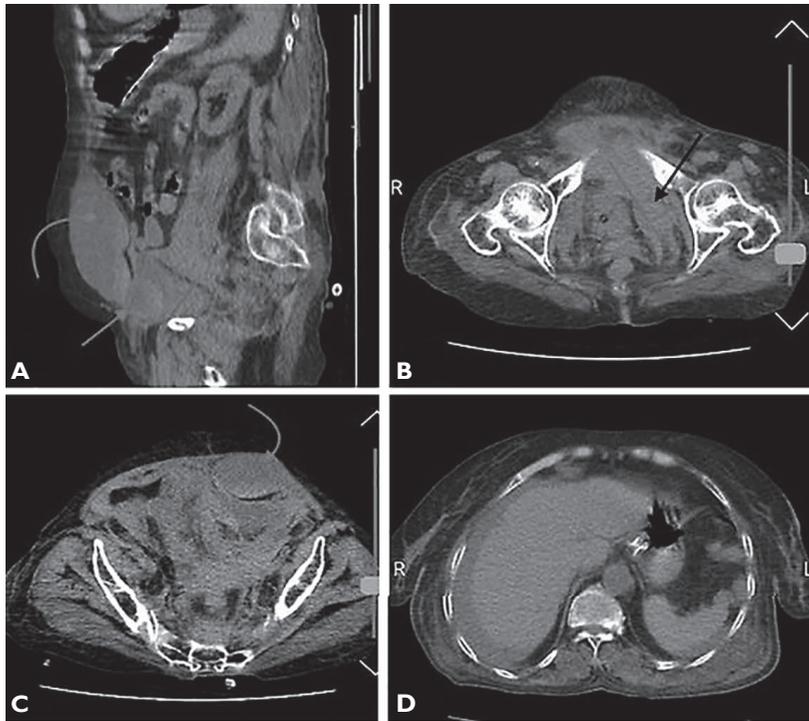


Figure 1 – Abdominal/pelvic computed tomography scan without contrast showing intramuscular haematomas. A) Sagittal view showing hyperdense fluid collection in left rectus muscle in favor of haematoma (curved arrowhead) and smaller haematoma in extraperitoneal space (direct arrowhead) with adjacent hyperdense free fluid in peritoneal space (direct line). B) Axial view which shows enlargement and faint hyperdensity of left obturator internus muscle extended to infra and supra pubic space. C) Axial view revealing haematoma in left rectus (arrowhead) with adjacent free fluid in peritoneal space (direct line). D) Axial view showing free fluid in perihepatic and perisplenic spaces.

to 80 mm Hg and the haemoglobin (Hb) dropped from 12.8 to 6.7 g/dl following the next few days.

The results of abdominal and pelvic ultrasound showed septated fluid collection susceptible of haematoma as well as small collections of fluid in perihepatic, and pelvic inter-loop spaces. Due to the low eGFR, abdominal and pelvic CT scans without contrast were performed which revealed haematomas in the left rectus (diameters of 106×49 mm) and obturator internus muscle (diameters of 45×23 mm). Signs of haemorrhage were seen in the anterolateral aspect of the bladder with extension to the paracolic spaces. Moderate collection of fluid was observed in both subdiaphragmatic, perihepatic and, perisplenic spaces (Figure 1).

Ecchymosis was first observed in her left groin and then gradually spread on her abdomen and back (Figure 2). The patient became febrile with diffuse abdominal and pelvic pain mainly in the LLQ. Gross hematuria and transient non-bloody diarrhea occurred next day after the onset of acute abdominal pain. She received intravenous fluid and overall 6 packed red blood cell until. The subsequent vital signs and Hb became stable and signs of hemostasis appeared. Surgical consultation was in favor of a conservative approach and continuation of supportive treatment. The white blood cells (WBC) count increased to 19,600 and then to a maximum of 26,500 per microliter (μl), and the activated partial thromboplastin time (aPTT) increased to 110 seconds on day 10. As shown, alanine and aspartate aminotransferases raised to 838 and 514 IU/l, respectively on day 9 and platelet count drop to 65,000/ μl on day 12.

Dose adjusted meropenem was administered in lieu of ceftriaxone. Prophylactic heparin was discontinued for a few days after stabilization of the patient's vital signs and normalization of the aPTT. The results of blood, urine; and stool cultures, creatine kinase-MB; and serologic markers for hepatitis B, C and human immune

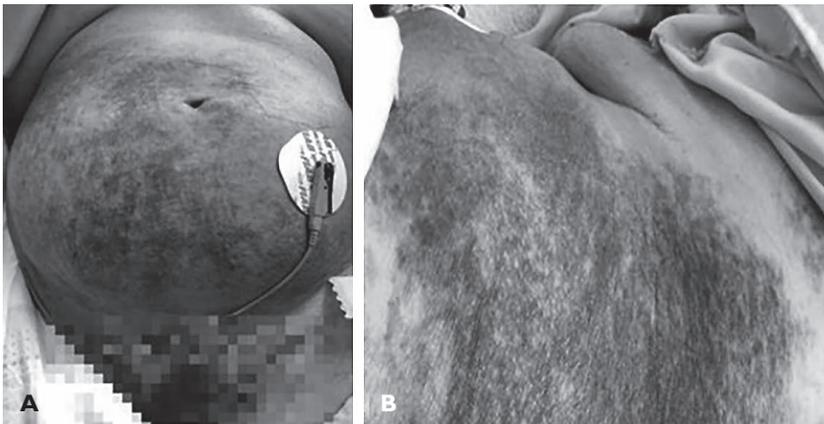


Figure 2 – The extension of subcutaneous haematomas in the abdomen (A), and back (B).

deficiency viruses were negative. Troponin checked four times during hospitalization showed negative results. The general condition of the patient improved thereafter.

At the end of the third week, the patient experienced an acute transient atrial fibrillation that was completely controlled by verapamil followed by metoprolol. Two days later, she was suspected to have deep venous thrombosis which was fortunately ruled out by Doppler ultrasonography. The general symptoms and laboratory tests began to improve. She was discharged from the hospital with improved Hb level (11.6 g/dl), blood urea nitrogen (BUN) = 19 mg/dl, creatinine = 1 mg/dl, WBC = 4,900/ μ l, platelet = 160,000/ μ l on day 25. On follow-up visit, ten days later, her general condition was good and recommended to be under the supervision of a cardiologist.

Discussion

Patients with severe COVID-19 seem to have an increased risk of bleeding as a result of imbalances in platelet production and disruption as well as disorders of the coagulation system. Our patient had both severe pulmonary and renal involvements due to COVID-19. On admission the patient had an eGFR of less than 20 ml/min/1.73 m² (BMI = 18.5 kg/m²) which showed she was a complicated COVID-19 case.

Bleeding is a common and potentially severe complication of acute and chronic renal failure. Patients with severe renal failure develop hemostatic disorders especially in the form of bleeding diatheses (Pavord and Myers, 2011; Lutz et al., 2014). Our patient did not have any history of chronic renal diseases and the risk factors for the progression of her disease were hypertension and hypertrophic cardiomyopathy as well as her age. Acute renal injury is one of the worse complications in COVID-19 patients that may mostly occur as a result of rhabdomyolysis, hypoxemia and dehydration (Pavord and Myers, 2011). Due to this severe complication, all the medications administered for our patient were adjusted based on the eGFR.

The sudden drop of blood pressure and haemoglobin as well as the occurrence of sudden abdominal pain and bulging in LLQ and subsequently the appearance of ecchymosis in the groins, abdomen and back made the diagnosis of internal bleeding due to COVID-19 more probable in this patient. The appearance of haematomas in abdominal/pelvic ultrasonography and CT scan confirmed this phenomenon. We did not have the facilities for angiography and embolization in our hospital and we could not transfer the patient to another center because of her critical condition either. Fortunately, the general conditions of the patient improved with supportive care after three days. During this critical condition the laboratory data showed the signs of acute inflammation and increased consumption including lower platelet count and fibrinogen; and increased WBC count, CRP (C-reactive protein), ESR (erythrocyte sedimentation rate), D-dimer, LDH (lactate dehydrogenase), ferritin, and aminotransferases.

Mattioli et al. (2020) reported bilateral neck and upper chest subcutaneous haematomas with painful swelling in a confirmed COVID-19 man, one week after his admission. A CT scan revealed bilateral and asymmetric haematomas of the sternocleidomastoid muscles. The patient had initial temporary renal impairment with thrombocytopenia and was on aspirin and low molecular weight heparin which could probably be a suggestion for the aggravation of the haemorrhagic complication (Mattioli et al., 2020). Nakamura et al. (2021) reported two confirmed COVID-19 patients treated with anticoagulants that developed haematoma in iliopsoas muscles. They suggested in patients with COVID-19, severe flank pain along with anemia and hypovolemic signs should be investigated for internal bleeding by performing a CT scan (Nakamura et al., 2021).

Besides thrombotic complications, bleeding is an important cause of morbidity in COVID-19 patients and the overall bleeding rate was estimated about 4.8% of the cases. It mostly occurred as a result of disseminated intravascular coagulation and thrombocytopenia (Al-Samkari et al., 2020).

D-dimer elevation at the time of admission was predictive of bleeding, thrombosis, critical illness and death in COVID cases (Shah et al., 2020; Moreno et al., 2021).

Conclusion

Bleeding tendency can occur in patients with COVID-19 but several others factors including complicated acute renal failure as well as prophylactic anticoagulant to prevent thrombosis can intensify the haemorrhage. Therefore, close supervision and proper management are recommended for complicated COVID-19 patients at risk of severe bleeding.

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Patella Fracture Identified Using Point-of-care Ultrasound

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Key words: Patella – Patella fracture – POCUS – Point-of-care ultrasound – Ultrasonography

Abstract: A 49-year-old female fell from standing. Her right knee extended into the air. She had acute right knee pain preventing weight-bearing. Her knee was most comfortable fully-extended. She could not flex it due to pain, nor extend it against resistance. Tenderness and a horizontal defect were noted over the anterior knee. Bedside ultrasound demonstrated a horizontally-fractured patella (confirmed on X-ray) with intact femoral and patellar tendons. She was put in a knee immobilizer and underwent surgery, with return to full function and activities. Ultrasound can identify patella fractures and help with early evaluation, management, and specialty referral, as well as ordering more-focused imaging. In one study, POCUS (point-of-care ultrasound) for patella fracture had 95% sensitivity, 63% specificity, 86% positive predictive value, and 83% negative predictive value. The dynamic nature of ultrasound allows a ruptured patella (87% sensitivity) or quadriceps tendon (100% sensitivity) to be excluded with high certainty.

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Introduction

Ultrasound is an increasingly-important tool to evaluate musculoskeletal conditions. Ultrasound can identify fractures, muscle tears, fluid collections, gas within tissue, and foreign bodies (Bonney et al., 2006; Yesilaras et al., 2014). This case describes the use of ultrasound in diagnosing a suspected patellar fracture and excluding alternative or concomitant diagnoses of patellar tendon or quadriceps tendon rupture.

Case report

A 49-year-old female with no past medical history presented after a slip and fall from standing on a wet kitchen floor. Her right knee extended into the air, and she had acute-onset right knee pain preventing weight-bearing. Her knee was most comfortable in full extension; she could not flex it due to pain. She could not extend her knee against resistance. Pain and a horizontal defect were noted over the anterior knee. Bedside ultrasound demonstrated a horizontally-fractured patella, with intact femoral and patellar tendons (Figures 1 and 2). The fracture was confirmed on X-ray (Figures 3 and 4). The patient was put in a knee immobilizer and referred to Orthopedic Surgery. She underwent surgery, with return to full function and activities.

Discussion

Patella fractures can occur through indirect (forceful extension) or direct (e.g. sports trauma, knee hitting dashboard) mechanisms. Most require surgery; non-operative treatment may be reasonable when there is an intact extensor mechanism and

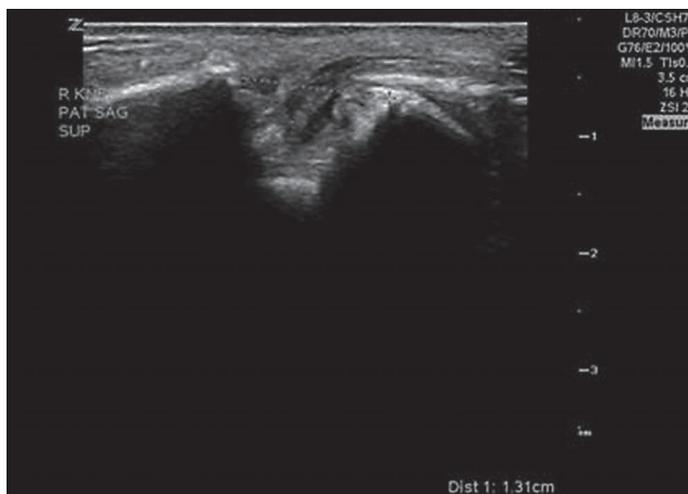


Figure 1 – Ultrasonographic image of the right patella using a linear L8-3 probe (Zonare Z One Pro Ultrasound System) in the sagittal plane overlying the patella demonstrates a 1.31 cm patellar cortex disruption superior-inferiorly.

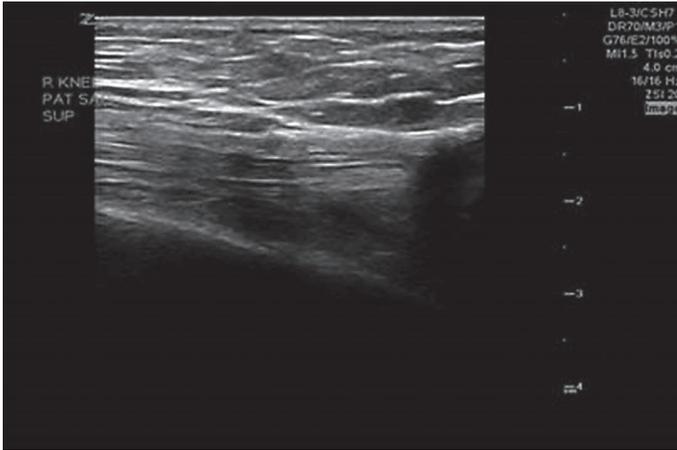


Figure 2 – Ultrasonographic sagittal-view image using a linear L8-3 probe (Zonare Z One Pro Ultrasound System) demonstrating intact right quadriceps tendon and no knee effusion.



Figure 3 – Lateral X-ray demonstrating mid-patella transverse fracture.

minimal intra-articular step-off (Solaro et al., 2011). Although plain film X-ray imaging is an excellent modality for identifying fractures, point-of-care ultrasound (POCUS) can be advantageous in fracture diagnosis and management. POCUS allows for earlier diagnosis, expectation-setting, and referral to a surgical specialist (if needed). POCUS can also inform more-focused imaging; for example, the provider can order patellar views (e.g. “sunrise” view) and tell the Radiologist to focus specifically on the patella. Additionally, POCUS can give the patient the psychological comfort of having objective evidence to support their chief complaint at an earlier time. Compared with CT (computed tomography) or MR (magnetic resonance), ultrasound is less costly (Bonney et al., 2006). Ultrasound can dynamically visualize the patellar



Figure 4 – Oblique X-ray demonstrating mid-patella transverse fracture.

tendon and quadriceps tendon to assess for rupture as an alternate cause of symptoms or a concurrent injury (Bianchi et al., 1994; Warden et al., 2007). Lastly, ultrasound has increased practicality for its ability to be used in locations without access to X-rays (e.g. wilderness, high school sports events).

Using a high-frequency linear transducer, a patella fracture can be identified as a disturbance in what would usually be a continuous bright line at the meeting point of the bone and soft tissue. A fracture can also be identified with POCUS as a hypoechoic collection, which is often indicative of a hematoma in the fracture space (Carter et al., 2016). Finally, ultrasound identification of lipohemarthrosis (synovial effusion with an echogenic layer of fat above the hypo/anechoic fluid [i.e. fat-fluid level]) suggests fracture, though this is a rare finding in patella fractures, and more often associated with distal femur or tibial plateau fractures (Costa et al., 2007).

For POCUS to be a viable substitution for or complement to plain film imaging, it must have a high sensitivity and specificity. In one study of 27 patients with knee trauma, Aljamil (2014) noted 19 with positive X-rays by sunrise view. Of those, POCUS identified 18 fractures (sensitivity = 95%). Of 8 patients with negative X-ray results, POCUS identified 5 patella fractures (specificity = 63%). In this population, the positive predictive value of an ultrasound was 86% and negative predictive value was 83.3%.

One condition that can contribute to a lower specificity and positive predictive value is a bipartite patella, which occurs in about 2% of the population (Weaver,

1977). A bipartite patella is characterized by an unfused accessory ossification center; the two separate sections are connected by thick fibrous tissue. Because of this division in the patella, a bipartite patella can be confused with a patella fracture. However, a bipartite patella has smooth edges at the separation points and higher-than-normal patella volume (with a bipartite patella, the sum of the true patella volume and that of the smaller section is greater than what would be expected of a normal patella) (Blankstein et al., 2001). Patients with a suspected patella fracture discovered by ultrasound should be asked if they are known to have a bipartite patella.

In sum, ultrasound is useful for identifying patella fractures and can help with early evaluation, management, and specialty referral, as well as ordering more-focused imaging. In a patient who is low-risk (by mechanism and physical examination) for patella fracture, a negative ultrasound can be reassuring no fracture is present. In addition, the dynamic nature of ultrasound allows a ruptured patella (87% sensitivity) (Bianchi et al., 1994) or quadriceps tendon (100% sensitivity) (Warden et al., 2007) to be excluded with high certainty.

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Annual Contents

No. 1

Primary Scientific Studies

Comparison of the Baska Mask[®] and Endotracheal Tube on Hemodynamic and Respiratory Parameters in Septoplasty Cases / *Kuşderci H. S., Torun M. T., Öterkuş M.* page 5

Effect of Microscopic Third Ventriculostomy (Lamina Terminalis Fenestration) on Shunt-needed Hydrocephalus in Patients with Aneurysmal Subarachnoid Hemorrhage / *Tabibkhomei A., Azar M., Taheri M., Ghalaenovi H., Fattahi A., Kheradmand H.* page 14

Laparoscopic Pectopexy: An Effective Procedure for Pelvic Organ Prolapse with an Evident Improvement on Quality of Life / *Karslı A., Karslı O., Kale A.* page 25

Case Reports

Acute Appendicitis in a Diabetic Child with *Salmonella* Infection / *Roupakias S., Apostolou M.-I., Anastasiou A.* page 34

Challenging Treatment of a Female Patient with Extensive Fournier's Gangrene – Case Report / *Kostovski O., Spasovska O., Trajkovski G., Antovic S., Kostovska I., Tosheska-Trajkovska K., Kuzmanovska B., Pejкова S., Jankulovski N.* page 39

Obstructive Jaundice Secondary to Pancreatic Head Metastasis of Malignant Amelanotic Melanoma as the First Clinical Manifestation / *Zeman J., Olivová L., Hrudka J., Hajer J., Rychlík I.* page 45

Instructions to Authors page 52

No. 2

Reviews

Extracorporeal Oxygenation Techniques in Adult Critical Airway Obstruction: A Review / *Pořízka M., Michálek P., Votruba J., Abdelmalak B. B.* page 61

Remarks on the Hormonal Background of the Male Equivalent of Polycystic Ovary Syndrome / *Stárka L., Dušková M.* page 73

Primary Scientific Studies

Comparison of the Chemiluminescence Immunoassay LIAISON® with the Radioimmunoassay for Aldosterone and Renin Measurement / *Uhrová J., Benáková H., Vaničková Z., Zima T.* page 80

Salmonella Paratyphi Infection: Use of Nanopore Sequencing as a Vivid Alternative for the Identification of Invading Bacteria / *Chmel M., Bartoš O., Beran O., Pajer P., Dresler J., Čurdová M., Holub M.* page 96

Case Reports

Rare Cause of Left Upper Abdominal Pain / *Aiyegbeni B., Jonnalagadda S., Creedon L., Teibe A.* page 106

Soft Tissue Perivascular Epithelioid Cell Tumour: An Unusual Finding / *Bermúdez Sagre M., Ospina Pérez C., Ortega Guatame J., Ospina Perez R., Lazada Martínez I., Jiménez Valverde J., Bolaño Romero M.* page 112

Instructions to Authors page 118

No. 3

Reviews

Idiopathic Hypersomnia and Depression, the Challenge for Clinicians and Researchers / *Galušková K., Šonka K.* page 127

Valproate-associated Movement Disorder: A Literature Review / *Rissardo J. P., Caprara A. L. F., Durante Í.* page 140

Comparison of the Morse Cone Connection with the Internal Hexagon and External Hexagon Connections Based on Microleakage – Review / *Bittencourt A. B. B. C., de Moraes Melo Neto C. L., Penitente P. A., Pellizzer E. P., dos Santos D. M., Goiato M. C.* page 181

Pelvic Floor Muscles Contribution in Surgical Outcome of Children with High-type Anorectal Malformations / *Roupakias S., Sinopidis X.* page 191

Primary Scientific Studies

Does Systemic Arterial Hypertension Change the Function of the Stomatognathic System? / *Lellis J. B. M., Borges T. de F., de Oliveira R. H., Palinkas M., Hallak J. E. C., Siéssere S., Regalo S. C. H.* page 201

Case Reports

Fatal Neutropenic Colitis and *Clostridium Septicum* Bacteremia in a Breast Cancer Patient / Holub M., Řezáč D., Čurdová M. [page 212](#)

Splenic Rupture and Massive Hemoperitoneum Due to Coagulopathy after *Atheris Viper* Snakebite / Valenta J., Stach Z., Vagenknechtová E., Hoskovec D. [page 216](#)

Oral Malignant Melanoma: A Case Report / Sen S., Sen S., Kumari M. G., Khan S., Singh S. [page 222](#)

Testing Positive for SARS-CoV-2 in Two Countries 105 Days Apart / Tshokey T., Choden J., Adhikari L., Thapa B., Wangchuk S. [page 228](#)

Instructions to Authors[page 233](#)**No. 4****Reviews**

Therapeutic Drug Monitoring of Protein Kinase Inhibitors in Breast Cancer Patients / Roušarová J., Šíma M., Slanař O. [page 243](#)

Short Review of Liposteroid: A Novel Targeted Glucocorticoid Preparation for Treatment of Autoimmune and Inflammatory Diseases / Saha B. K., Milman N. T. [page 257](#)

Primary Scientific Studies

Evaluating the Effect of Conservative Therapy in Patients with Wilkes Stage III Temporomandibular Joint Derangement / Machoň V., Levorová J., Beňo M., Hirjak D., Drahoš M., Foltán R. [page 269](#)

Evaluation of the Effect of Radiofrequency Denervation on Quality of Life of Patients with Facet Joint Syndrome by Oswestry Disability Index Score and Visual Analogue Scale Score / Gündoğdu Z., Öterkuş M., Karatepe Ü. [page 278](#)

The Effects of Hyperemesis Gravidarum on the Oral Glucose Tolerance Test Values and Gestational Diabetes / Bayraktar B., Balıkoğlu M., Bayraktar M. G., Kanmaz A. G. [page 285](#)

Case Reports

Supine Percutaneous Nephrolithotomy in a Patient with Solitary Lung: A Case Report and Literature Review / Danacioğlu Y. O., Arıkan Y., Akkaş F., Şam E., Özlü D. N., Emir N. S., Atar F. A. [page 294](#)

Spontaneous Multiple Haematomas in a Patient with Severe COVID-19 Fully Recovered with a Conservative Approach / Alavi-Naini R., Gorgani F., Rahmati Z., Pourdehghan S., Keikha M., Farzad Z. [page 300](#)

Patella Fracture Identified Using Point-of-care Ultrasound / *Richman M., Kieffer A., Moss R., Dexeus D.*

page 308

Instructions to Authors

page 313

Annual Contents

page 317

Annual Nominal Index

page 321

Annual Referee Index

page 323

Annual Nominal Index

ISSN 1214–6994

- Abdelmalak B. B. 2/61–72
 Adhikari L. 3/228–232
 Aiyegbeni B. 2/106–111
 Akkaş F. 4/294–299
 Alavi-Naini R. 4/300–307
 Anastasiou A. 1/34–38
 Antovic S. 1/39–44
 Apostolou M.-I. 1/34–38
 Arıkan Y. 4/294–299
 Atar F. A. 4/294–299
 Azar M. 1/14–24
 Balıkoğlu M. 4/285–293
 Bartoš O. 2/96–105
 Bayraktar B. 4/285–293
 Bayraktar M. G. 4/285–293
 Benáková H. 2/80–95
 Beňo M. 4/269–277
 Beran O. 2/96–105
 Bermúdez Sagre M. 2/112–117
 Bittencourt A. B. B. C. 3/181–190
 Bolaño Romero M. 2/112–117
 Borges T. de F. 3/201–211
 Caprara A. L. F. 3/140–180
 Chmel M. 2/96–105
 Choden J. 3/228–232
 Creedon L. 2/106–111
 Čurdová M. 2/96–105; 3/212–215
 Danacioğlu Y. O. 4/294–299
 de Moraes Melo Neto C. L. 3/181–190
 de Oliveira R. H. 3/201–211
 Dexeus D. 4/308–312
 dos Santos D. M. 3/181–190
 Drahoš M. 4/269–277
 Dresler J. 2/96–105
 Durante Í. 3/140–180
 Dušková M. 2/73–79
 Emir N. S. 4/294–299
 Farzad Z. 4/300–307
 Fattahi A. 1/14–24
 Foltán R. 4/269–277
 Galušková K. 3/127–139
 Ghalaenovi H. 1/14–24
 Goiato M. C. 3/181–190
 Gorgani F. 4/300–307
 Gündoğdu Z. 4/278–284
 Hajer J. 1/45–51
 Hallak J. E. C. 3/201–211
 Hirjak D. 4/269–277
 Holub M. 2/96–105; 3/212–215
 Hoskovec D. 3/216–221
 Hrudka J. 1/45–51
 Jankulovski N. 1/39–44
 Jiménez Valverde J. 2/112–117
 Jonnalagadda S. 2/106–111
 Kale A. 1/25–33
 Kanmaz A. G. 4/285–293
 Karatepe Ü. 4/278–284
 Karslı A. 1/25–33
 Karslı O. 1/25–33
 Keikha M. 4/300–307
 Khan S. 3/222–227
 Kheradmand H. 1/14–24
 Kieffer A. 4/308–312
 Kostovska I. 1/39–44
 Kostovski O. 1/39–44
 Kumari M. G. 3/222–227
 Kuşderci H. S. 1/5–13
 Kuzmanovska B. 1/39–44
 Lellis J. B. M. 3/201–211
 Levorová J. 4/269–277
 Lozada Martínez I. 2/112–117
 Machoň V. 4/269–277
 Michálek P. 2/61–72
 Milman N. T. 4/257–268
 Moss R. 4/308–312
 Olivová L. 1/45–51
 Ortega Guatame J. 2/112–117
 Ospina Pérez C. 2/112–117
 Ospina Perez R. 2/112–117
 Öterkuş M. 1/5–13; 4/278–284

- Özlü D. N. 4/294–299
Pajer P. 2/96–105
Palinkas M. 3/201–211
Pejkova S. 1/39–44
Pellizzer E. P. 3/181–190
Penitente P. A. 3/181–190
Pořízka M. 2/61–72
Pourdehghan S. 4/300–307
Rahmati Z. 4/300–307
Regalo S. C. H. 3/201–211
Řezáč D. 3/212–215
Richman M. 4/308–312
Rissardo J. P. 3/140–180
Roupakias S. 1/34–38; 3/191–200
Roušarová J. 4/243–256
Rychlík I. 1/45–51
Saha B. K. 4/257–268
Şam E. 4/294–299
Sen S. 3/222–227
Sen S. 3/222–227
Siéssere S. 3/201–211
Šíma M. 4/243–256
Singh S. 3/222–227
Sinopidis X. 3/191–200
Slanař O. 4/243–256
Šonka K. 3/127–139
Spasovska O. 1/39–44
Stach Z. 3/216–221
Stárka L. 2/73–79
Tabibkhooei A. 1/14–24
Taheri M. 1/14–24
Teibe A. 2/106–111
Thapa B. 3/228–232
Torun M. T. 1/5–13
Tosheska-Trajkovska K. 1/39–44
Trajkovski G. 1/39–44
Tshokey T. 3/228–232
Uhrová J. 2/80–95
Vagenknechtová E. 3/216–221
Valenta J. 3/216–221
Vaničková Z. 2/80–95
Votruba J. 2/61–72
Wangchuk S. 3/228–232
Zeman J. 1/45–51
Zima T. 2/80–95

Annual Referee Index

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