ISSN: 2158-284X Volume 12, Number 8, August 2021

Scientific Research Publishing

International Journal of Clinical Medicine

ISSN: 2158-284X

https://www.scirp.org/journal/ijcm

Journal Editorial Board

ISSN: 2158-284X (Print) ISSN: 2158-2882 (Online)
https://www.scirp.org/journal/ijcm

International Journal of Clinical Medicine, 2021, 12, 307-356
https://www.scirp.org/journal/ijcm
ISSN Online: 2158-2882
ISSN Print: 2158-284X

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Volume 12 Number 8 August 2021

International Journal of Clinical Medicine (IJCM)
Journal Information

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International Journal of Clinical Medicine, 2021, 12, 307-315
https://www.scirp.org/journal/ijcm
ISSN Online: 2158-2882
ISSN Print: 2158-284X

Effect of High-Order Aberrations and Satisfaction on Cataract Patients Implanted with Four Types of AcrySof Blue Light Filtering Intraocular Lens

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How to cite this paper: Wu, W., Yu, S.Y. and Ma, S.S. (2021) Effect of High-Order Aberrations and Satisfaction on Cataract Patients Implanted with Four Types of AcrySof Blue Light Filtering Intraocular Lens. *International Journal of Clinical Medicine*, **12**, 307-315.
https://doi.org/10.4236/ijcm.2021.128027

Received: July 11, 2021
Accepted: August 2, 2021
Published: August 5, 2021

Abstract

Objective: The objective is to evaluate the visual acuity, high-order aberrations and satisfaction in the cataract patients with the implantation of different types of AcrySof blue light filtering intraocular lens, which would provide the clinical guidance for the selection of individualized intraocular lens. **Methods:** From January 2019 to December 2020, the patients with age-related cataract in Guangzhou Red Cross Hospital were equally randomized to be divided into four groups. 20 patients (20 eyes) were implanted with AcrySof (SN60WF), which was the blue light filtering single focus group; 20 patients (20 eyes) were implanted with blue light filtering aspheric multifocal intraocular lens (AcrySof ReSTOR IOL +3.0D, SN6AD1), which was the multifocal intraocular lens group; 20 patients (20 eyes) were implanted with aspheric astigmatism correction intraocular lens (Toric SN6AT), which was the astigmatism group; 20 patients (20 eyes) were implanted with blue filtering aspheric multifocal astigmatism correction intraocular lens (AcrySof ReSTOR IOL +2.5D IQ, SV25T0), which was the ART group. Three months after the operation, the patients were followed up with slit lamp to check the visual acuity, including uncorrected distance visual acuity (UCDVA), uncorrected near visual acuity (UCNVA), best corrected distance visual acuity, (BCDVA); the questionnaire surveys on the satisfaction of different intraocular lens implantation (far and near vision, glare, halo and abnormal visual symptoms); the iTrace visual function analyzer was used to check the total high-order aberrations (spherical aberration, wisdom aberration and Clover aberration) in the 3 mm pupil diameter. **Results:** Three months after cataract surgery, Amer-

ican Simplified version of questionnaire survey showed that the scores of near removing glasses in the multifocal group and the ART group were significantly better than those in the single focus group and the astigmatism group ($P < 0.05$); there was no significant difference in the satisfaction of far removing glasses, glare and halo in each group ($P > 0.05$). Three months after cataract surgery, there were statistically significant differences about UCDVA, BCDVA and UCNVA among the four groups ($F = 18.189$, $P < 0.001$), the UCNVA in the multifocal group and ART group was significantly better than that in the single focus group and the astigmatism group ($P < 0.01$). The difference of higher-order aberrations (total higher-order aberrations, wisdom aberrations, spherical aberrations, clover aberrations) was no statistically significant among the four groups ($P > 0.05$). **Conclusion:** Different types of AcrySof blue light filtering intraocular lens implantation could improve the far vision and satisfaction of cataract patients, without different higher-order aberrations. Multifocal intraocular lens and ART intraocular lens could significantly improve the far vision of patients and reduce the dependence on near glasses.

Keywords

Cataract, Intraocular Lens, High-Order Aberrations, Blue Light Filtering

1. Introduction

With the aging of the population, there were more and more age-related cataract patients. At present, according to the visual quality requirements of different cataract patients, different types of intraocular lens implantation could be selected, so as to achieve the requirements of accurate refractive cataract surgery.

With the continuous improvement of intraocular lens (IOL) materials and manufacturing technology, the continuous upgrading of surgical equipment, and the development of surgical technology, cataract surgery has been upgraded from simple vision restoration to the refractive cataract surgery stage in pursuit of higher visual quality, which not only meets the long, medium and near vision pursuit of cataract patients, could also meet the need of preventing blue light and correcting astigmatism in cataract patients [1]. However, the higher-order aberrations of lens are positively correlated with age and increase with age [2]. In recent years, with the application of wavefront aberration technology in the field of ophthalmology, the use of wavefront aberrometer to detect the high-order aberrations produced by intraocular lens could objectively evaluate the optical visual quality of different AcrySof IOLs [3]. Therefore, the high-order aberrations and satisfaction of higher-order aberrations with the implantation of different blue light filtering intraocular lens could be evaluated by questionnaire survey and iTrace, which could provide a theoretical basis for individualized selection of intraocular lens for cataract patients.

2. Materials and Methods

2.1. Research Population

From January 2019 to December 2020, 80 patients (80 eyes) with age-related cataract underwent phaco combined with intraocular lens implantation, including 30 male patients (30 eyes) and 50 female patients (50 eyes), aged 60 - 90 years, in Guangzhou Red Cross Hospital. They were equally randomized to divided into four groups. 20 patients (20 eyes) were implanted with AcrySof (SN60WF), which was the blue light filtering single focus group; 20 patients (20 eyes) were implanted with a blue light filtering aspheric multifocal intraocular lens (AcrySof ReSTOR IOL +3.0D, SN6AD1), which was the multifocal intraocular lens group; 20 patients (20 eyes) were implanted with aspheric astigmatism correction intraocular lens (Toric SN6AT), which was the astigmatism group; 20 patients (20 eyes) were implanted with blue filtering aspheric multifocal astigmatism correction intraocular lens (AcrySof ReSTOR IOL +2.5D IQ, SV25T0), which was the ART group.

Exclusion criteria: 1) which were surgical complications (abnormal pupil, rupture of lens capsule, inability to implant intraocular lens, posterior capsule opacification, lens deviation, cystoid macular edema, etc.); 2) Severe dry eye, corneal disease, previous history of corneal refractive surgery or internal eye surgery, fundus diseases, optic neuropathy, uveitis, ocular trauma, etc.; 3) One eye had undergone cataract surgery and intraocular lens implantation.

2.2. Routine Examination before Operation

Preoperative examinations included uncorrected far vision, best corrected far vision, intraocular pressure, slit lamp test, fundus examination, IOL Master examination, and iTrace examination.

2.3. Operation Method

All operations were performed by experienced surgeons. Cataract phacoemulsification was performed routinely. Different types of intraocular lenses were implanted into the capsular bag (Alcon Company, USA). Astigmatic and ART intraocular lenses were implanted. The axial position of intraocular lens was positioned preoperative, the viscoelastic agent was removed in the capsular bag and behind the IOL, the target axis of the IOL was adjusted, and the optical part of the IOL was pressed gently to adhere to the posterior capsule finally.

2.4. Follow-Up

All patients were checked at 1 week, 1 month, 3 months and 6 months after operation, including visual acuity, intraocular pressure, slit lamp and fundus examination. Three months after operation, UCDVA and BCDVA were checked by international standard logarithmic visual acuity chart; the uncorrected near visual acuity (UCNVA) was checked by jeger near visual acuity chart.

2.5. The Questionnaire Survey of Visual Acuity

The American simplified version of the "quality of life questionnaire after multifocal IOL implantation" was used to investigate the condition of lens removal, symptoms of discomfort and surgical satisfaction, and the data were recorded. A questionnaire survey was conducted in three months after cataract surgery in each group, including the dependence of patients on glasses, halo and glare (Table 1).

2.6. iTrace Aberrometer Examination

Three months after the operation, the patient sat down in the dark room, placed his mandible on the mandibular pad, watched the red light spot indicator light in the center of placido disc, asked the patient to open his eyes as much as possible, and collected the data of 3.0 mm pupil diameter, and repeated the measurement and examination for 3 times in each eye. The total higher-order aberration, spherical aberration, coma and Clover aberration of 3 mm pupil diameter were recorded.

2.7. Statistical Methods

SPSS 26.0 was used for statistical analysis, which was $\overline{\chi} \pm S$ form, after the normality test, using single factor analysis of variance, chi square test, $P < 0.05$ as the difference was statistically significant.

3. Results

3.1. Clinical Baseline Data

There was no significant difference in the clinical baseline data, mainly including gender and age among the groups ($P > 0.05$) (Table 2).

Table 1. Visual quality satisfaction questionnaire for patients after cataract surgery.

Survey	4	3	2	1
1. Do you wear glasses (far vision)?	Never	Occasionally	Often	Always
2. Do you wear glasses (near vision)?	Never	Occasionally	Often	Always
3. Do you have glare, light halo phenomenon?	Never	Occasionally	Often	Always
4. How satisfied were you with this cataract surgery?	Always	Often	Occasionally	Never

Table 2. The results of the clinical baseline data.

Group	Single focus group	Multifocal group	Astigmatism group	ART group	*P* value
Gender					
Male (n)	10	11	9	10	>0.05
Female (n)	10	9	11	10	>0.05
Age (years)	66 ± 8.3	67 ± 8.8	65 ± 8.2	62 ± 8.8	>0.05

3.2. Slit Lamp Inspection

It was showed that there were no obvious complications after implantation of different types of intraocular lens among the groups by slit lamp on 1 day, 1 week, 1 month and 3 months. The cornea was generally transparent, the depth of anterior chamber was normal, the pupil was normal, the intraocular lens was located in the capsular bag, without obvious displacement and posterior capsule opacification.

3.3. Questionnaire Survey

There was significant difference on taking off glasses when near vison among the four groups ($\chi^2 = 167.688$, $P < 0.001$); The multifocal group and ART group were better than the single focus group and astigmatism group on taking off glasses when near vison ($P < 0.05$); There was no significant difference in the degree of satisfaction among the four groups ($P > 0.05$). One patient in the monofocal group complained about light halo during the day and glare at night, one patient in the multifocal group complained about light halo during the day and glare at night, and no patient complained about light halo or glare at night in the ART group. There was no nocturnal movement disorder among the four groups. During the follow-up, it was found that the demand for near vision after cataract surgery was related to the daily living habits and the refractive state of the contralateral eye also affected the lens removal rate (**Figure 1**).

3.4. Visual Acuity

It was significantly different about the UCDVA, BCDVA, UCNVA of the four groups in 3st months after cataract surgery ($F = 18.189$, $P < 0.001$). The UCNVA of the four groups was significantly different in the third month after cataract surgery ($P < 0.001$). There was no significant difference in UCDVA and BCDVA among the four groups ($F = 0.191$, $P = 0.902$; $F = 0.393$, $P = 0.759$) (**Figure 2**).

3.5. Comparison of Higher-Order Aberrations in the 3 mm Pupil in the Four Groups

There was no significant difference in the higher-order aberrations (total higher-order aberrations, wisdom aberrations, spherical aberrations, clover aberrations) of the four groups in 3st months after cataract surgery ($P > 0.05$). There was no significant difference in total higher-order aberrations and spherical aberrations among the groups ($F = 0.348$, $P = 0.791$; $F = 1.563$, $P = 0.215$) (**Figure 3**).

4. Discussion

With the continuous improvement and development of intraocular lens material technology, intraocular lens has developed from hard crystal to foldable soft crystal, from colorless to diversified, with the appearance of colored intraocular lens, from spherical crystal to aspheric crystal, from single focus to multifocal

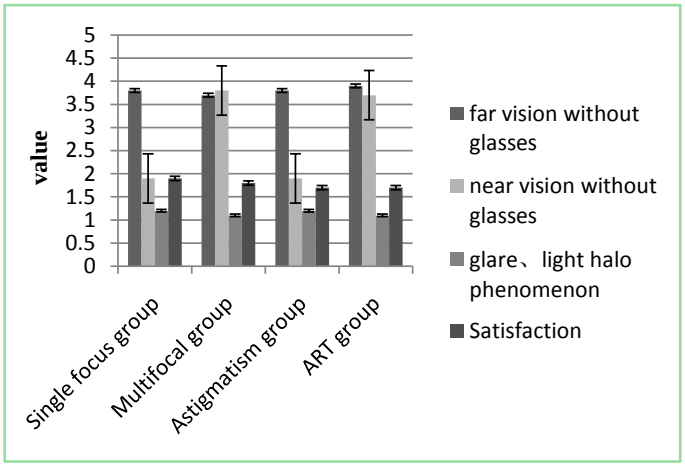

Figure 1. Questionnaire survey of postoperative visual quality in cataract patients.

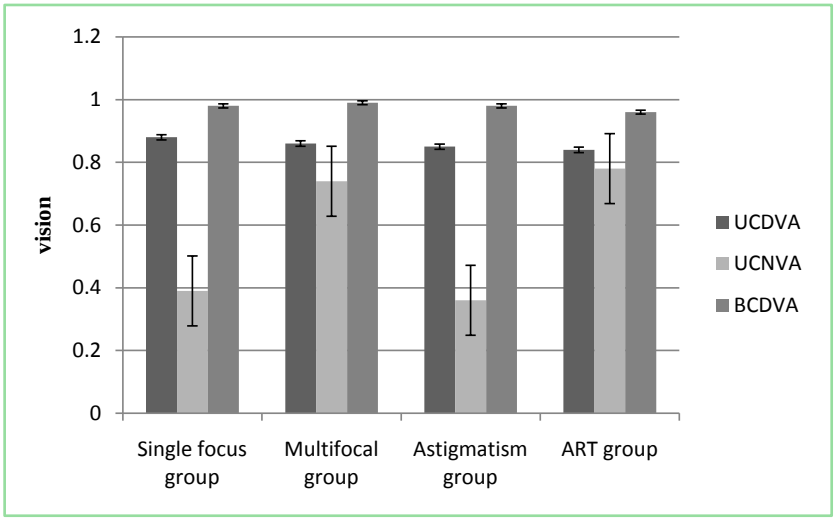

Figure 2. Comparison of visual acuity in the four groups after cataract surgery.

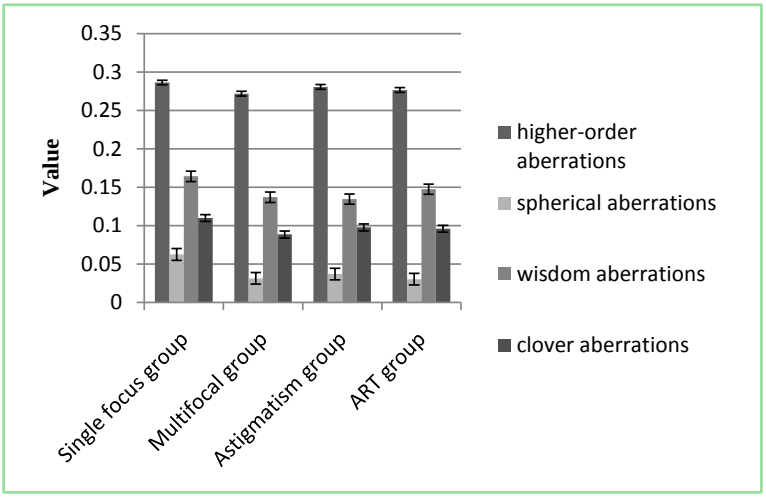

Figure 3. Comparison of higher-order aberrations in 3 mm pupil diameter in the four groups after cataract surgery.

crystal, from single focus aspheric crystal to astigmatism correction multifocal crystal, The improvement of visual quality of cataract patients after surgery is more and more obvious, not only visible and clear, but also comfortable and persistent [4] [5] [6] [7] [8]. Studies have found that blue light filtering intraocular lens could prevent macular damage caused by blue light, but will the implantation of blue light filtering intraocular lens affect the visual quality and cause visual discoloration in cataract patients? We have not found the phenomenon of visual discoloration and private complaints through questionnaire survey [9] [10] [11].

We found that the far vision and the best corrected far vision were very good in the four different types of foldable blue light filtering intraocular lens, including blue light filtering single focus aspheric intraocular lens (SN60WF), blue light filtering multifocal intraocular lens (SN6AD1), blue light filtering aspheric astigmatism correction intraocular lens (Toric SN6AT), the blue filtered aspheric multifocal astigmatism correction intraocular lens (ART). However, the near vision of the SN6AD1 and ART intraocular lens has obvious advantages; they could provide far vision and near vison. Only a few patients have postoperative glare and halo, but there was no case of visual discoloration. Most cataract patients have good objective distant vision after surgery, but a few patients are still dissatisfied with the visual quality, such as poor night vision, glare, halo and so on. Wavefront aberration is more and more widely used in the clinical application of cataract surgery combined with intraocular lens implantation. Therefore, the application of iTrace system to evaluate the visual quality of intraocular lens after cataract surgery could provide an objective basis for the selection of intraocular lens implantation in cataract surgery [3] [12] [13].

Many studies have found that blue light filtering intraocular lens could filter short wavelength blue light, protect retinal pigment cells, reduce the damage of blue light to retinal pigment epithelium, improve the sleep quality of patients after cataract surgery, reduce the risk of age-related macular degeneration, and reduce visual fatigue and glare [9] [14] [15] [16].

5. Conclusion

In conclusion, different types of AcrySof foldable blue light filtering aspheric intraocular lens implantation were safe, and the effect of early visual quality investigation was satisfied. According to different occupational and economic conditions, different distance vision requirements, whether there is regular corneal astigmatism, personalized selection of different types of intraocular lens, could effectively improve the visual quality of different cataract patients after surgery. It is an important personalized pursuit of refractive cataract surgery that is "clear, comfortable and persistent". The clinical guidance for the selection of individualized intraocular lens still needs study furtherly.

Fund Project

This study was supported by western medicine project of Guangzhou Health

Committee in 2021 (20211A011022); Guangzhou Planned Project of Science and Technology (No. 202102080447); Guangzhou General Science and Technology Project of Health and Family Planning (No. 20211A011016); The Science Foundation of Guangzhou First People's Hospital (No. M2019020).

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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International Journal of Clinical Medicine, 2021, 12, 316-327
https://www.scirp.org/journal/ijcm
ISSN Online: 2158-2882
ISSN Print: 2158-284X

The Use of Standardized Reporting and Time-in-Range in the Management of Diabetes: A Consensus Report

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How to cite this paper: Al Sifri, S., Alshaikh, A., Bin-Abbas, B., Sheshah, E., Al Sabaan, F., Al-Dawish, M., Al-Dubayee, M., Al-Zaman, N., Al-Dahash, R.A., Alzahrani, S. and Issak, E.R. (2021) The Use of Standardized Reporting and Time-in-Range in the Management of Diabetes: A Consensus Report. *International Journal of Clinical Medicine*, **12**, 316-327.
https://doi.org/10.4236/ijcm.2021.128028

Received: July 1, 2021
Accepted: August 2, 2021
Published: August 5, 2021

Abstract

Introduction: The exhaustion of healthcare resources due to the rising prevalence in Saudi Arabia mandates the search for each method that can help in better control of diabetes. **Methods:** The gathered task force gathered to develop an explicit, evidence-based consensus for the use of time-in-range targets as guidance for better glycemic control while using continuous glucose monitoring (CGM). This article has the recommendations of this expert panel. **Results:** HbA1c and self-monitoring blood glucose (SMBG) are not enough to detect blood glucose (BG) fluctuations on a daily basis. The incorporation of technology like FreeStyle Libre with its applications like Libre View is now used in many institutes in Saudi Arabia. This system is comprehensive and has all the standardized metrics needed. However, training and support are always needed. Barriers and challenges include the awareness & experience of the technology, the time barrier, the patients' barriers, the technical barriers, and of course, the availability barrier. All the barriers and challenges should be dealt with by designing new training programs. **Conclusion:** The expert

panel recommended using CGMs technology in people with type 1 diabetes (T1DM) children and adults, type 2 diabetes (T2DM) on multiple insulin injections, gestational diabetes (GDM) who need further glycemic control, and those at high risk for hypoglycemia. In addition, we recommend using them for a short period for those who require intensive BG control or during acute illness or stress. In addition, Ambulatory Glucose Profile (AGP) could be used as an educational tool for any individuals with DM to study the impact of certain elements of lifestyle modifications on their immediate BG level.

Keywords

Diabetes, Time in Range, Glycemic Control, HbA1c

1. Introduction

Worldwide, by the year 2045, diabetes mellitus (DM) prevalence is expected to be 9.9%, with a total number of 629 Million [1]. The Kingdom of Saudi Arabia (KSA) has a rising prevalence of DM [2], with the consequent exhaustion of healthcare resources.

In 2019, the American Diabetes Association (ADA) coined and published its first recommendations for the time-in-range (TIR) targets to guide those who help in the management of DM as well as people with DM achieve better glycemic control by the utilization of the continuous glucose monitoring (CGM) [3]. The consensus panel included researchers from all geographic regions to ensure that the recommendations can be generalizable [4].

A panel of experts in DM was gathered to generate a clear, evidence-based consensus for the use of TIR targets as guidance for better glycemic control while using CGM. This manuscript presents the recommendations of this task force.

2. Available Metrics for Blood Glucose Monitoring

Fasting blood glucose (FBG) level, postprandial blood glucose (PPBG) level, and random blood glucose (RBG) level—metrics for blood glucose (BG) monitoring—were used once for the diagnosis and management of DM. However, they give only a snapshot of the glycemic status at a certain point in time. Glycated hemoglobin (HbA1c) and fructosamine were also introduced as metrics for glycemic control over a duration ranging from two weeks to three months. The introduction of self-monitoring blood glucose (SMBG) helps in glycemic control daily; however, to reflect the actual status, it should be carried out at least seven times per day, which is sometimes not practical. All those lead to the evolution of continuous blood glucose monitoring systems (CGMs), particularly in those people who are in intensive insulin therapy. Consequently, new metrics have been developed to reveal new insights into the short-term glucose dynamics; this is the topic of this consensus [5] [6].

2.1. Glycated Hemoglobin (HbA1c) Is Not Enough Metric for Glycemic Control on a Daily Basis

Elevated HbA1c is a significant contributor to complications in people with type 1 DM (T1DM), as confirmed by the DM Control and Complications Trial (DCCT). In addition, the UK Prospective Diabetes Study (UKPDS) confirmed how the control of BG affects health outcomes in type 2 DM (T2DM) [7] [8].

However, HbA1c has its limitations. First, it does not show the glycemic level and variability daily, as it just shows an average level of BG for the last three months.

Second, HbA1c is inaccurate in people with anemia, hemoglobinopathies, and pregnancy [9] [10] [11] [12]. In addition, it does not reveal the rapid changes in BG levels daily; thus, adjustment of therapy is not easy. Moreover, there is a racial difference in the accuracy of HbA1c because of different glycation rates [9]. Therefore, even though HbA1c has been evidenced valuable measure and validated as a risk factor for DM complications, it seems not helpful for glycemic control on a personal level as it reflects only a piece of the severity of hyperglycemia and glycemic variability are contributing to the pathogenesis of complications [13] [14].

2.2. Self-Monitoring Blood Glucose (SMBG) Also Has Its Limitations as a Metric for Glycemic Control

SMBG has been associated with better management in T1DM and T2DM. Nevertheless, it requires a finger-stick and it only gives a snapshot for one point in time; therefore, it does not show the trend or the rate of change of BG levels. Thus, using it alone may result in improper treatment decisions. Moreover, it often fails to detect hypoglycemia, either nocturnal or asymptomatic [15]-[22].

3. The Advent of Continuous Blood Glucose Monitoring Systems (CGMs)

The search for new methods for BG monitoring was continuous to address the limitations in HbA1c and SMBG, leading to the development of real-time CGM (rtCGM) and flash glucose monitoring (FGM). The former tracks the glucose level uniformly, providing real-time measurements, while the latter, at the time of checking, shows continuous glucose measurements retrospectively. Both types facilitate monitoring of the time spent in the target glycemic range; TIR.

Nevertheless, only rtCGM can warn users if their BG level is trending toward hypoglycemia or hyperglycemia, while FGM requires scanning of the sensor to reveal these trends, where newer generations of FGM are available with optional alarm functionality. Plentiful studies have demonstrated that the use of CGM improves both glycemic control and quality of life in different populations with T1DM or T2DM. In addition, one meta-analysis has shown that the frequency and persistence of its utilization of rtCGM are directly correlated to its benefit [9] [23]. Moreover, a meta-analysis has shown that the use of Flash glucose monitoring was associated with a clinically significant reduction in

HbA1c [24].

A critical note about CGMs is validating their performance, whereas FGM is factory-calibrated, indicating that no validation against SMBG is required. The most common metric used to assess CGMs performance is the mean absolute relative difference (MARD), which is the mean of the absolute errors between all CGMs values and the reference values. The lower the MARD is, the better the performance is [9]. However, the methodology for calculating MARD has not yet been standardized, so this would be misleading [25].

3.1. Continuous Blood Glucose Monitoring Systems in Saudi Arabia

In KSA, insulin pump therapy and CGMs are now available and increasing as a modality for better management of DM and as an educational tool. The new user-friendly generations of CGMs encouraged people with DM to use this technology. The initiation of reimbursement of these tools by the national health bodies and insurance organizations paved the way in front of the healthcare professional to explore the recent technologies for better glycemic control and its subsequent improvements in the quality of life of their patients. All these are reflected in reducing the cost of illness and the burden of DM. CGMs are available in Saudi Arabia with all its four categories: rtCGM like the Dexcom; FGM like the FreeStyle Libre; blinded (professional) CGM like the Guardian; and the unblinded CGM. Although CGMs have become the gold standard in managing patients who are in intensive insulin therapy, some physicians are reluctant to utilize them, most probably due to the lack of experience and knowledge with this technology.

3.2. The Clinical Targets for CGMs Data Interpretation

In 2019, the international panel of diabetes experts demonstrated ten metrics with their target range in the CGM data interpretation with a consensus on the TIR to complement HbA1c. These metrics include the number of days CGMs has worn (recommended 14 days); the percentage of time CGMs is active (recommend 70% of data from 14 days); mean BG; glucose management indicator (GMI); glycemic variability (% CV); time-above-range (TAR) with two levels; time-in-range (TIR); and time-below-range (TBR) in two levels. In addition, the expert panel set the accepted target in each metric for T1DM, T2DM, and older/high-risk T1DM or T2DM, and for pregnant women with T1DM, T2DM, or gestational diabetes (GDM) [3].

The new term GMI replaced the term estimated A1C. It is based on the CGM-derived mean BG in the previous 14 days [14]. In addition, different research studies showed the correlation between HbA1c and the TIR. One was conducted upon 545 patients with T1DM and the other upon 1137 patients with T1DM and T2DM [26] [27]. TIR was validated as an outcome measure for DM complications like retinopathy and microalbuminuria [28].

3.3. Integrating Continuous Glucose Monitoring Systems into Clinical Practice

CGMs provide current and future BG data and display them in numerical and graphical ways, along with glucose trends. Retrospective analysis of CGMs historical data can help in carbohydrate counting and lifestyle modifications. Moreover, some CGMs have an alert feature, which is crucial for those with frequent hypoglycemia. In addition, the data-sharing ability and trend arrows can help in better glycemic control. Each type of CGMs has its advantages and disadvantages. The accuracy, the need for calibration, the easy applicability, and the cost are among the critical factors when choosing one of them.

4. CGMs Metrics

4.1. Time-in-Range

In general, the term TIR refers to the total time spent in a target BG range (70 - 180 mg/dL) or the more strict range (70 - 140 mg/dL) in some conditions. Of course, it adds a valuable piece of information about the current level of glycemic control at a specific time. That also has led to new terms like times below range (TBR) and times above range (TAR), which gave a better quantification of the level of BG control. TIRs can help people with DM watching the improvement or deterioration in the amount of clinically significant hyperglycemia or hypoglycemia over time [9] [29].

4.2. Hypoglycemia

In people with DM, particularly T1DM, hypoglycemia is a common complication of treatment and is a significant barrier to glycemic control. In adults with T2DM on insulin or sulfonylureas, severe hypoglycemia, defined as needing assistance, is more frequent when HbA1c is at the lowest or highest levels. Quantification of the risk for hypoglycemia can be carried out using the low BG index (LBGI). However, LBGI, when based on CGM data, tends to underestimate the risk to some extent [29] [30] [31] [32]. Grading hypoglycemic events is essential in managing DM, specifically when the CGM levels indicate BG levels < 54 mg/dL for ≥two hours (**Table 1** & **Figure 1**) [9].

4.3. Glycemic Variability

Another important CGM metric is glycemic variability (CV). A CV < 36% means stable BG levels, and CV ≥ 36% means unstable levels [30]. The relationship between CV to DM complications, cognitive function, and quality of life has been studied and established. Therefore, it has been accepted as an important and valuable marker for glycemic control [31] [32] [33] [34]. It gives a better insight into the dynamicity of the BG levels and their fluctuations. It is a waveform process that has an amplitude, frequency, and duration. It contributes to the risks of hyperglycemia and hypoglycemia. The higher the CV, the higher is the association to mortality in the intensive care setting [35]-[41].

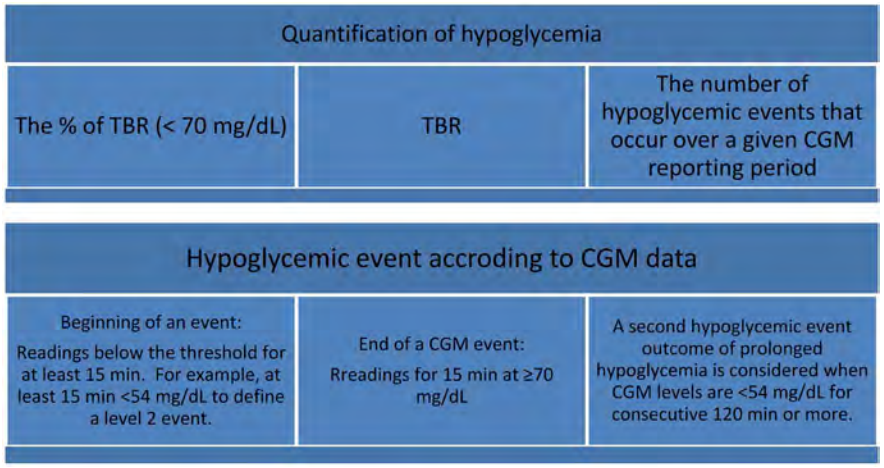

Figure 1. Quantification of hypoglycemia.

Table 1. Categorization of hypoglycemia.

Level 1	Level 2	Level 3
BG value (70 - 54 mg/dL), with or without symptoms.	BG value < 54 mg/dL, with or without symptoms.	Severe hypoglycemia, denotes cognitive impairment, is not defined by a specific BG value.
Minimization of the time spent in this range will reduce the risk of developing more clinically significant hypoglycemia.	Clinically significant hypoglycemia, requires immediate attention.	Requires external assistance for recovery.

5. The Need for a Glucogram Similar to an Electrocardiogram

Using standardizing reporting is beneficial in the clinical decision-making in DM management. Several reporting tools, such as the standardized Ambulatory Glucose Profile (AGP) report (**Figure 2**), have been developed using at least 14-consecutive-days CGM data with 70% of readings [42] [43] [44]. Several expert panels previously adopted the AGP and recommended it as a standard tool for picturing CGM data [9] [45].

Moreover, integrating these metrics into the electronic records of people with DM is of utmost importance as they can facilitate communication with patients and help them self-manage their DM [46].

Different types of graphs help figure out the exact situation of BG control and BG distribution in one day or in a certain period in time (**Figure 3(a)**). These reports can be printed, certain areas of hypo or hyperglycemia can be marked and discussed with patients efficiently in relation to their daily routine (**Figure 3(b)**). In addition, the graphs can be daily, each day in a line graph (**Figure 3(c)**). In addition, another graph can show a summary and give how much time of the 14 days the device was active (**Figure 2**).

The four key metrics that require attention are data sufficiency (a minimum of two weeks of CGM use); the percentage of time (or minutes) on TIR, TAR & TBR;

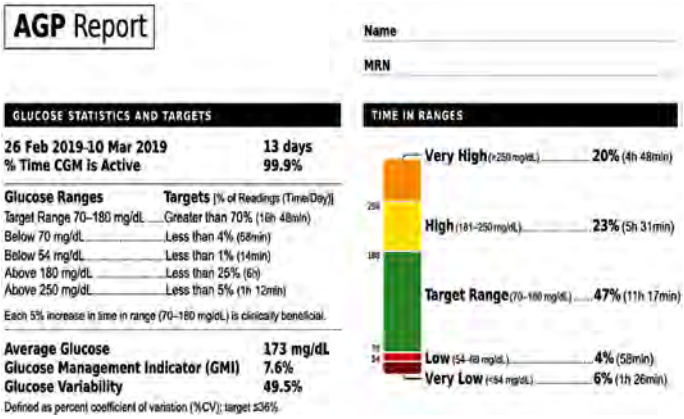

Figure 2. Ambulatory Glucose Profile (AGP) Report-Metrics and glucose pattern summary. For illustrative purposes, the outputs from the FreeStyle Libre Health Management System software (Abbott Laboratories). The Ambulatory Glucose Profile (AGP). ([a]2021 International Diabetes Center at Park Nicollet, Minneapolis, MN. AGPreport.org).

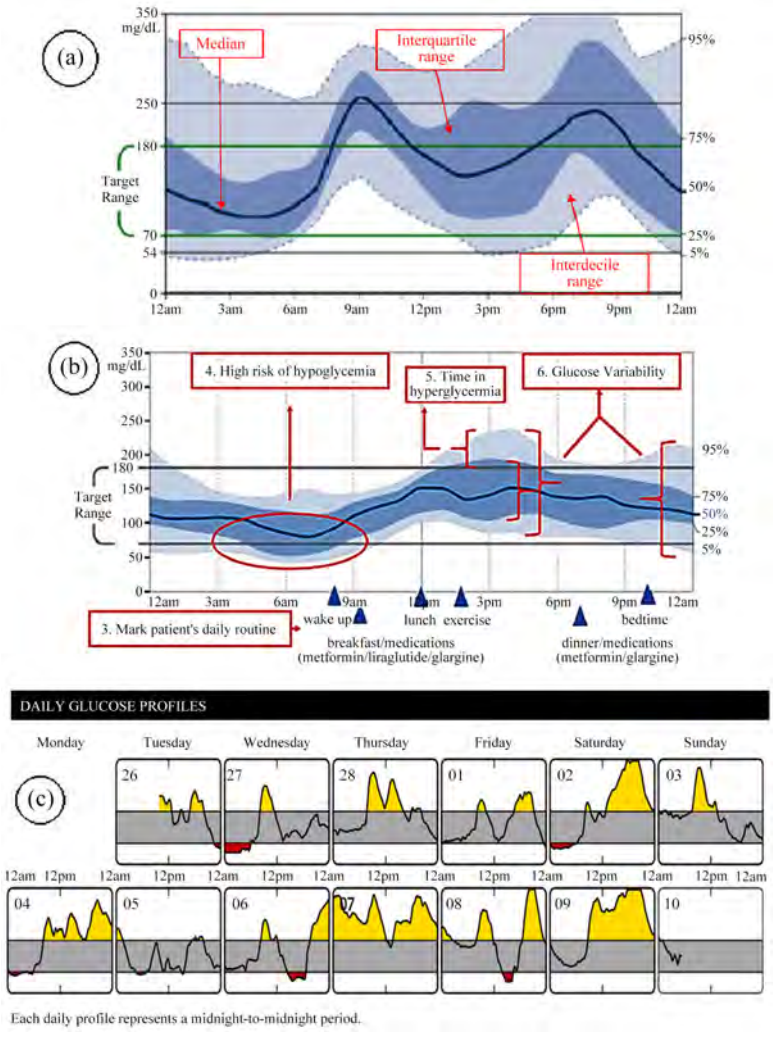

Figure 3. Ambulatory Glucose Profile: (a) glucose distribution as if happening over a period of 24 hours; (b) Areas to target for management; (c) glucose distribution in different days. For illustrative purposes, the outputs from the FreeStyle Libre Health Management System software (Abbott Laboratories). The Ambulatory Glucose Profile (AGP). ([a]2021 International Diabetes Center at Park Nicollet, Minneapolis, MN. AGPreport.org).

CV, which indicates the level of glycemic variability over the period reported; glucose management indicator (GMI) which replaced the term estimated HbA1c. The patients using CGMs need to check their BG by fingerprick whenever there is low blood sugar, rapidly changing BG level if symptoms do not match BG reading if sensor glucose does not match BG, and confirmatory check pre-prandial. However, newer algorithms of improved accuracy would require a confirmatory fingerstick in case of symptoms not matching the readings. Training for the patients is essential for using the AGP and managing their BG accordingly. One important note mentioned is that despite no calibration is needed, still, finger-stick glucose checks are needed.

6. Conclusions and Recommendations

Statement 1: If we are to improve our healthcare programs in line with international evidence and technology, we need to redesign programs, re-organize and redirect our resources, and focus on our needs and goals. In diabetes care, we need to adopt new helpful technologies in an integrated, planned, shared, and structured model of care in line with the significant reform objectives of our health system.

Statement 2: HbA1c and SMBG are not enough to detect BG fluctuations daily.

Statement 3: Daily use of CGM provides the ability to obtain immediate feedback on the current level, and the trend of glucose provided by CGMs allows people with DM to act in response instantaneously and appropriately according to these data.

Statement 4: In clinical practice, metrics like TIR, TBR, TAR, GMI, and CV are valuable clinical targets that complement the laboratory HbA1c. They are an integral component of day-to-day DM management.

Statement 5: We recommend using CGMs technology in people with T1DM children and adults, T2DM on multiple insulin injections, GDM who need further glycemic control, those at high risk for hypoglycemia. In addition, we recommend using them for a short period for those who require intensive BG control or during acute illness or stress. In addition, AGP could be used as an educational tool for any individuals with DM to study the impact of some aspects of lifestyle modifications on their immediate BG level.

Statement 6: The incorporation of CGMs technology like FreeStyle Libre with its applications like Libre View is now used in many institutes in Saudi Arabia. This system is comprehensive and has all standardized metrics needed. However, training and support are always needed. In addition, two complementary ways are needed; one is the clinical evidence of its benefits, and the second is its impact on the budget (is it cost-saving?).

Statement 7: Barriers and challenges include the awareness & experience of the technology, the time-barrier, the patients' barriers, the technical barriers, and of course, the availability barrier. All the barriers and challenges should be dealt with by designing new training programs.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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International Journal of Clinical Medicine, 2021, 12, 328-341
https://www.scirp.org/journal/ijcm
ISSN Online: 2158-2882
ISSN Print: 2158-284X

Correlation between Expression Differences of Epithelial-Mesenchymal Transition (EMT) in Cholangiocarcinoma Tissue

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How to cite this paper: Liu, Q., Rao, X., Cai, H.X. and Guo, J.C. (2021) Correlation between Expression Differences of Epithelial-Mesenchymal Transition (EMT) in Cholangiocarcinoma Tissue. *International Journal of Clinical Medicine*, **12**, 328-341.
https://doi.org/10.4236/ijcm.2021.128029

Received: July 23, 2021
Accepted: August 10, 2021
Published: August 13, 2021

Abstract

Background: By studying the expression of epithelial-mesenchymal transition regulators in cholangiocarcinoma and intrahepatic duct stones, the correlation between the expression of epithelial-mesenchymal transition regulators and cholangiocarcinoma was revealed. **Objective:** The objective is to investigate the correlation between the expression of epithelial-mesenchymal transition (EC) regulatory factors and cholangiocarcinoma in patients with intrahepatic duct stones and cholangiocarcinoma, to investigate the relationship between clinicopathological features and prognosis, and to observe the expression of molecular markers of epithelial-mesenchymal transition (EMT) in intrahepatic duct stones and bile duct carcinoma. **Methods:** Twenty cases of primary cholangiocarcinoma, 20 cases of intrahepatic cholangiolithiasis complicated with cholangiocarcinoma, and 20 cases of intrahepatic cholangiolithiasis specimens were collected from the Fourth People's Hospital and the friendly medical unit of Haikou. Immunohistochemistry was used to detect the expression differences of EMT-related molecular markers Twisit1, Twisit2, E-cadherin, N-cadherin, and Vimentin in paraffin sections of normal intrahepatic bile duct tissues and patients with intrahepatic duct stones and cholangiocarcinoma. **Results:** Immunohistochemical staining revealed epithelial-mesenchymal transition (EMT) in intrahepatic cholangiocarcinoma tissue, intrahepatic cholangiolithiasis with cholangiocarcinoma, intrahepatic cholangiolithiasis with normal intrahepatic cholangiolithiasis, such as Sit1, Twisit2, E-cadherin, N-cadherin, and Vimentin proteins were different. The expression of E-cadherin was decreased in cholangiocarcinoma tissue and intrahepatic cholangiolithiocarcinoma combined with cholangiocarcinoma ($P < 0.05$), while the expression of N-cadherin and Vimentin was up-regulated ($P < 0.05$). The expression of Twisit1 and Twisit2 had no difference ($P >$

0.05). There was no difference in the expression of intrahepatic bile duct stones and EMT ($P > 0.05$). **Conclusion:** The expression of E-cadherin, the molecular marker of EMT, was down-regulated, while the expression of N-cadherin and Vimentin was up-regulated. Age, gender, depth of tumor invasion, degree of tumor differentiation and lymph node metastasis were correlated with the expression of EMT in intrahepatic cholangiocarcinoma.

Keywords

Intrahepatic Bile Duct Stones, Hepatobiliary Cell Carcinoma, Organizations, EMT. Immunohistochemical

1. Brief Introduction

Intravenous cholangiocarcinoma (ICC) usually refers to the primary tumors in the hepatic duct, also known as peripheral bile duct or bile duct cell carcinoma, which originates from the secondary and above bile ducts in the liver. Malignant tumor is a serious threat to human health, and its mortality rate ranks first in both the world and China. According to the Global Cancer Statistics published by the World Health Organization in 2011 [1], Cholangiocarcinoma (CCA) originates from bile duct epithelial cells and is the most common malignant tumor in the liver and biliary system except bile duct carcinoma. According to different anatomical locations, cholangiocarcinoma can be divided into intrahepatic cholangiocarcinoma (IHCC), hilar cholangiocarcinoma Perihilar CCA (PHCC), and distal cholangiocarcinoma (DCC). Recent studies have reported that the incidence and mortality of cholangiocarcinoma are on the rise. Cholangiocarcinoma is aggressive and metastases early and more than 2/3 of patients have lost the opportunity of surgery when diagnosed. Moreover, the effect of adjuvant therapy for cholangiocarcinoma still needs to be further verified. The median overall survival for patients with cholangiocarcinoma was only 15 months. Therefore, it is of great significance to further clarify the molecular mechanism of the occurrence and development of cholangiocarcinoma and to search for early diagnostic indicators and effective therapeutic targets of cholangiocarcinoma for improving the prognosis of patients. The etiology of cholangiocarcinoma is still unclear, but some relatively clear risk factors include primary sclerosing cholangitis [2], intrahepatic bile duct calculi [3], bile duct cyst, hepatic fluke [4], etc. Other possible risk factors include diabetes mellitus, HBV [5] and HCV virus infection [6]. However, the pathogenesis of intrahepatic cholangiocarcinoma has not yet been determined. With the continuous development of medical diagnostic techniques and the deepening of the understanding of this disease, considerable progress has been made in the study of the risk factors for its incidence, such as intrahepatic cholangiolithiasis, primary sclerosis cholangitis, congenital cholangitis cyst, etc. [7]. China is a country with a high incidence of intrahepatic bile duct stones, so intrahepatic bile duct stones are considered to be a common cause of intra-

hepatic bile duct carcinoma in China. Studies have shown that about 10% of patients with intrahepatic bile duct stones may develop into intrahepatic bile duct carcinoma [8]. Hepatobiliary calculus with cholangiocarcinoma (HCWC) and hepatobiliary calculus associated with bile duct carcinoma was described. Many special factors above intrahepatic bile duct calculi-related bile duct carcinoma lead to its low early diagnosis rate, poor prognosis, high mortality rate, and even an increasing trend year by year. Therefore, more and more attention has been paid to the disease at home and abroad, and the research on the pathogenesis and prognostic factors will become an inevitable trend. Epithelial-mesenchymal transition (EMT) has increasingly become a hot research direction to explain the mechanism of tumor metastasis and invasion. The specific process of EMT includes loss of adhesion between cells, depolarization of cells, enhanced ability of cell invasion and migration, etc. The morphology of mesenchymal cells is conducive to the migration of tumor cells to distant organs and the maintenance of stem cell characteristics and is conducive to the transformation of tumor cells to other cell types in the initial and developmental stages of metastasis. However, the role and mechanism of EMT in cholangiocarcinoma are less studied. Therefore, it is of great value to further clarify the mechanism of EMT in cholangiocarcinoma for exploring its metastatic mechanism. Early diagnosis can significantly improve the therapeutic effect and prognosis of cholangiocarcinoma.

Unfortunately, at present, most patients with cholangiocarcinoma are diagnosed in the advanced stage and lose the best opportunity for surgical treatment. Therefore, the research on early cholangiocarcinoma and even precancerous lesions and the establishment of effective screening and diagnosis methods will play a decisive role in the prevention and control of cholangiocarcinoma. In the field of cholangiocarcinoma treatment, with the deepening of research, the treatment of cholangiocarcinoma is developing towards the direction of high pertinence and individualization, which is mainly determined by the molecular biological characteristics of cholangiocarcinoma cells. The individualized treatment of tumor requires the establishment of accurate and effective diagnostic indicators to group patients, so as to provide the basis for prognosis judgment and treatment program selection. Tumor molecular typing will play an important role in this field.

2. Research Objects and Methods

2.1. Subjects

Twenty patients with primary cholangiocarcinoma, 20 patients with intrahepatic cholangiolithiasis complicated with cholangiocarcinoma, and 20 patients with intrahepatic cholangiolithiasis were collected from the Fourth People's Hospital of Haikou during January 2020 to December 2020, and the case data of 20 paraffin pathological specimens were collected. Normal bile duct tissue (*i.e.*, normal bile duct tissue 2 cm away from the margin of tumor or stone tissue) was used as control.

Inclusion and exclusion criteria:

1) The patient was pathologically diagnosed as intrahepatic cholangiocarcinoma, and patients with mixed hepatocellular and cholangiocarcinoma were excluded.

2) The patient was the first to find ICC, and the patients with postoperative recurrence of ICC were excluded.

3) ICC patients treated with radical surgery were excluded from ICC patients treated with palliative surgery.

4) Hepatitis related ICC patients with metabolic syndrome, intrahepatic bile duct stones, schistosoma liver disease, alcoholism, primary sclerosing cholangitis or congenital intrahepatic bile duct cystic dilatation should be excluded, and those with hepatitis C infection should be considered.

Each patient in this study was approved by the Ethics Committee of the Fourth People's Hospital of Haikou City. This study was conducted in strict accordance with the Helsinki Declaration, and informed consent was signed. Paraffin white tablets for the experiment were prepared by the Department of Pathology (4 μm/tablet).

2.2. Experimental Methods

2.2.1. Immunohistochemical Staining

1) slice and bake: 4 μm slice and bake at 60˚C for 90 minutes.

2) Dewaxing and rehydrating: after the paraffin section is put into the bracket, it is immersed in xylene for 15 minutes, and then washed with distilled water, it is repeated again. Then the slices were soaked in 100%, 95%, 85% and 75% ethanol solutions for 5 minutes successively, and then rinsed thoroughly with distilled water repeatedly.

3) Heat repair antigen: using high temperature and high pressure method, the antigen repair solution was boiled in the pressure cooker and then put into the rinsed section, and then continued to heat and boil for 5 minutes. After cooling, the antigen repair solution was washed with PBS for 3 times, each time for 3 minutes.

4) Sealing: 3% hydrogen peroxide was added to the section as the sealing solution and soaked at room temperature to inactivating endogenous peroxidase. After sealing for 10 minutes, the section was taken out and put on the scaffold. The section was washed with PBS for 3 times, 5 minutes each time, and then placed on the shaker.

5) Incubation of primary antibody: drop the properly diluted primary antibody and put it in a wet box at 4˚C overnight. After removal, rewarm at room temperature at 37˚C for 45 minutes, discard the primary antibody, and rinse with PBS for 3 times with at least 5 minutes for each rinse.

6) Incubation of the secondary antibody: drop appropriate secondary antibody to cover the specimen according to the instructions of the kit. Incubate at room temperature of 37˚C for 60 minutes, rinse with PBS after discarding the

secondary antibody, and repeat for 3 times.

7) DAB dyeing: DAB dyeing shall be performed according to the instructions of DAB kit. The real-time situation of dyeing shall be judged at any time. The dyeing time shall be determined according to the concentration of dyeing.

8) Re-staining: Drops of hematoxylin were added for nuclear re-staining. After 30 seconds of reaction, PBS was fully rinsed.

9) Dehydration sealing: the slices were placed in 75%, 85%, 95% and 100% ethanol solutions in turn and soaked for dehydration from low to high, for 2 minutes each time. After PBS rinsing, the slices were placed in xylene for 3 minutes and the excess xylene was erased. Drop neutral gum sealing piece, cover glass sealing piece, as for room temperature air drying pieces.

10) Put the air-dried wafer under a microscope for observation and interpretation.

2.2.2. Observation and Analysis of the Results of Immunohistochemical Staining

Positioning results:

E-cadherin was mainly expressed in the cell membrane, N-cadherin was expressed in the cell membrane and cytoplasm, Twist1 and Twist2 were mainly expressed in the cytoplasm, and Vimentin was expressed in the cytoplasm.

Judgment criteria:

1) The brown-yellow particles in the cells were regarded as positive staining, and the cells were scored according to the degree of cell staining: 0 for no obvious staining, 1 for light yellow, 2 for dark yellow, and 3 for brown.

2) Randomly observe the sample area of each patient section, count 100 cells from each area, and then grade the specimen according to the ratio of positive cells to the total number of cells: When the percentage of positive stained bile duct cells in the total number of cells is less than 10%, 0 marks, 10% - 25% is 1 mark, 25% - 50% is 2 marks, 50% - 75% is 3 marks, and more than 75% is 4 marks. Calculate the product of cell staining depth score and cell number score. If the product is 0, it is negative (−), 1 - 4 is weak positive (+), 5 - 8 is moderate positive (++), and more than 9 is strong positive (+++). Set ± as (low) negative expression and ++/++ as (high) positive expression. The results of all specimens were determined by three senior professional physicians in the Department of Pathology, and the counting data were averaged. After the data were collected and verified, the data were recorded and processed.

2.2.3. Statistical Analysis

The measurement data were expressed by means ± standard deviation (SDS), and the independent sample t test, χ^2 test and correlation analysis were used for data analysis. Kaplan-Meier method was used to draw survival curves, and log-rank test was used to compare the differences. Statistical analysis was performed using SPSS 23.0 software (SPSS, Chicago, IL, USA), and the statistical analysis and mapping were performed in GraphPad Prism 6.0 software (San Diego, CA, USA). $P < 0.05$ was considered statistically significant.

3. Results

3.1. Intrahepatic Bile Duct Stones + Normal Tissues and the Expression of Molecular Markers Related to EMT

There is no difference in the expression of molecular markers (see Figures 1(b)-(f)) related to intrahepatic bile duct stones + normal tissue and EMT(see Figure 1(a)). All images were under 40 × 10 microscope, and there was no difference in intrahepatic bile duct stones + normal tissue and EMT expression ($P > 0.05$).

3.2. E-Cadherin and the Expression of Normal Bile Duct Tissue and Hepatocholangiocarcinoma

E-cadherin expression (normal bile duct tissue as shown in Figure 2(a) and hepatobiliary duct cell carcinoma as shown in Figure 2(b)). All images showed decreased E-cadherin expression under 40 × 10 microscopy.

Immunohistochemical results showed as shown in Figure 2, the positive expression of E-cadherin in cholangiocarcinoma tissues was 5 cases, accounting for 25% of the total, while the positive expression of E-cadherin in normal bile duct tissues was 16 cases, accounting for 80% of the total. The positive expression of E-cadherin in cholangiocarcinoma tissues was significantly down-regulated, as shown in Table 1 ($P < 0.01$).

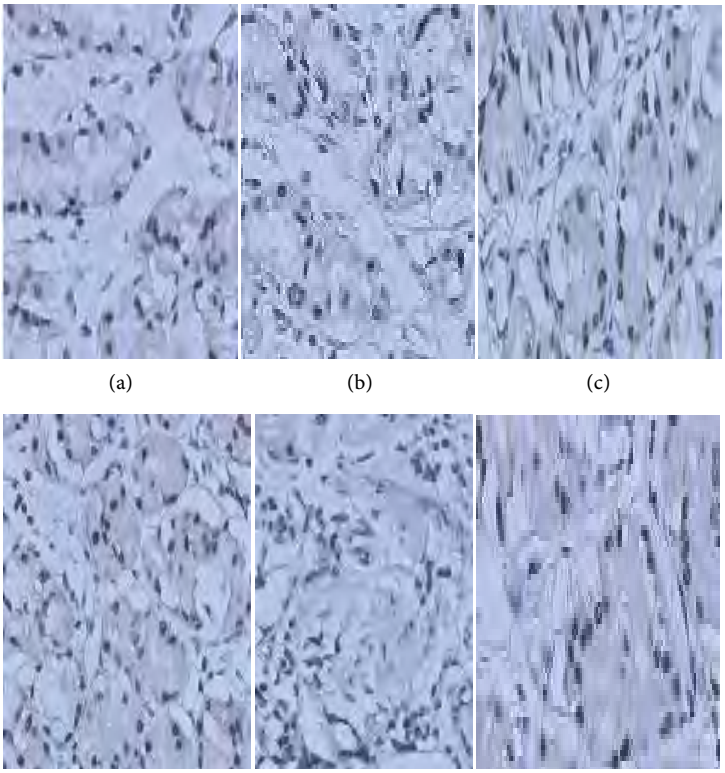
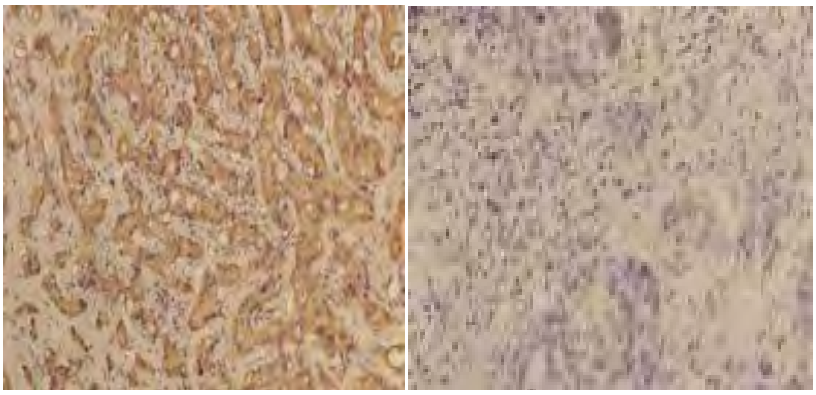


Figure 1. (a) Normal bile duct tissue; (b) Twisit1; (c) Twisit2; (d) E-cadhern; (e) N-cadhern; (f) Vimentin.



(a) (b)

Figure 2. (a) Normal bile duct tissue; (b) Intrahepatic cholangiocarcinoma.

Table 1. Expression of E-cadherin in normal bile duct tissues and bile duct carcinoma tissues ($P < 0.01$).

Tissue types	N	negative − or +	positive ++ or +++
Normal bile duct tissue	20 (%)	14 (70)	6 (30)
Intrahepatic cholangiocarcinoma	20 (%)	15 (75)	5 (25)

3.3. Expression of E-Cadherin and Intrahepatic Bile Duct Stones with Intrahepatic Cholangiocarcinoma

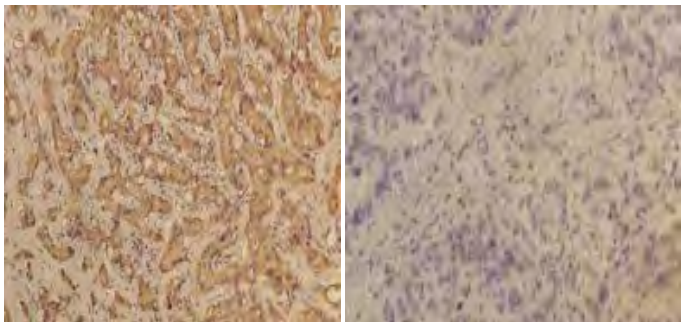
E-cadherin expression (normal bile duct tissue as shown in **Figure 3(a)** and intrahepatic bile duct stones with intrahepatic bile duct carcinoma as shown in **Figure 3(b)**), resulting in decreased E-cadherin expression.

Immunohistochemical results showed as shown in **Figure 3**, the positive expression of E-cadherin in intrahepatic bile duct stones and intrahepatic bile duct carcinoma was 6 cases, accounting for 33.3% of the total, while 15 cases, accounting for 75% of the total, were found in normal bile duct tissues. The positive expression of E-cadherin in intrahepatic bile duct stones and intrahepatic bile duct carcinoma was significantly down-regulated. See **Table 2** ($P < 0.01$).

3.4. N-Cadherin and the Expression of Normal Bile Duct Tissue and Hepatocholangiocarcinoma

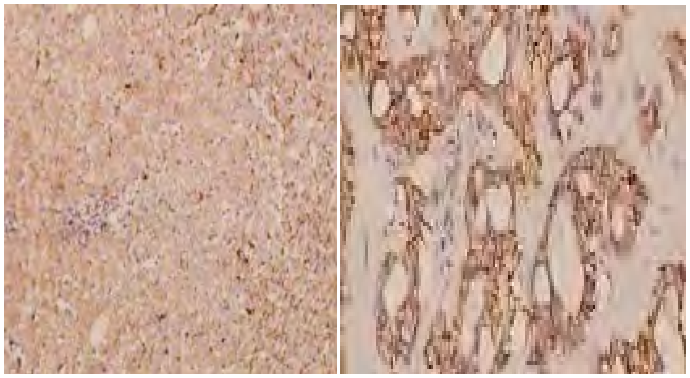
Expression of N-cadherin (normal bile duct tissue see **Figure 4(a)** and hepatobiliary duct cell carcinoma see **Figure 4(b)**), resulting in elevated N-cadherin expression.

Immunohistochemical results showed as shown in **Figure 4**, the positive expression of N-cadherin in cholangiocarcinoma tissues was 15 cases, accounting for 75% of the total, while the positive expression of N-cadherin in normal bile duct tissues was 6 cases, accounting for 20% of the total. The positive expression of N-cadherin in cholangiocarcinoma tissues was significantly up-regulated, as shown in **Table 3** ($P < 0.01$).



(a) (b)

Figure 3. (a) Normal bile duct tissue; (b) Stone + intrahepatic cholangiocarcinoma.



(a) (b)

Figure 4. (a) Normal bile duct tissue; (b) Intrahepatic cholangiocarcinoma.

Table 2. Expression of E-cadherin in normal bile duct tissue, intrahepatic bile duct stones and intrahepatic bile duct carcinoma ($P < 0.01$).

Tissue types	N	negative − or +	positive ++ or +++
Normal bile duct tissue	20 (%)	5 (25)	15 (75)
Stone + intrahepatic cholangiocarcinoma	20 (%)	14 (70)	6 (30)

Table 3. Expression of N-cadherin in normal bile duct tissues and bile duct carcinoma tissues ($P < 0.01$).

Tissue types	N	negative − or +	positive ++ or +++
Normal bile duct tissue	20 (%)	14 (70)	6 (30)
Intrahepatic cholangiocarcinoma	20 (%)	5 (25)	15 (75)

3.5. N-Cadherin and the Expression of Intrahepatolithiasis + Intrahepatic Cholangiocarcinoma

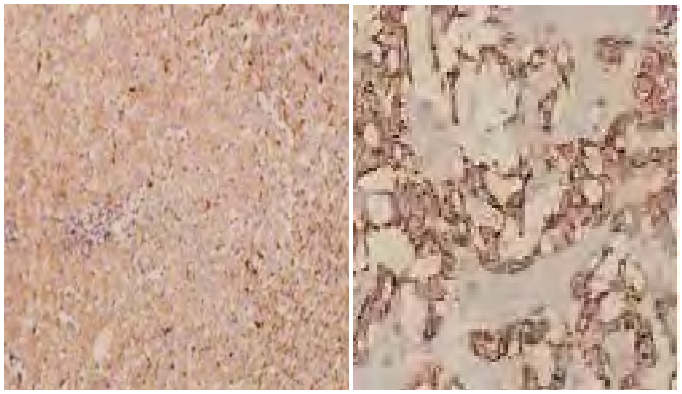
Expression of N-cadherin (normal bile duct tissue see **Figure 5(a)** and intrahepatic bile duct stones + intrahepatic bile duct carcinoma see **Figure 5(b)**), resulting in increased expression of N-cadherin.

Immunohistochemical results showed as shown in Figure 5, the positive expression of N-cadherin in intrahepatic bile duct stones and intrahepatic bile duct carcinoma tissues was 15 cases, accounting for 75% of the total, while 5 cases in normal bile duct tissues, accounting for 25% of the total. The positive expression of N-cadherin in intrahepatic bile duct stones and intrahepatic bile duct carcinoma tissues was significantly up-regulated. See Table 4 ($P < 0.01$).

3.6. Vimentin and the Expression of Orthohepatocholangiocarcinoma

Vimentin expression in normal bile duct tissue see Figure 6(a) and hepatobiliary duct cell carcinoma see Figure 6(b), resulting in elevated Vimentin expression.

Immunohistochemical results showed as shown in Figure 6, the positive expression of N-cadherin in cholangiocarcinoma tissues was 16 cases, accounting for 80% of the total, while the positive expression of N-cadherin in normal bile duct tissues was 7 cases, accounting for 35% of the total. The positive expression of N-cadherin in cholangiocarcinoma tissues was significantly up-regulated, as shown in Table 5 ($P < 0.01$).



(a) (b)

Figure 5. (a) Normal bile duct tissue; (b) Stone + intrahepatic cholangiocarcinoma.

(a) (b)

Figure 6. (a) Normal bile duct tissue; (b) Intrahepatic cholangiocarcinoma.

Table 4. Expression of N-cadherin in normal bile duct tissue, intrahepatic bile duct stones and intrahepatic bile duct carcinoma ($P < 0.01$).

Tissue types	N	negative − or +	positive ++ or +++
Normal bile duct tissue	20 (%)	15 (75)	5 (25)
Stone + intrahepatic cholangiocarcinoma	20 (%)	5 (25)	15 (75)

Table 5. Expression of Vimentin in normal bile duct tissues and bile duct carcinoma tissues ($P < 0.01$).

Tissue types	N	negative − or +	positive ++ or +++
Normal bile duct tissue	20 (%)	13 (65)	7 (35)
Intrahepatic cholangiocarcinoma	20 (%)	4 (20)	16 (80)

3.7. Vimentin and the Expression of Intrahepatic Bile Duct Stones + Intrahepatic Cholangiocarcinoma

Vimentin expression (normal bile duct tissue see **Figure 7(a)** and intrahepatic bile duct stones + intrahepatic bile duct carcinoma see **Figure 7(b)**), resulting in elevated Vimentin expression.

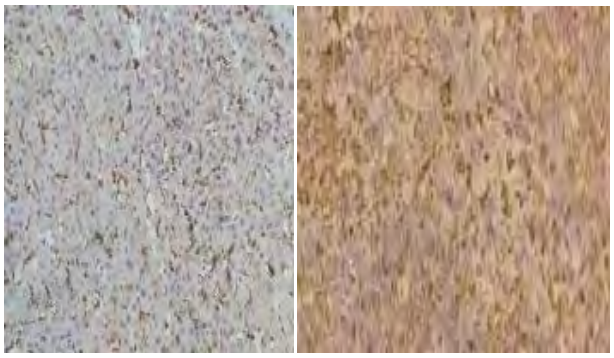
Immunohistochemical results showed as shown in **Figure 7**, the positive expression of N-cadherin in intrahepatic bile duct stones and intrahepatic bile duct carcinoma tissues was 16 cases, accounting for 80% of the total, while in normal bile duct tissues, there were 4 cases, accounting for 20% of the total. The positive expression of N-cadherin in intrahepatic bile duct stones and intrahepatic bile duct carcinoma tissues was significantly up-regulated. See **Table 6** ($P < 0.01$).

3.8. Twist1, Twist2 and the Expression of Intrahepatic Cholangiocarcinoma Cells and Intrahepatolithiasis + Intrahepatic Cholangiocarcinoma

The expression of Twisit1 see (**Figure 8(b)** + **Figure 8(c)**) and Twisit2 see **Figure 8(d)** + **Figure 8(e)** (normal bile duct tissues (see **Figure 8(a)**) and intrahepatic bile duct cancer cells and intrahepatic bile duct stones + intrahepatic bile duct cancer cells) showed no difference in Twisit1 and Twisit2 ($P > 0.05$).

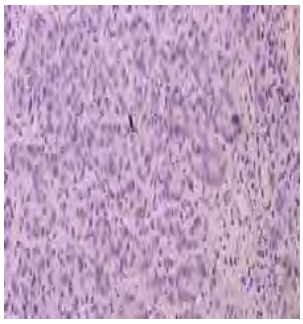
4. Discusssion

In recent years, it is crucial to find molecular markers and prognostic indicators for the early diagnosis of cholangiocarcinoma, improve the ability of early diagnosis and surgical resection rate, and further clarify the molecular mechanisms related to the invasion and metastasis of cholangiocarcinoma, so as to find effective therapeutic targets for improving the overall therapeutic effect of cholangiocarcinoma patients. The development, invasion, and metastasis of malignant tumors is a sequential, multistep process that includes local invasion, invascular

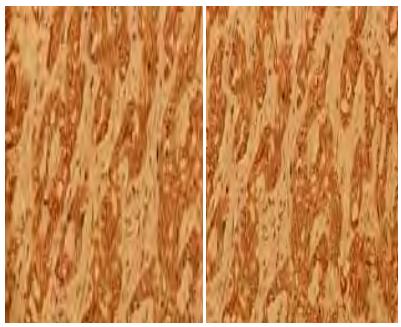


(a) (b)

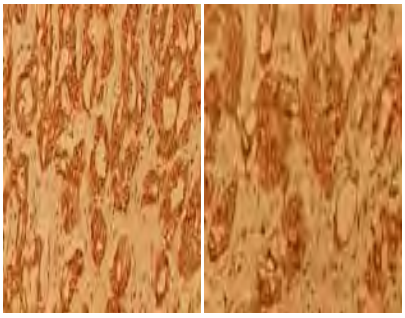
Figure 7. (a) Normal bile duct tissue; (b) Stone + intrahepatic cholangiocarcinoma.



(a)



(b) (c)



(d) (e)

Figure 8. (a) Normal bile duct tissue; (b) Intrahepatic cholangiocarcinoma; (c) Stone + intrahepatic cholangiocarcinoma; (d) Intrahepatic cholangiocarcinoma; (e) Stone + intrahepatic cholangiocarcinoma. Twisit1 (b, c), Twisit2 (d, e).

Table 6. The expression of Vimentin in normal bile duct tissue, intrahepatic bile duct stones and intrahepatic bile duct carcinoma ($P < 0.01$).

Tissue types	N	negative − or +	positive ++ or +++
Normal bile duct tissue	20 (%)	16 (80)	4 (20)
Stone + intrahepatic cholangiocarcinoma	20 (%)	4 (20)	16 (80)

penetration, stagnation and primary survival of distant targets, and finally the formation and colonization of micrometastases. In recent years, more and more studies have confirmed that epithelial-mesenchymal transformation is the key mechanism of the occurrence and development of various tumors, including cholangiocarcinoma, and plays an important role in invasion and metastasis [9]. Recently, epithelial-mesenchymal transformation has become an increasingly popular research direction to explain the mechanism of tumor metastasis and invasion. Ectomesenchymal into traditional theory of epithelial is divided into three type, and the associated with tumor invasion and metastasis of ectomesenchymal into 3 type of epithelium is a nonpolar connected to the basement membrane of epithelial cells in a series of regulation and control mechanism under the action of the corresponding change, loss of epithelial cell polarity characteristics, into a mesenchymal phenotype characteristics of cells capable of movement. Epithelial cells and mesenchymal cells exist in all organs of the human body, and each has its own characteristics: epithelial cells have polarity and close connections between cells, and their mobility and activity are poor. The mesenchymal cells do not have the polarity and tight intercellular junctions of epithelial cells and thus gain mobility. When tumor cells from epithelial cells after mesenchymal phenotype and function of cytoskeleton remodeling occurs, the adhesion between cells and cell loss and the activity of the cells and protein hydrolysis ability increase, thus gain the ability to break through the extracellular matrix and basement membrane, in interaction with neighboring cells and matrix and after immune escape, Finally, new colonization is formed in distant organ parts, and tumor invasion and metastasis are realized [10] [11].

Epithelial-mesenchymal transformation is therefore an important step in tumor invasion and metastasis. Furthermore, EMT is a process required for early metastasis of tumor cells by the combined action of inhibition of expression of genes that maintain epithelial characteristics and activation of mesenchymal phenotypes. EMT mechanism mediated process of invasion and metastasis of tumor cell proliferation regulation by various factors, has the characteristics of the differentiation, in solid carcinoma cells follow four steps [12]: 1) Through the connections between cells is reduced, the rearrangement of the cytoskeleton structure, with movement of phenotypic cell layer separation from the highly structured; 2) Isolated cells destroy the integrity of the basement membrane through active proteolysis, and then invade the surrounding stroma in a specific form. Once in the tumor stroma, cells can effectively interact with a variety of

stromal and inflammatory cell types, further enhancing their invasive properties; 3) Tumor cells infiltrate into new vasculature with the help of local tumor microenvironment, and then spread far away through lymphatic and/or circulatory systems; 4) By moving from blood vessels to distant ectopic tissue parenchyma and colonization, the cells restart the uncontrolled proliferation program.

5. Conclusion

Epithelial-mesenchymal transformation of bile duct carcinoma can make cells lose the characteristics of epithelial cells. In this study, the expression of epithelial phenotypic marker E-cadherin protein decreased or even disappeared, the expression of intracellular skeleton protein molecular keratin decreased, and the expression of characteristic markers N-cadherin and Vimentin of mesenchymal cells were up-regulated. Most of these EMT molecular markers are associated with tumor progression and poorer prognosis [13] [14]. We believe that these EMT-related phenotypic changes may be caused by the co-regulation of autocrine and paracrine signals released in the tumor microenvironment, including cytokines, growth factors, EMT-related stimulators, oncogenes, tumor suppressor genes and regulatory factors, and these signals have different associations with hypoxia and chronic inflammation. The EMT-like changes of bile duct carcinoma were induced jointly. In this study, the positive expression of Twist1 and Twist2 in tumor cells of patients with cholangiocarcinoma was unrelated to the clinical data and prognosis of tumor embolism, lymph node metastasis, depth of tumor invasion, degree of tumor differentiation, and disease-free survival of patients. The expression of Twist1 and Twist2 was consistent in tumor cells. Due to the small sample size, the influence of Twist1 and Twist2 on patients with cholangiocarcinoma still needs to be further explored.

Foundation Project

This study was supported by Hainan Provincial Basic (Project No. 819MS144).

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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International Journal of Clinical Medicine, 2021, 12, 342-350
https://www.scirp.org/journal/ijcm
ISSN Online: 2158-2882
ISSN Print: 2158-284X

Long-Term Efficacy Analysis of Exclusive Enteral Nutrition for the Treatment of Abdominal Abscess in Crohn's Disease

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How to cite this paper: Ding, N., Yang, Q.F., Chen, H.P., Hu, M.T., Yan, H. and Gao, X. (2021) Long-Term Efficacy Analysis of Exclusive Enteral Nutrition for the Treatment of Abdominal Abscess in Crohn's Disease. *International Journal of Clinical Medicine*, **12**, 342-350.
https://doi.org/10.4236/ijcm.2021.128030

Received: July 13, 2021
Accepted: August 13, 2021
Published: August 16, 2021

Abstract

Objective: The objective is to explore the long-term efficacy of total enteral nutrition in the treatment of abdominal abscess in Crohn's disease. **Methods:** Patients treated with EEN in our hospital and whose abdominal abscess disappeared after 12 weeks of treatment were included, and the data of abscess recurrence and surgical treatment during follow-up were included. **Results:** A total of 44 consecutive cases meeting the criteria were included. The 1-year and 2-year recurrence rates were 22.5% and 39.9% respectively. Among the patients with recurrence, 10 patients chose EEN treatment again, and 5 patients received direct surgical treatment. Of the patients who chose to undergo EEN treatment again, 8 still eventually required surgery. The 1-year operative rate was 16.9%, and the 2-year operative rate was 35.6%. The median operative time was 33.3 (95% CI: 21.3, 45.4) months. **Conclusions:** The 2-year cumulative incidence of recurrence of abdominal abscess in CD patients whose abdominal abscess disappeared after EEN was 39.9%, and the 2-year cumulative surgical rate was 35.6%. The operative stomy rate decreased after EEN, and the primary anastomosis rate increased significantly.

Keywords

Crohn's Disease, Enteral Nutrition, Abdominal Abscess, Long-Term Efficacy

1. Introduction

Crohn's disease (CD) can cause serious complications such as intestinal fistula, abdominal abscess, and intestinal stenosis during the course of disease. Studies showed that the cumulative incidence of CD complicated with intestinal fistula/abdominal abscess was up to 33% in 10 years after diagnosis, and up to 50% after 20 years of diagnosis [1]. Our data suggest that CD with abdominal abscess

accounts for about 47% of penetrating CD patients, indicating that abdominal abscess represents one of the common penetrating behaviors. Currently, anti-infective therapy is the primary choice for the treatment of CD patients with abdominal abscess, and the requirement for percutaneous drainage is determined according to abscess size and location [2]. Previous studies found that, after anti-infection and percutaneous drainage, 50% - 83% of the patients still required surgical drainage of the abscess and removal of the affected intestine, and the postoperative recurrence rate of intestinal fistula/abdominal abscess was up to 13% [3] [4] [5] [6] [7]. In addition, because these patients are often in the active stage of moderate to severe disease accompanied by malnutrition, conventional remission induction regimens such as hormones or biologics may aggravate the progression of this disease. Moreover, these patients often do not need emergency surgery or cannot tolerate surgery due to malnutrition. Therefore, there are certain difficulties and challenges in the treatment of CD patients with abdominal abscess.

Guideline on Enteral Nutrition of the European Society for Parenteral Enteral Nutrition (ESPEN) points out: for other patients, the main role of enteral nutrition is to improve the nutritional state and promote growth and development; for CD patients, enteral nutrition has special significance: it can be used for acute phase therapy, perioperative nutrition, and maintenance of remission. In current studies on exclusive enteral nutrition (EEN) for the treatment of CD, however, few literatures reported the value of EEN in the treatment of abdominal abscess. The results of a recent prospective observational study at our site [8] suggest that a 12-week EEN therapy can safely and effectively facilitate clinical remission, mucosal healing, reduction of inflammatory indexes, imaging remission, and reduction of surgical rate in active CD patients with abdominal abscess.

In recent years, in order to avoid surgery and occurrence of postoperative complications, the gastroenterologists proposed "SNAP" (sepsis and skin care, nutritional support, definition of anatomy and surgical procedure) treatment strategy. This strategy recommends that, for patients with abdominal abscess or intestinal fistula, it should extend the conservative treatment time and postpone the operation as much as possible. It is recommended that emergency treatment, including anti-infection, maintenance of water and electricity balance, pain relief and skin care, be given first, followed by nutritional therapy and efficacy evaluation. After which, the anatomy of gastrointestinal tract should be clarified, and surgical treatment can be performed if necessary. In the study on EEN for the treatment of CD with abdominal abscess conducted at our site as mentioned above [8], all therapeutic procedures followed the SNAP strategy, the patients were provided with necessary anti-infection, skin care, and EEN for 12 weeks, and meanwhile the intestinal conditions were timely assessed to determine the necessity of surgery. Abdominal abscess disappeared in 76% of the patients after treatment. This indicates that SNAP strategy and EEN are clearly effective on CD complicated with abdominal abscess.

However, current studies on EEN for the treatment of CD patients with abdominal abscess, including the results of previous studies of this site, have paid more attention to short-term efficacy. Further observation and research are needed to determine the long-term outcomes of patients who have achieved clinical remission of CD and shrinkage or disappearance of the abscess after short-term EEN therapy.

Therefore, this study was designed to retrospectively analyze the clinical data of CD patients with spontaneous abdominal abscess after EEN therapy in our hospital from January 1, 2014 to December 1, 2017 in order to explore the long-term efficacy of EEN on CD patients with abdominal abscess.

2. Subjects and Methods

2.1. Study Subjects

Patients who received EEN from January 1, 2014 to December 1, 2017 in this hospital and the abdominal abscess disappeared after 12 weeks of treatment (regardless of whether there was active CD or continuing medication).

Inclusion Criteria:

1) Patients aged 18 - 60 years, male or female;

2) Confirmed CD diagnosis, CTE/MRE-measured long diameter of abdominal abscess ≥ 1 cm, CTE/MRE-confirmed disappearance of abdominal abscess after 12 weeks of EEN therapy;

3) EEN has been discontinued.

Exclusion Criteria:

1) Children, pregnant and lactating patients;

2) Newly added hormones/biologics/immunosuppressants during EEN (excluding hormones/biologics/immunosuppressants administered before EEN);

3) Surgical operations within the imminent period of abdominal abscess (3 months), suspected surgery-related abscess.

2.2. Study Methods

This single-center retrospective study included a total of 44 consecutive cases meeting the criteria. In the cases of abscess recurrence or surgery, the patients were observed until abscess recurrence/surgery has occurred; for patients without recurrence, the observation continued until October 1, 2019. The primary observation endpoints of this study were the recurrence rate and time of abdominal abscess (abscess recurrence rate and the time from initial recurrence to EEN discontinuance were calculated). In addition, it was necessary not only to clarify surgical rate and method (one-stage anastomosis or enterostomy) of patients after EEN but also to specify the time from surgical operation to EEN discontinuance. Collection time points included: the beginning of EEN, 12 weeks of treatment, abscess recurrence/operation after EEN discontinuance, and follow-up to the most recent comprehensive reexamination for patients without recurrence.

The data were collected by retrieving inpatient electronic medical record sys-

tem of our hospital, and the collection time points included: the beginning of EEN, 12 weeks of treatment, abscess recurrence/operation after EEN discontinuance, and follow-up to the most recent comprehensive reexamination for patients without recurrence. The collected data included demographic data, CD course, CD clinical classification, and imaging data (combined enterocutaneous fistula, intestinal fistula, intestinal adhesion and entanglement, and intestinal stenosis).

The relevant definitions of this study were as follows:

Spontaneous abdominal abscess was defined as the abdominal abscess that had a diameter ≥ 1 cm determined by imaging and was caused by inflammatory penetration, unrelated to intestinal surgery, but enterocutaneous fistula/abdominal abscess emergent within 3 months after the operation was considered to be surgery-related. Abscess recurrence was defined as the recurrent abscess at the same site as before treatment.

2.3. Statistical Methods

All involved quantitative data were subject to t-test, and all qualitative data were subject to chi-square test. $P < 0.05$ was considered to have statistical difference. Kaplan-Meier method was used to calculate the long-term recurrence rate and surgical rate of the abscess. All data were analyzed and processed using SPSS 25.0 (SPSS, Chicago, IL) statistical software.

3. Results

From January 1, 2014 to December 30, 2017, this site included a total of 44 CD patients with spontaneous abdominal abscess in this study for regular follow ups. Table 1 summarizes the detailed demographic characteristics of the patients. The median follow-up time for all patients was 26.3 (13.3, 42.8) months.

3.1. Long-Term Abscess Recurrence Rate in CD Patients Whose Abdominal Abscess Disappeared after 12 Weeks of EEN Therapy

By the end of this study, a total of 16 patients (36.4%) experienced recurrence of abdominal abscess, among them, the recurrence occurred at other site in 1 case (2.3%) and at the same site in 15 cases (34.1%). The 1-year abscess recurrence rate was 22.5%, the 2-year abscess recurrence rate was 39.9%, and the median recurrence time was 63.4 (95% CI: 13.8, 113.0) months. The cumulative recurrence rate of abscess was shown in Figure 1.

3.2. Long-Term Abscess Surgical Rate in CD Patients Whose Abdominal Abscess Has Disappeared after 12 Weeks of EEN Therapy

By the end of this study, a total of 20 patients (45.5%) had undergone surgical treatment. The 1-year operation rate was 16.9%, the 2-year operation rate was

35.6%, and the median operation time was 33.3 (95% CI: 21.3, 45.4) months. Patient's long-term cumulative surgical rate was shown in Figure 2.

Table 1. All basic demographic data (n = 44).

Clinical symptoms	Number of cases n (%)
Sex	
Male	27 (61.4)
Female	17 (38.6)
Family History	
None	44 (100)
Site of Disease	
Colon	0 (0.0)
Distal ileum	17 (38.6)
Ileocolon	27 (61.4)
Upper digestive tract	0 (0.0)
Upper gastrointestinal involvement	
Yes	13 (29.5)
Past history of intestinal surgery	
Yes	12 (27.3)
Perianal lesion	
Yes	31 (70.5)

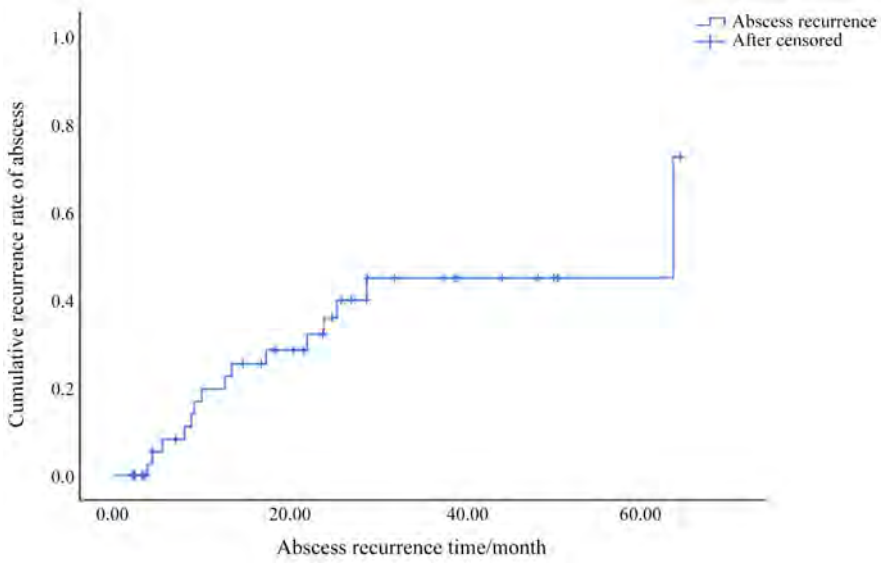

Figure 1. Cumulative recurrence rate of abscess in CD patients whose abdominal abscess has disappeared after 12 weeks of EEN therapy.

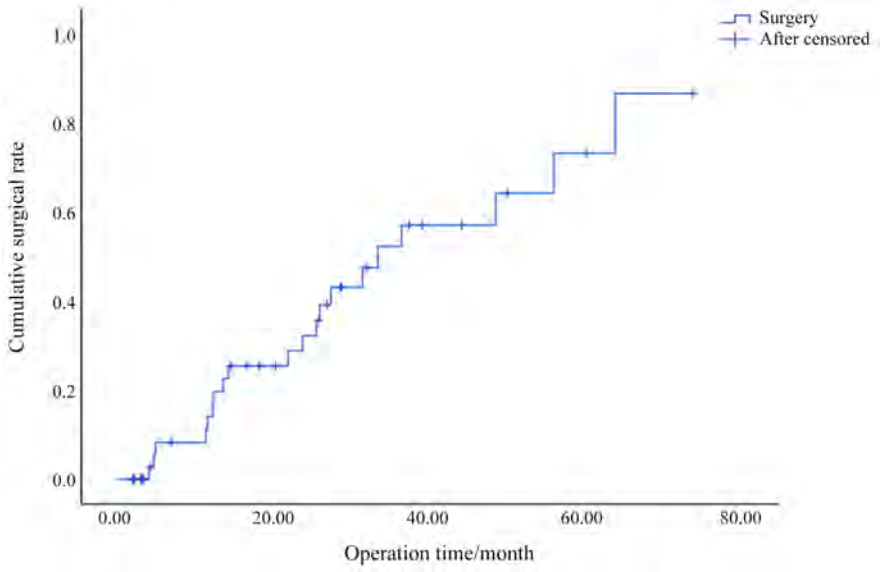

Figure 2. Cumulative surgical rate of CD patients whose abdominal abscess has disappeared after 12 weeks of EEN therapy.

3.3. Enterostomy Rate Following Recurrence in CD Patients Whose Abdominal Abscess Has Disappeared after 12 Weeks of EEN Therapy

By the end of the study, a total of 15 patients (34.1%) experienced abscess recurrence, among them, 13 patients (29.5%) switched to surgical treatment as the final outcome, and only 2 patients (4.5%) avoided surgery after active medication.

Among all 15 patients experiencing abscess recurrence, 10 cases (66.7%) tried the second round of EEN, followed by further evaluation of the intestinal lesions, including 2 cases (13.3%) avoiding surgery and 8 cases (53.3%) eventually receiving surgical treatment; the remaining 5 patients (33.3%) directly underwent surgery without receiving the second round of EEN.

We included the 13 patients who finally underwent surgery after abscess recurrence as the study subjects and grouped them by EEN following abscess recurrence in order to compare enterostomy between the 2 groups of patients (see Table 2). The results showed that the proportion of enterostomy was lower in patients receiving EEN after abscess recurrence than in patients directly undergoing surgery without receiving EEN therapy, and the difference had statistical difference ($P < 0.05$).

Table 2. Comparison of enterostomy rate following recurrence after CD patients with spontaneous abdominal abscess have been cured by EEN.

	With enterostomy	Without enterostomy	P
Direct operation after recurrence	4 (80.0)	1 (12.5)	**0.032**
Operation after repeated EEN following recurrence	1 (20.0)	7 (87.5)	

4. Discussion

Abdominal abscess is a common serious complication during the course of CD. The current opinions on its treatment principle are anti-infection plus abscess drainage, and enterectomy if the patients are unresponsive to the above treatment [1] [9]; because patients with active CD often have concomitant malnutrition, it is necessary to actively improve their nutritional state and control CD inflammatory activities before surgery in order to reduce the risk of postoperative complications [10]. As mentioned above, a recent prospective study at our site suggests that EEN is able to achieve clinical remission, mucosal healing, reduction of inflammatory indexes, imaging remission, and reduction of surgical rate [8]. In the Chinese Consensus on Nutritional Treatment of Inflammatory Bowel Disease (2018), it is clearly stated that EN is the primary choice for CD patients with abdominal abscess/intestinal fistula under the prerequisite of adequate drainage, and surgery can be avoided in some simple small intestinal fistulas that may heal spontaneously after EN or PN therapy [11]. Therefore, EEN is an effective treatment protocol for CD complicated with abdominal abscess; it can not only be used as a preoperative preparation for patients requiring surgical intervention but also cure abdominal abscess in patients who do not need surgery. However, the long-term recurrence rate and surgical rate of CD complicated with abdominal abscess cured after short-term EEN therapy are still unknown, and no clear report is readily available. This part of the study aimed to determine the long-term abscess recurrence rate and surgical rate of CD patients with spontaneous abdominal abscess cured after EEN therapy.

Our study results showed that, by the end of this study, 16 of the 44 CD patients whose abdominal abscesses disappeared after EEN therapy experienced abscess recurrence, among which, the abscess recurred at the same site in 15 patients, and the abscess recurred at other sites in 1 patient. The 1-year abscess recurrence rate was 22.5%, the 2-year abscess recurrence rate was 39.9%, and the median recurrence time was 63.4 (95% CI 12.8, 113.0). Among these recurrent cases, 10 patients selected repeated EEN, and 5 patients received direct surgery; 8 of the patients selecting repeated EEN eventually needed surgical intervention. Therefore, 13 patients eventually underwent surgery, the 1-year operation rate was 16.9%, the 2-year operation rate was 35.6%, and the median operation time was 33.3 (95% CI 21.3, 45.4) months. Among the patients undergoing surgery, 8 cases selected one-stage anastomosis, and 12 cases received enterostomy, in staged operations; patients undergoing surgery after EEN mostly selected one-stage operation, while patients undergoing direct surgery after the recurrence of abdominal abscess more often selected staging operations. The difference between these 2 groups had statistical significance ($P < 0.05$), suggesting that EEN was a protective factor for one-stage surgery. Currently, there are few studies on the long-term efficacy of EEN on CD complicated with abdominal abscess at home and abroad. A recent randomized and controlled study compared the effect of EEN on postoperative complications in adult CD patients using nutritional and

inflammatory indexes as the preoperative nutritional therapy endpoints in China. The results showed that both nutritional indexes and inflammatory indexes were improved in patients undergoing surgery after EEN. In the meantime, EEN therapy significantly reduced enterostomy rate and the incidence of postoperative complication in these patients [12]. Our study findings were similar to the results of this study, and EEN indeed reduced the surgical rate in these patients. The long-term surgical rate after EEN was 45.5%, the recurrence rate was 34.1%, and the enterostomy rate after EEN was 40%. The one-stage anastomosis rate significantly increased, while postoperative complications decreased. In summary, this part of the study still has some shortcomings; it is necessary to increase the number of cases not only to further confirm the current conclusions but also to analyze the risk factors related to the long-term recurrence rate and surgical rate.

In conclusion: The 2-year recurrence rate of CD complicated with spontaneous abdominal abscess cured after EEN is 39.9%, and the 2-year surgical rate is 35.6%. After EEN, enterostomy rate decreases, while one-stage anastomosis rate significantly increases.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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International Journal of Clinical Medicine, 2021, 12, 351-356
https://www.scirp.org/journal/ijcm
ISSN Online: 2158-2882
ISSN Print: 2158-284X

Autonomic Dysreflexia Severity between Urodynamics and Cystoscopy in Patients with Spinal Cord Injury above T6

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How to cite this paper: Zhen, H.Y., Huang, T.H., Yang, X.Y., Liu, Q.L., Li, Q.Q., Huang, M.P. and Chen, H. (2021) Autonomic Dysreflexia Severity between Urodynamics and Cystoscopy in Patients with Spinal Cord Injury above T6. *International Journal of Clinical Medicine*, **12**, 351-356.
https://doi.org/10.4236/ijcm.2021.128031

Received: July 19, 2021
Accepted: August 20, 2021
Published: August 23, 2021

Abstract

Objective: The objective is to evaluate autonomic dysreflexia (AD) severity between urodynamics and cystoscopy in patients with spinal cord injury (SCI) above thoracic 6 (T6). **Design:** It is a cross-sectional survey. **Subject and methods:** The study was carried out in 22 patients with SCI above T6 who underwent both procedures of urodynamics and cystoscopy; all patients developed episodes of AD. The systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured and recorded at the beginning and during the various stages of the two examinations. AD was defined as a rise in SBP above 20 mm Hg. **Results:** There was no significant difference in SBP and DBP at baseline before urodynamics and cystoscopy. Both urodynamics and cystoscopy triggered episodes of AD. The volume of water instilled during cystoscopy was typically standard and smaller (150 mL) in comparison with urodynamics, where volume varied depending on cystometric bladder capacity (the mean bladder volume in our study was 234.86 ± 139.06 mL). The SBP was significantly different between cystoscopy and urodynamics (49.23 ± 23.07 mm Hg and 35.14 ± 15.75 mm Hg, respectively; P = 0.023). **Conclusions:** Although bladder distension during cystoscopy was less than that in urodynamics, the severity of AD was more pronounced during cystoscopy. It is recommended that monitoring of cardiovascular parameters during these procedures should be routinely performed.

Keywords

Autonomic Dysreflexi, Spinal Cord Injury, Urodynamics, Cystoscopy

1. Introduction

Spinal cord injury (SCI) is a significant cause of morbidity and mortality in developed nations, with a global annual incidence of 1:25,000 [1] [2]. Bladder dysfunction and autonomic dysreflexia (AD) are common outcomes of cervical and high thoracic SCI. AD is clinically defined as an elevation in systolic blood pressure (SBP) ≥ 20 mm Hg from baseline in response to noxious or innocuous stimuli below injury level [3]. It is an acute disease with symptoms ranging from mild, such as headache, sweating, hot flashes, piloerection, and anxiety, to severe [4] [5] [6] [7] [8], such as arrhythmia, including atrial fibrillation, and high SBP above 300 mmHg, which may lead not only to cerebral hemorrhage but also to convulsions and death [9] [10] [11]. Several stimuli can lead to AD, but the most common triggering factor is bladder distension, which accounts for up to 85% of cases [12]. The commonest urological procedures that can lead to AD are cystoscopy and urodynamics, secondary to bladder filling. The risk of inducing AD has been shown to be reduced with flexible cystoscopy in a cohort of six of 39 patients who had previously had AD during rigid cystoscopy [13] [14]. Considering the differences in the technique of cystoscopy and urodynamics, including the filling rate and method of filling, the severity of AD might be also difference between these two procedures. In this study, we evaluate the severity of AD in individuals with SCI at or above thoracic 6 (T6) level performed both urological procedures of urodynamics and cystoscopy.

2. Materials and Methods

A total of 22 consecutive patients with SCI at or above the T6 neurological level underwent both urodynamic and cystoscopic examinations during a 1-year period were screen. Only individuals who developed episodes of AD were selected included into this study. Exclusion criteria were the presence of additional neurological disorder or history of cardiovascular or genitourinary system disorder. The sex, age, duration of injury, the SCI level and class according to the American Spinal Cord Injury Association (ASIA) Impairment Scale (AIS) classification of the patients were recorded.

The urodynamics examination was performed following the standards of the International Continence Society. The examination consisted of cystometry with warm sterile water (37.1˚C) filled at a fixed 30 mL per minute rate through a pump to a double lumen catheter (6 Fr, Laborie,) while patients were supine. Abdominal pressure was measured with an intrarectal balloon catheter (10 Fr, Laborie). Filling was stopped when the patient subjectively reported the sensation of fullness, urine leakage occurred or bladder filling reached 400 mL.

Cystoscopy was conducted with the patient in a lithotomy position; 150 mL of warm sterile water (37.1˚C) were instilled into the bladder. The filling rate varied from 30 to 50 mL per minute through gravity filling while a rigid cystoscope was introduced into the urethra. When the scope entered the bladder, a systematic inspection of the bladder mucosa was carried out. Once cystoscopy was completed, the scope was withdrawn and bladder was emptied.

Before both of the two procedures, 10 mL of 2% lidocaine jelly was introduced intra-urethrally. The systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured and recorded at the beginning and every 1minute infused during urodynamic and cystoscopic examinations. AD was defined as a rise in SBP above 20 mm Hg.

Statistical analysis Statistical analyses were performed by using SPSS 13.0 software (SPSS Inc., Chicago, IL, USA). The paired t test was used in the comparison of filling beginning and end SBP, DBP values of the patients. A P-value below 0.05 was considered statistically significant.

3. Results

Demographic and clinical features of the patients in the study were presented in Table 1. The mean age was 40.73 ± 14.43 years, mean injury duration 1.05 ± 1.60 years. Of the 22 patients, 16 (72.7%) were cervical and 6 (27.3%) were thoracic. The distribution of the American Spinal Injury Association Impairment Scale (AIS) scores were: 12 (54.5%) Grade A, 3 (13.6%) Grade B, 6 (27.3%) Grade C and 1 (4.5%) Grade D.

Table 2 displays the SBP, DBP at baseline and changes during the urodynamics and cystoscopy. SBP and DBP at baseline before the two examinations were similar in these individuals. Both urodynamics and cystoscopy triggered episodes of AD. The volume of water instilled during cystoscopy was typically standard and smaller (150 mL) in comparison with urodynamics, where volume varied depending on bladder capacity (the mean bladder volume in our study was 234.86 ± 139.06 mL). The SBP change were significantly different between cystoscopy and urodynamics (49.52 ± 23.07 mm Hg and 35.14 ± 15.75 mm Hg respectively; P = 0.023). Though DBP increase during AD, there are no different change between cystoscopy and urodynamics (P = 0.052).

Table 1. The demographic and clinical features of the patients in the study.

Variables	n =22
Age, year	
Mean ± SD	40.73 ± 14.43
Sex, N (%)	
Male	21 (95.5%)
Femal	1 (4.5%)
Disease duration, year	
Mean ± SD	1.05 ± 1.60
Level of spinl cord injury, N (%)	
Cervical	16 (72.7%)
Thoracic	6 (27.3%)
AIS grade, N (%)	
A	12 (54.5%)
B	3 (13.6%)
C	6 (27.3%)
D	1 (4.5%)

SD: standard deviation; SCI: spinal cord injury; AIS: American spinal injury association impairment scale.

Table 2. The SBP, DBP at baseline and changes during the urodynamics and cystoscopy.

	Urodynamics	Cystoscopy	P-value
SBP baseline(mm Hg)	109.09 ± 8.76	109.27 ± 9.19	0.947
SBP changes (mm Hg)	35.14 ± 15.75	49.23 ± 23.07	0.023
DBP baseline(mm Hg)	69.77 ± 7.43	69.95 ± 7.61	0.936
DBP changes (mm Hg)	16.95 ± 9.579	23.41 ± 11.68	0.052

SBP: systolic blood pressure; DBP: diastolic blood pressure.

4. Discussion

AD might not been aware well by the physicians and healthcare professionals who were outside of specialist spinal injury centres, leading to delays in treatment and potentially life-threatening consequences for patients [15]. Especially some patients might not be aware of being at risk [16] as AD can occur asymptomatically, also known as silent AD, *i.e.*, without any clinical symptoms. Neurogenic lower urinary tract dysfunction (NLUTD) is a common consequence after SCI [17]. As stimuli from the lower urinary tract are the most common causes of AD, reportedly in 75% - 85% of cases [12]. Urodynamic investigation is the gold standard to evaluate lower urinary tract function and routine urodynamic study of SCI patients is crucial for clinical decision making [18] [19]. Cystoscopy is not only a normal inspection for NLUTD, but also is required when performed the treatment of bladder stone or Botulinum Toxin A bladder injection.

In our study though the volume of water instilled during cystoscopy was smaller in comparison with urodynamics, the increase in SBP during cystoscopy was signifificantly higher than urodynamics. Differences in the technique of each procedure, including the filling rate and method of filling, could be one reason explain the difference in severity of AD between cystoscopy and urodynamics. Other stimuli in addition to bladder distention might also be contributing to the development of AD during cystoscopy, such as urethral stimulation during cystoscopy [20]. The physiology of urethral afferents was different from bladder, it could be excited by low-threshold mechanical stimulation induced by movements of a urethral catheter, but not respond sensitive to bladder distension [21]. In our study when perform cystoscopy we uses a rigid cystoscope (21 Fr) which was larger in size than catheters required for urodynamics (6 Fr). So cystoscopy includes greater stimulation of the urethra and bladder neck afferents during the procedure through urethral/prostate/internal sphincter passage and dilation, which could then provides more intense afferent stimulation to the spinal cord and trigger more pronounced episodes of AD.

AD is a diagnosis of which all health professionals interacting with patients with SCI should be aware. In particular, as the commonest cause is genitourinary, the urologist should also be particularly careful whilst investigating patients with SCI.

5. Conclusion

Although bladder distension during cystoscopy was less than that in urodynamics, the severity of AD was more pronounced during cystoscopy. It is recommended that monitoring of cardiovascular parameters during these procedures should be routinely performed.

Funding

This study was supported by: Medical Scientific Research Foundation of Guangdong Province, China (grant number A2021221). Traditional Chinese Medicine of Guangdong Province, China (grant number 20212034).

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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