OCULAR SURFACE DISORDERS AND ITS ASSOCIATED FACTORS AMONG INTENSIVE CARE UNIT PATIENTS

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DISCLAIMER

I hereby certify that the work in this dissertation is my own except for the quotations, some figures and summaries which have been duly acknowledged. I declare that I have no financial interest in the instrument and the computer software used in this study.

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ABSTRAK

Pengenalan Pesakit di Unit Rawatan Rapi menghadapi peningkatan risiko gangguan permukaan okular.

Objektif Untuk menentukan prevalen gangguan permukaan okular dan mengkaji faktor-faktor yang berkaitan dengannya di unit rawatan rapi.

Metodologi Kajian keratan rentas telah dijalankan dari November 2020 hingga Disember 2021 melibatkan 166 pesakit di Unit Rawatan Rapi, Hospital Selayang dan Hospital Universiti Sains Malaysia. Kriteria pengecualian termasuk trauma muka yang melibatkan kawasan orbit, penggunaan ubat topikal dan sebarang patologi okular segmen anterior yang sedia ada. Diagnosis dibuat berdasarkan penilaian klinikal dari masa pecah air mata, pewarnaan fluorescein kornea dan ujian Schirmer. Faktor-faktor yang berkaitan dengan gangguan permukaan okular dinilai. Analisis statistik regresi logistik mudah dan berganda telah dilakukan menggunakan SPSS Inc versi 26.

Keputusan Seramai 166 pesakit telah didaftarkan dalam kajian ini. Purata umur ialah 51.8 (14.32). Purata tempoh tinggal di unit rawatan rapi ialah 11.5(9.31) hari. Seratus tiga puluh lima pesakit (81%) memerlukan pengudaraan, 114 (68.7%) memerlukan penenang dan 67 (40.4%) memerlukan inotropik. Lagophthalmos dikenal pasti dalam 49 pesakit (29.5%). Prevalen gangguan permukaan okular dalam pesakit Unit Rawatan Rapi adalah 63.3%. Nisbah kemungkinan berikut (95% selang keyakinan) untuk gangguan permukaan okular dianggarkan

menggunakan model regresi logistik berganda: perempuan: 5.97 (1.18, 30.22) dan tempoh tinggal ICU: 2.58. (1.84, 33.63).

Kesimpulan Gangguan permukaan okular adalah perkara biasa dalam pesakit Unit Rawatan Rapi. Prevalens adalah 63.3%. Faktor risiko berkaitan yang paling penting yang terdedah kepada penyakit permukaan okular ialah jantina wanita dan tempoh kemasukan ke unit rawatan rapi.

ABSTRACT

Introduction Patients in Intensive Care Unit are at increased risk of ocular surface disorders.

Objective To determine the prevalence and its associated factors of ocular surface disorders in intensive care units.

Methodology A cross sectional study was conducted from November 2020 until December 2021 involving 166 patients in Intensive Care Unit, Hospital Selayang and Hospital Universiti Sains Malaysia. Exclusion criteria includes facial trauma involving orbital region, usage of topical medication and any pre-existing anterior segment ocular pathologies. Diagnosis made based on clinical assessments from tear break up time, corneal fluorescein stain and Schirmer's test. Factors related to ocular surface disorders were assessed. Statistical analysis of simple and multiple logistic regression was performed using SPSS Inc version 26.

Result A total of 166 patients were enrolled in this study. The mean age was 51.8 ± 14.32. The mean length of stay in the ICU was 11.5 ± 9.31 days. One hundred and thirty-five patients (81%) required ventilation, 114 (68.7%) required sedation and 67 (40.4%) required inotropes. Lagophthalmos was identified in 49 patients (29.5%). The prevalence of ocular surface disorders in the Intensive Care Unit patients was 63.3%. The following odds ratios (95% confidence intervals) for ocular surface disorders were estimated using the multiple logistic regression model: female: 5.97 (1.18, 30.22) and length of ICU stay: 2.58. (1.84, 33.63).

Conclusion Ocular surface disorders are common in Intensive Care Unit patients. The prevalence is 63.3%. The most important associated risk factors that predispose to ocular surface disease were female gender and length of Intensive Care Unit hospitalisation.

Chapter 1

Introduction

1. INTRODUCTION

1.1 Definition and Classification of OSD

Ocular surface disorders (OSD) is defined as a group of ocular disorders that affect various component of the ocular surface. Though the prevalence of OSD is quite high, unfortunately, cases often go undiagnosed or undertreated, due to a lack of understanding of symptoms, and inaccurate evaluation of OSD. OSD results from increased in tear osmolarity leading to inflammation and disruption of the ocular surface. OSD includes conditions like dry eye disease (DED), blepharitis and meibomian gland dysfunction (MGD), allergic eye diseases (AED), chemical and thermal burns and so on. OSD can severely affect eyesight and quality of life, and its complication may lead to blindness.

OSD has been reviewed and based on latest guideline by Cornea, External Disease, and Refractive Society (CEDARS) that combines the latest evidence-based approaches, there are five key CEDARS' disease subtypes:

• **Subtype 1:** Aqueous deficiency. Main manifestation is characterised by a reduction in lacrimal gland secretions, which contribute to aqueous component of the tear film. Pathological destruction of the lacrimal gland, or scarring and blockage of its ducts, can prevent secretions from reaching the ocular surface. Injury, surgery, systemic conditions and topical agents can reduce corneal sensation, causing neurogenic inflammation that leads to decreased gland activity.

• **Subtype 2**: Blepharitis/meibomian gland dysfunction (MGD) which can be evaporative and non-evaporative. MGD can be asymptomatic or symptomatic. Symptomatic cases may be

restricted to the lids or be associated with MGD-related OSD that includes evaporative dry eye. Abnormal meibomian gland leads to dysfunction lipid film and leads to evaporative dry eyes.

• **Subtype 3**: Goblet cell deficiency/mucin deficiency. In this subtype patient has related to chemical burn, contact lens overwear, or have Stevens-Johnson Syndrome. Glaucoma medication also leads to goblet cell loss, decreasing mucins which leads to evaporation.

• **Subtype 4**: Exposure. Exposure due to lagophthalmos (incomplete closure of eyelid), previous ptosis surgery, Bell's palsy, trauma, scarring and Parkinson's disease.

• **Subtype 5:** Dysfunctional Tear Syndrome/Co-conspirators. The term 'co-conspirators' refers to conditions affecting the tear film and ocular surface that may either exacerbate dry eye or masquerade as dry eye. These could include superior limbic keratoconjunctivitis, medicamentosa, Thygeson's superficial punctate keratitis, mucus fishing syndrome, contact-chemical toxicity, allergic/atopic conjunctivitis, conjunctivochalasis, ocular allergy and glaucoma drops.

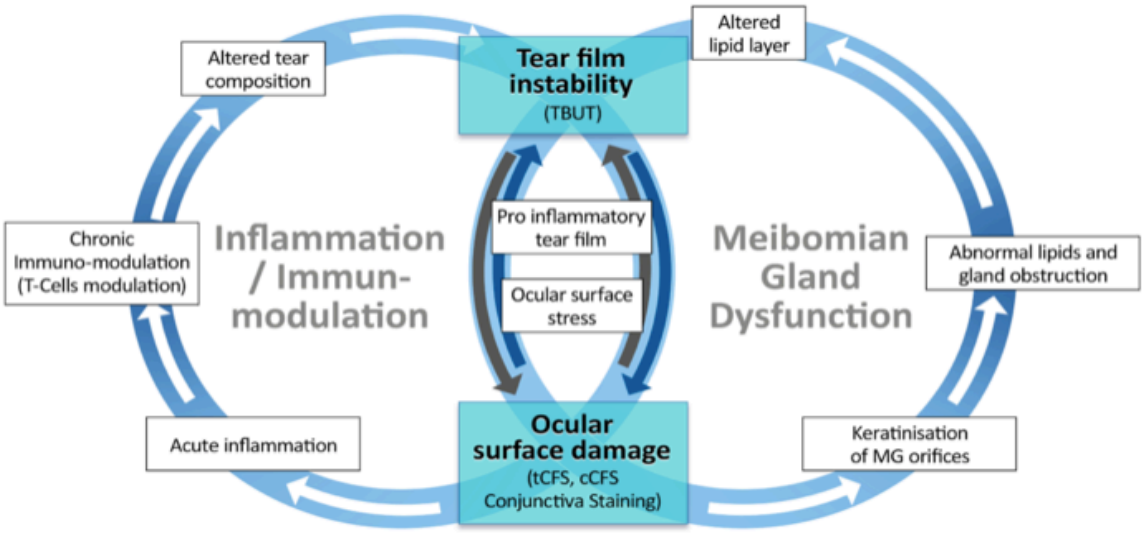

Figure 1.1: Vicious Circle of Dry Eye Disease

1.2 Ocular Defence Mechanism

Eye protects itself through various mechanism. Eyelid acts as a mechanical barrier to external insult and blinking which not only mechanically protective by a reflex arc, but it also helps to distribute uniform tear film. Precorneal tear film, composed of 3 layers namely lipid layer, aqueous layer and mucin layer has its own protective mechanism. Lipid layers combine with eyelid closure during sleep keeps eye moisture during sleep, with addition effect of Bells phenomenon (Parkin *et al*., 2000).

Production and maintenance of tear film are vital. Tear film contains nutrients and provide oxygenated environment towards avascular cornea (Koroloff *et al*., 2004). Aside from this, it has antimicrobial properties such as lysozyme, beta-lysin, lactoferrin, interferon, immunoglobulins, complements, that inhibit growth of bacteria (Gipson *et al*., 2004).

Epithelium that overlies the conjunctiva and cornea also play a vital role. Epithelium of cornea has glycocalyx, which promotes adhesion of tear film to the ocular surface. Furthermore, intact integrity of it will deny any microbial invasion. Conjunctival epithelium forms a mucous membrane that protects and form a barrier against injury and microorganism (Marshall *et al*., 2008).

The core mechanism is tear hyperosmolarity, which is the hallmark of the disease. It damages the ocular surface both directly and by initiating inflammation. Tear hyperosmolarity results when lacrimal secretion is reduced but it can also happen with normal secretion as a result of evaporative process. Tear hyperosmolarity is considered to set up a cascade of signalling events within surface epithelial cells, that leads to the release of inflammatory mediators and proteases.

Such mediators, together with the tear hyperosmolarity itself, are conceived to cause goblet cell and epithelial cell loss and damage to the epithelial glycocalyx. Damage is reinforced by inflammatory mediators from activated T-cells, recruited to the ocular surface. The net result is the tear film instability which leads at some point to early tear film break-up. This break-up exacerbates and amplifies tear hyperosmolarity and completes the vicious circle of events that lead to ocular surface damage. Several drugs in systemic use, such as antihistamines, beta-blockers, antispasmodics, diuretics and some psychotropic drugs, cause a reduction in lacrimal secretion and are risk factors for ocular surface disease (Frederick, James and Willian, 2012). The tear hyperosmolarity and epithelial injury, stimulates corneal nerve endings, leading to symptoms of discomfort, increased blink rate and, potentially, a compensatory reflex increase in lacrimal tear secretion.

1.3 Clinical Presentations of OSD

Presentation varies and can overlap from one subtype to another. All the subtypes can overlap with each other: example, aqueous deficiency can overlap with blepharitis/MGD and exposure-related OSD. Blepharitis/MGD can also overlap with goblet cell deficiency, which can additionally overlap with exposure-related disease. Reduce blink rate, lid laxity and position, reduce tear film break up time (TBUT), abnormal Schirmer's testing, and fluorescent staining of cornea and conjunctiva are seen in OSD.

1.4 Assessment of Ocular Surface Disorders

1.4.1 Tear Film Break Up Time (TBUT)

The TBUT method assesses tear film stability. More than 10 seconds defined as normal and values less than 10 seconds as abnormal.

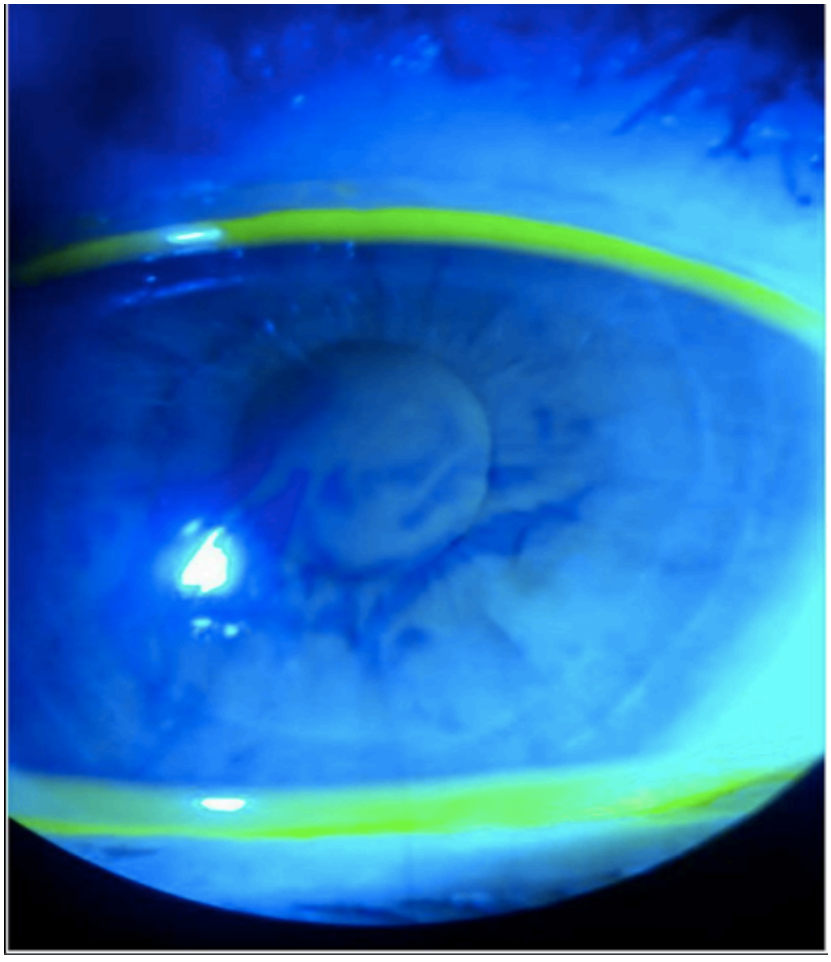

Figure 1.2 Tear break up time

1.4.2 Corneal and Conjunctival Staining

There are many dyes on the market, but the most common is fluorescein. Rose Bengal and Lisamine Green are two more examples. More than one dot of fluorescein staining on the corneal surface indicates the presence of corneal staining. The Baylor scale, the National Eye Institute grading system, the Oxford scale, and the van Bijsterfeld scale are some of the more commonly used staining scales.

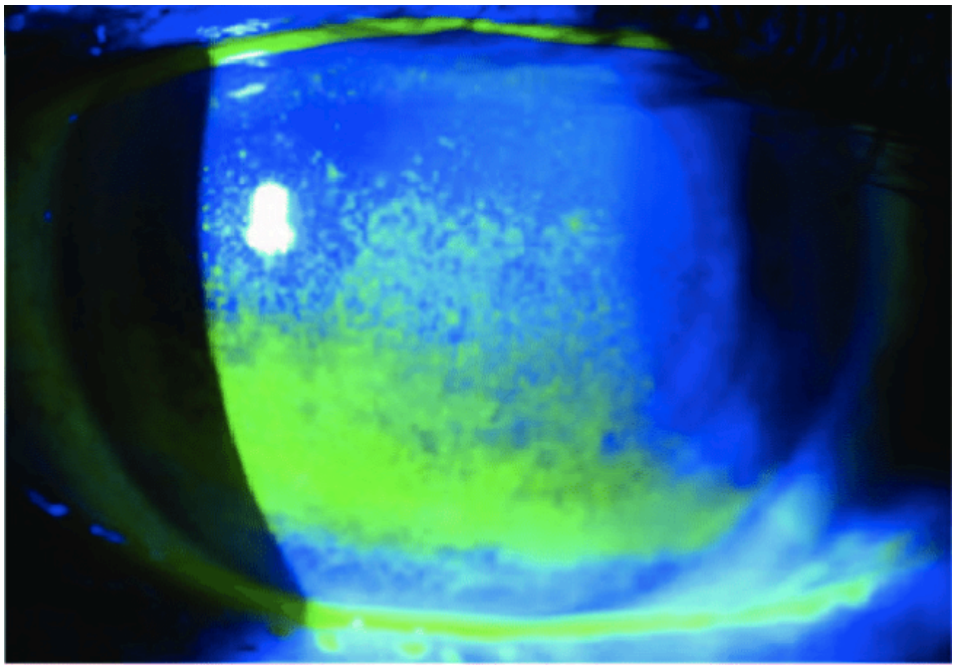

Figure 1.3: Corneal fluorescein stain

1.4.3 Schirmer's Test

Schirmer's test is the most common and Schirmer scores, representing the length of wetting (in mm) on the strip, are routinely used as a key diagnostic criterion for dry eye. The test involves the insertion of a small piece of filter paper into the lower fornix of the eye. There are two variations of the Schirmer's test: Schirmer's I measure total tear secretion (basal and reflex). Schirmer's II is a measure of reflex secretion only and involves nasal stimulation following insertion of the strip. A variation of the Schirmer's I allow measurement of basal secretion involves the application of topical anaesthetic prior to strip insertion. Although performing the Schirmer's I with anaesthesia may provide a more accurate picture of basal secretion, the utility and overall effectiveness of anaesthetic administration in conjunction with the Schirmer is controversial.

Recent advancement has emerged in diagnosing OSD. These new technologies such as impression cytology, confocal microscopy, tear film interferometry, objective measurement of tear meniscus by optical coherence tomography, esthesiometry, tears osmolarity, rapid testing for inflammatory markers, and ocular surface scraping will aid in accuracy and objective assessment of OSD (Jeng *et al.*, 2013).

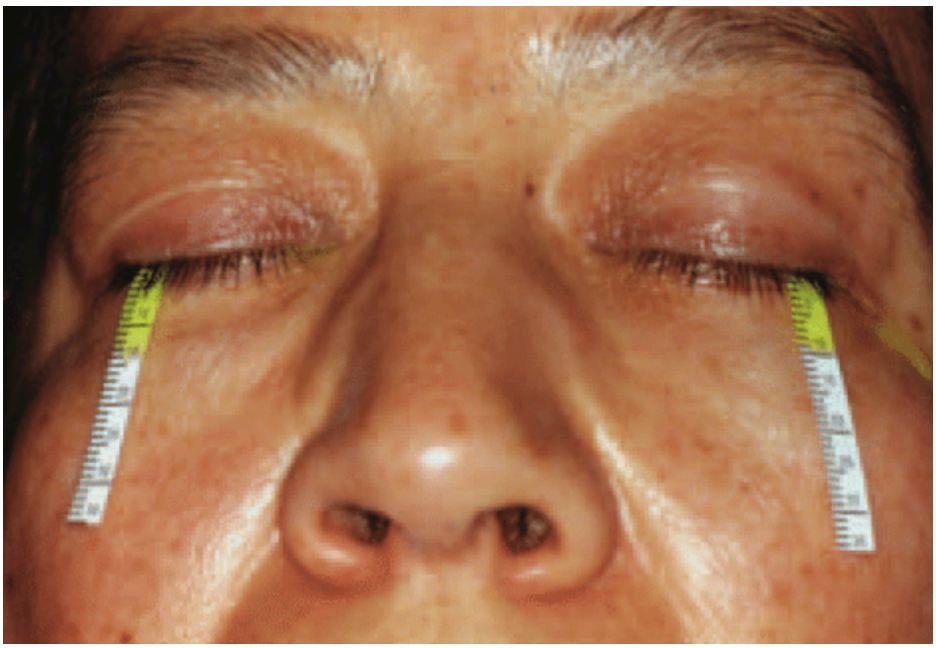

Figure 1.4: Schirmer's test

1.5 Treatment of Ocular Surface Disorders

Managing OSD is challenging even for experienced clinician. Presentation is complex and overlapping, but fortunately it can still be managed effectively by medical or surgical treatment. Generally, management comprises of the following:

1.5.1 Eliminate exacerbating factors

Many topical drops have preservative, therefore the use of preservative free will benefit patient and reduce irritancy on ocular surface (Park, Lee and Kook, 2002). Other than that, any known allergy should be avoided.

1.5.2 Lubricants

A normal physiological tear film is essential in protecting ocular surface. Lubricant or so-called tear substitute not only wets the cornea but also dilutes surface irritants. There are many examples

of lubricants that made up of basic substance hyaluronate, carmellose, hypromellose, polyvinyl alcohol, and paraffin. Lubricants with lipids are also available. Other alternative lubricants such as autologous serum is expansive and not readily available.

1.5.3 Control inflammation

As we know that inflammatory process is involved in the pathophysiology of the disease, by giving anti-inflammatory will aid in preserving ocular surface. The choice of steroids and frequency depends on cases. More potent steroid used in severe allergic cases and weak steroids are used in mild cases. Cyclosporin topical drops has also shown to benefit patient in the long run, and not acute setting (Saini *et al.*,2015). They are effective in controlling the inflammation without having the side effects of steroids.

1.5.4 Management of persistent corneal epithelial defect

Therapeutic contact lens can be applied once infection has been ruled out or treated. Many available such as hydrogel, silicone, and others. Severe cases may need the use of rigid gas permeable scleral contact lens to prevent excessive evaporation.

1.5.5 Surgical management

This are reserved for cases that failed medical therapy or it is due to other form of ocular disease. In patient with aqueous deficient dry eye, puncta plug or permanent occlusion will alleviate patient symptoms. Apart from that those who had persistence epithelial defect may benefit from temporary tarsorrhaphy and is indicated in patient who is unconscious and bed bound.

1.6 OSD and ICU Patients

OSD is common in ICU, with 20-40% developed corneal epithelial defects (Hearne, Hearne, Montgomery et al., 2018). The ocular surface is normally protected by the ability to produce tears, blink, close eyes during resting. All the mechanism of protecting the surface is disrupted in intensive care unit, increasing the risk of developing ocular surface disease.

Exposure keratopathy is part of OSD, a clinical syndrome initiated by incomplete eye closure and tear film defect leading to damage of a spectrum of severity and extend. A combination of risk factors predispose critically ill patients to OSD, either from the treatment such as mechanical ventilation (Kuruvilla et al., 2015), sedation and muscle relaxants, or from patient factor such as reduced consciousness, reduced tear production, reduced blink rate (Masoudi Alavi, Sharifitabar, Shaeri et al., 2013), impaired corneal reflex, incomplete eye closure, and vascular permeability (Rosenberg and Eisen, 2008). Although resolves once the patient recovers, it may cause morbidity to patient in term of corneal scarring and permanent visual loss.

The health of the surface of the eye, depends on the ability to produce tears, to blink and to close the eyes with rest or sleep. All these mechanisms can be impaired either by disease (e.g. facial oedema, reduced conscious level, peripheral or central neurological injury) or by treatments (e.g. the drying effects of gas flows from continuous positive airway pressure (CPAP) or oxygen masks). Muscle relaxants reduce the tonic contraction of the orbicularis muscle around the eye, which normally keeps the lids closed, and sedation reduces blink rate and impairs the blink reflex. Whatever the cause, those unable to close the eye for themselves, or in whom blinking rates are substantially reduced, are at increased risk of damage to the surface of the eye. This risk is higher in those mechanically ventilated, due to greater length of stay, use of sedative or paralysing drugs

and the effects of positive pressure ventilation. Furthermore, the ICU protocol with regards to eye care has not been established and standardised in this type of patients. This may lead to devastating eye complications such as exposure keratopathy, infective keratitis, permanent cornea scar, cornea melting and perforation and persistent poor vision.

Most patient admitted to ICU had metabolic dysfunction, require respiratory support and unconscious. The ability to maintain physiological barrier is impaired. With the use of medication in sedation, this will inhibit orbicularis oculi muscle and leads to incomplete closure of eyelid or lagophthalmos. Not only that this medication affects Bell's phenomenon and render patient to develop nocturnal lagophthalmos (Płaszewska-Żywko et al., 2021). The longer the patient stays in ICU, the longer cornea is exposed and leads to exposure keratopathy.

ICU patient who are intubated can either be endotracheal or tracheostomy. Endotracheal intubation can increase internal jugular venous pressure which eventually lead to chemosis and periocular congestion. This congestion reduces perfusion and cell turnover, with the background of metabolic disturbances, this will result in impaired healing. It is reported that the incidence of ocular surface disease is more in those receiving endotracheal intubation (Oh EG *et al.*, 2008).

1.7 RATIONALE OF THE STUDY

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Several published studies conducted in other countries such as the United Kingdom, the United States of America, and some of Southeast Asian countries, revealed a high prevalence of ocular surface disease in ICU patients. However, research on the prevalence of ocular surface disease in ICU patients in Malaysia is still limited.

Our aim is to prove that there are significant numbers of OSD cases in ICU patients due to instability of corneal tear film. Thus, it is of paramount important to perform early identification of patients with OSD and recognize its associated factors to minimise potential ocular surface complications, leading to significant poor vision. We also hope that this study will aid in emphasising eye care as they were no standard ICU protocol for management of eye care in Malaysia.

Chapter 2

Study Objectives

2.1 RESEARCH OBJECTIVE

2.1.1 GENERAL OBJECTIVE

To determine the prevalence of ocular surface disorders and its associated factors among Intensive Care Unit patients.

2.1.2 SPECIFIC OBJECTIVES

i. To determine the prevalence of ocular surface disorders among Intensive Care Unit patients.

ii. To determine the associated risk factors of ocular surface disorders among Intensive Care Unit patients.

2.2 RESEARCH QUESTIONS

1. What is the prevalence of ocular surface disorders in Intensive Care Unit ?
2. What are the associated risk factors in Intensive Care Unit patients that predispose to ocular surface disorders?

2.3 RESEARCH HYPOTHESIS

There are associated risk factors of developing ocular surface disorders among Intensive Care Unit patients.

Chapter 3

Methodology

3.1 RESEARCH DESIGN

Comparative cross-sectional study

3.2 POPULATION, LOCATION OF STUDY, DURATION OF STUDY

3.2.1 STUDY POPULATION

A total of 166 patients were recruited from Hospital Selayang and Hospital Universiti Sains Malaysia. The study population was patients in Intensive Care Unit during the study period and fulfilled the selection criteria.

3.2.2 PLACE OF STUDY

1. Hospital Selayang, Selangor
2. Hospital Universiti Sains Malaysia, Kubang Kerian, Kelantan

3.2.3 STUDY DURATION

December 2020 till December 2021

3.3 SAMPLING METHOD SAMPLE SIZE CALCULATION

3.3.1 SAMPLING METHOD

Convenience sampling method applied for OSD patients in ICU, Hospital USM and Hospital Selayang from December 2020 until December 2021 that fulfil the criteria recruited in the study. Consent obtained from patient or next of kin and estimated ten minutes of assessment in each patient for both eyes.

3.3.2 SAMPLE SIZE CALCULATION

3.3.2.1 SAMPLE SIZE CALCULATION FOR OBJECTIVE 1

To determine the proportion of ocular surface disorders among intensive care unit patients.

The sample size was calculated based on the formula.

$$; n = \frac{Z^2 P(1-P)}{d^2}$$

Pourhoseingholi, M. A., Vahedi, M., & Rahimzadeh, M. (2013). Sample size calculation in medical studies. Gastroenterology and hepatology from bed to bench, 6(1), 14–17.

Z=	the statistic corresponding to level of confidence, 95%, 0.196
P=	expected prevalence (that can be obtained from same studies or a pilot study conducted by the researchers)
d=	is precision (corresponding to effect size).

Z=	1.96	Z^2=	3.8416
P=	0.6	P (1-P)=	0.24
d=	0.08	d^2=	0.064
		n=	144.06

3.3.2.2 SAMPLE SIZE CALCULATION FOR OBJECTIVE 2

To determine the associated risk factors of ocular surface disorders among intensive care unit patients. The sample size was calculated based on two proportions using Excel software. APA: Arifin, W. N. (2022). Sample size calculator (web). Retrieved from http://wnarifin.github.io

Factors	**Ref**	**P0**	**P1**	**n**	**n+10%**
Sedation	Imanaka HJ et al.	0.15	0.4	49	55
Gender (female vs male)	Imanaka HJ, et al.	0.16	0.5	29	33
Length of ICU Hospitalisation	Imanaka HJ, et al.	0.11	0.3	70	78

The total number of subjects required for this study was taken based on the highest number of sample size calculation in each group. The total sample size is 166 participants.

3.4 DEFINITION OF TERMS

3.4.1 Ocular surface disorders

The most current definition of ocular surface disorders states that it is a multifactorial disease of the ocular surface that results in symptomatic discomfort, visual disturbances, and tear film instability with progressive histopathologic and clinical changes to the ocular surface.

3.4.2 Intensive Care Unit

It is an organized system for the provision of care to critically ill patients that provides intensive and specialized medical and nursing care, an enhanced capacity for monitoring, and multiple modalities of physiologic organ support to sustain life.

3.4.3 Tear film Break Up Time (TBUT) test

TBUT is the time measured from when the eyelid is opened to the appearance of the first dry spot formation after the instillation of the fluorescein stain into the inferior fornix of conjunctiva.

3.4.4 Fluorescein stain

Fluorescein is a green-tinted dye that fluoresces under blue light.

3.4.5 Schirmer's Test

Measures amount of tear produce.

3.5 SELECTION CRITERIA

3.5.1 Inclusion criteria

1. Patients in ICU who were admitted for more than 24hour
2. Age of 18 and above
3. All intubated patient and non-intubated patient

3.5.2 Exclusion criteria

1. Any pre-existing corneal and anterior segment pathology such as keratoconus, cornea scar, cornea oedema and pterygium
2. History of cornea, refractive and glaucoma surgery
3. Steven Johnson Syndrome with severe ocular involvement
4. Facial trauma involving orbital region
5. Presence of active corneal and conjunctival infection
6. Chronic usage of topical medication

3.6 RESEARCH TOOLS

3.6.1 Schirmer strip, Optitech Eyecare, Allahabad, India

Optitech Eyecare filter paper (Schirmer strip) was used in the Schirmer test to measure the filter paper wetness as an indicator of ocular surface wetness from aqueous tear production. The measurement of the strip is 35mm long and 5mm wide.

Figure 3.1 : Optictech Eyecare filter paper