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Augev Method and an Innovative Use of Vocal Spectroscopy in Evaluating and Monitoring the Rehabilitation Path of Subjects Showing Severe Communication Pathologies

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Abstract

A strongly connotative element of developmental disorders (DS) is the total or partial impairment of verbal communication and, more generally, of social interaction. The method of Vocal-verb self-management (Augev) is a systemic organicistic method able to intervene in problems regarding verbal, spoken and written language development successfully. This study intends to demonstrate that it is possible to objectify these progresses through a spectrographic examination of vocal signals, which detects voice phonetic-acoustic parameters. This survey allows an objective evaluation of how effective an educational-rehabilitation intervention is. This study was performed on a population of 40 subjects (34 males and 6 females) diagnosed with developmental disorders (DS), specifically with a diagnosis of the autism spectrum disorders according to the DSM-5. The 40 subjects were treated in "la Comunicazione" centers, whose headquarters are near Bari, Brindisi and Rome. The results demonstrate a statistical significance in a correlation among the observed variables: supervisory status, attention, general dynamic coordination, understanding and execution of orders, performing simple unshielded rhythmic beats, word rhythm, oral praxies, phono-articulatory praxies, pronunciation of vowels, execution of graphemes, visual perception, acoustic perception, proprioceptive sensitivity, selective attention, short-term memory, segmental coordination, performance of simple rhythmic beatings, word rhythm, voice setting, intonation of sounds within a fifth, vowel pronunciation, consonant pronunciation, graphematic decoding, syllabic decoding, pronunciation of caudate syllables, coding of final syllable consonant, lexical

decoding, phoneme-grapheme conversion, homographic grapheme decoding, homogeneous grapheme decoding, graphic stroke.

Keywords

Re-Educational Method, Learning Difficulties, Developmental Disorders, Vocal Spectroscopy

1. Introduction

The method of Vocal-Verb Self-management (AUGEV) [1] is a systemic organic-educational and re-educational method aimed at overcoming interferences in verb-interplay communication [2] through the development of neuro-psycho-physiological learning bases [3]. The vocal verb adjective indicates a twofold purpose of this method that is aimed on one hand at promoting verbal structure learning, on the other at perceiving and using verbal language acoustic qualities [4]. This method is therefore a re-education path aimed at subjects with linguistic and communication difficulties of different degrees [5]: subjects with problems of phono-articulatory setting, subjects with pathologies of verbal-social-relational communication (autism disorders, aphasia, dyspraxia [6], attention deficit and hyperactivity disorder) and subjects with learning difficulties (dyslexia, dysgraphy, dysorthography, dyscalculism).

In subjects with serious problems of verbal communication, particularly in cases of language absence, the gap in regular and physiological development becomes increasingly pronounced with age progress, as it emerges:

1) a lack or partial use and training of pneumophonic coordination functions in expiratory phase [7];

2) an altered resonance of laryngeal sound in supraglottic cavities (pharyngeal, mesopharynx, nasopharynx) [8];

3) an altered sensation and perception of personal and others' vocal productions with following inactivation of phonatory feedbacks [9], which are essential to develop quality and quantitative voice self-control, to improve phonatory emissions and therefore to produce correctly the mnemonic process;

4) an inability to discriminate and "finalize" sounds coming from the surrounding environment.

These serious obstacles, therefore, in being aware of phonatory control mechanisms, in discriminating voices as well as one's voice above all, leave out the subject from speakers' reality [10], towards which he/she shows even greater inattention and lack of interest [11].

The main purpose of this method is to acquire spoken and written communication through developing physiological and neuro-psychological learning assumptions.

Based on neural interconnections among various cortical areas [3], AUGEV method uses simultaneous, integrated, interacting and interconnected multiple

stimulations of an esteroceptive (hearing-view), proprioceptive (muscle-taouch) and endoceptive (mucosa) nature, organized in 4 operating paths called: audio-visual-touch-speech, phono-kinesthesia and phono-linguistics, which find their highest enhancement in prosodic read-writing, electively aimed at pursuing an adequate learning process goal [12].

The method aims at helping a person to realize oneself as an harmonious unit which includes physical-motor and psycho-intellectual elements.

In particular, the method is recognized in three fundamental assumptions that characterize different rehabilitative actions:

1) The intrinsic connection between word and movement. In fact, it enhances the body as a medium of verbal learning based on the principle that structural elements of spoken language can be taught by linking vocal emissions to body movements [13] so that they can be more easily internalized to achieve smoother and more verbal expressive performances. Body mediation, which consists in functionally connecting verbal phonetic structures to body expressions and rhythms, is therefore the main didactic communication means through exercises in which a constant association is established among postures, gestures and voice. Motor acts have been organized with great precision, respecting some founding principles of mechanical physics and in particular static and dynamics [14] applied to human body [15].

2) The connection existing between spoken language and music [16], then verbal expression musicality and its corresponding expressiveness in music [17]. Since cortical areas assigned to functions of acoustic memory, and in particular those which preside over the processing of verbal solicitations, are sensitive to musical stimulations [18], AUGEV method includes exercises based on presentating sound solicitations as in a sung form, therefore exercises of listening and reproduction of melodic vocal sequences exemplifying the most recurrent rhythmical and tonal structures of spoken language [19]. Verbal messages are also presented and formulated in association with appropriate bodily movements, so that sound events and body gestures are analogically related to each other and mutually reinforcing.

3) The association of sounds and movements with simple graphic representations and immediately accessible. These are functionally important since they spatialize sounds [20] so that a subject can visualize their fundamental parameters: frequency (whose perceptual correlation is the height), duration (or emission time) and amplitude (whose perceptive correlation is intensity) [21].

Thanks to all these elements, a subject can gradually and physiologically [22] [23] acquire language basic structures [24] (words and their sentence combinations) and dynamics that regulate it (syntax and prosody) [25] in order to have access to its fruition and interpersonal communication use [26].

Peculiarities of systemic the organicistic method "*Verb-vocal self-management*"

A typical characteristic of this method, denoting its absolute innovation and effectiveness, is the punctual and precise perceptual enhancement carried out

among them by the main learning areas [27] (visual, acoustic, proprioceptive-tact-motor, verbal-motor...).

For example, this is perceptually and simultaneously strengthened by visual-graphic and phono-acoustic stimulations when the subject performs a tact-motor activity.

Similarly, this happens when stimulations specifically affect the other areas mentioned above: phono-acoustic activities are, in fact, coordinated with tactile-motor and visual-graphic information, whereas stimulations in visual area are combined with tactile-motor and acoustic-type activities.

This operative model allows—thanks to evocating sensory-perceptual information firmly anchored among them—the activation of acoustic, phonatory, visual, tactile and proprioceptive-motor feedbacks, which are fundamental for making any learning activity stable and coordinated [28], avoiding that an area develops in a prevalent or deficient way compared to the others.

Coordination and correspondence, which facilitate their use among stimulations, generate an important increase in duration and attention levels, elements that allow the subject to start the execution of activities (**Figure 1**).

This method applies to all age groups, pre-school children, adolescents and adults as well as to any cognitive-intellectual level.

AUGEV method consists of two stages: a preliminary and an operational one.

The first one concerns the evaluation of compromised areas in subjects with altered verb-vocal production through psychodiagnostics [29] [30], in order to organize a detailed rehabilitation program. The second one is conceived in such a way as to be customized according to a subject's needs and difficulties, respecting the perceptive-gnosic development considered from a general physiological perspective [31]. Operational stage consists of 3 phases, respectively called synchresis, analysis and synthesis [32].

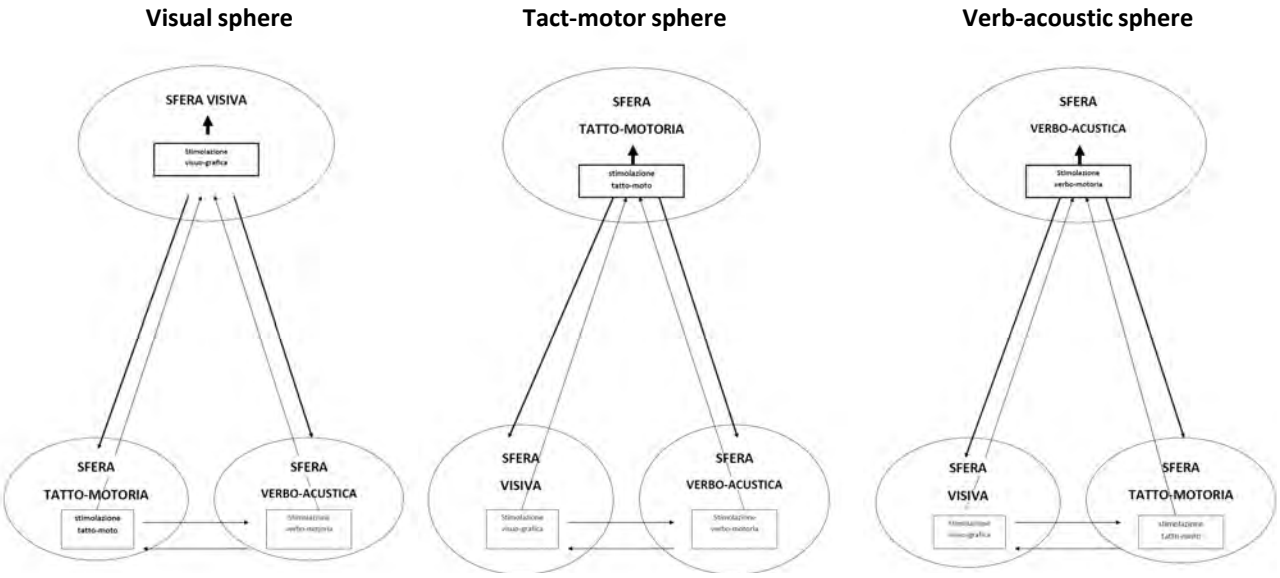


Figure 1. Coordinated cooperation of the learning spheres.

(Synchresis)

Synchresis stimulates the attention to simple and global sensory-perceptive information (auditory, visual, tactile and motor).

These stimulations leave weak and generic perceptive traces [33].

During this phase, a subject is guided by the operator who favors initiation of cognitive processes (attention, perception, memory, thought and language) [34] through coordinated and simultaneous multiple stimulations that exploit a mechanism of repetitiveness to activate a sense-perceptive feedback process that allows the subject to create and store correct and basic motor and verb-motor patterns.

(First Analysis)

After activating cognitive development which is globally realized by syncretic phase, a subject is analytically helped to achieve conscious and selective learning [35], a fundamental step to acquire knowledge, to use them at the right time and to conquer the others independently [36].

In this phase, it is possible to evaluate the activation of important perceptive areas: visual, acoustic and proprioceptive sensitivity [3].

The subject is no longer guided as in syncresis, but only helped by the operator who sets himself up as a model: a selective attention gradually activated by analysis activities makes it possible to start an imitative capacity.

2. Method

This research work is a systematic study on case histories that aims at analyzing the effects of applying AUGEV method, which was adopted at logopsicopedagogical centers "La Comunicazione" in the headquarters of Bitritto (Bari), Brindisi and Rome between 2002 and 2017. The study involved 40 subjects, 34 males and 6 females, whose age was between 2 and 21 years with a diagnosis being included into developmental disorders (DS), specifically with a diagnosis of the autism spectrum disorders according to the DSM-5 [29]. Personal data, in particular those on health, were treated in accordance with the responsibilities established by the regulations of the good clinical practice (legislative decree 211/2003). At the time of taking charge of those subjects at the center, we take a look at the clinical analysis performed by a specialist physician (neurologist, audiologist, phoniatrist, etc.) and then we proceed to functionally evaluating individual learning areas carried out by a multidisciplinary team, to start then the operational phase of applying AUGEV method. Based on the emerged results, an initial assessment of development degree of various learning areas is made and a targeted and personalized omnidirectional systemic rehabilitative educational intervention is developed. After a treatment period, patients are re-evaluated with the same diagnostic protocol performed at the beginning. The evaluation at the beginning and during subsequent checks is noted in medical records.

Clinical records of subjects with autism and autism specimens were analyzed in order to identify any progress, resulting from applying AUGEV method in

different learning areas: cognitive-behavioral, motor and linguistic.

In particular, data was inserted and processed using SPSS software (Statistical Package for Social Science) to calculate univariate descriptive statistics by frequency distribution and the bivariate ones by contingency tables. In order to evaluate the meaning of relationship in double entry tables, χ^2 test was adopted, taking into consideration only those tables for which p value was lower than 0.05.

It is essential to specify that in this study only data related to Syncresis phase and those related to the initial part of analytical phase were examined, called actually First Analysis to simplify. A following study will socialize the data concerning completion of educational-rehabilitation process implemented by Augev method.

However, the most significant analysis of data has concerned objective surveys carried out through vocal spectrographic examination.

Actually, physical-acoustic parameters of each subject's voice were found with a computerized sonograph: Fundamental Frequency (F_0), First and Second Forming (F_1 and F_2), Duration (T) and Phonatory Energy (E).

Monitoring was performed by comparing "captured" values during spectrographic recording with a standardized reference range which shows average values classified by age and sex.

It should be noted that frequencies (F_0, F_1, F_2) are measured in Hertz (Hz), Emission time in seconds (sec) and Phonatory energy in decibel (dB).

Method operating modes: Syncresis and First Analysis

Syncretic activities proposed in **motor area** involve the body as a whole and the subject, who is initially guided, experiences all space "dimensions" and individual movement succession over time.

In particular, 8 exercises of general dynamic coordination (summarized by graphical symbols) are provided during synchresis phase, which create tension states and large muscular district relaxation which facilitate the emission of vocal sounds associated with them [37].

The subject performs movements with the arms by moving them upwards, downwards or sideways, and makes coordinated leg movements (bends or lateral displacements) and listens to vocalic emissions spatialized by those motor acts (high, low, long, short sound, intense, weak). Sound stimulations are produced by an instrument and therefore "vocalized" by the operator. They are characterized by simple iterant sound combinations presented with the aim of improving acoustic sensitivity towards sounds in order to improve the ability to adapt to models [38].

By doing an activity that acts as a bridge between motor and linguistic areas, a recognition of rhythmic differences among words with different tonic accent [39] is also started by simple finger strokes on a support surface: very simple words are obviously proposed in synchresis, such as monosyllables (you, there, no, etc.) or bisyllables (mother, bread, ball, etc. or father, so, why, etc.)

In **linguistic area**, a subject is trained to listen to vowel sounds and is helped in their production.

These fundamental sounds during language practice are "hooked" even better at a perceptive level, thanks to their graphic trace (writing), which the subject begins to perform with the operator's help. The movements performed to execute each grapheme are sonorized by the operator who proactively highlights its specificities: its voice will therefore go upwards, downwards or it remains constant by being coordinated with the graphic section being created. Thus, the subject begins to familiarize with main melodic movements of linguistic expressions, that is, the interrogative, exclamatory, affirmative and suspensive ones [40].

A perceptual coordination that comes to be realized in each activity has an immediate implication in the cognitive-behavioral area [41]: a subject begins to feel capable of performing required tasks and then shows always greater interest towards them, gradually eliminating any behavioral intemperance that signaled an inadequacy perception [42].

Analytical phase activities proposed in **motor area** aim to achieve a segmental coordination, which is essential for a subject to experience dynamic potentials of body individual parts.

Exercises are performed in different postures and include movements aimed at indicating pre-established body points; as in syncresis, motor acts are combined with phonatory emissions that harmonize with body movements. The same sound concatenations are also spatialized by graphic scales that a subject has to perform with fingers.

In this phase, the acquisition of three fundamental sound parameters takes progressively place: the frequency perceived as sound height (acute and severe sounds), the emission time and the amplitude whose perceptive correlation is intensity (loud and weak sounds) [43], only generically presented in synchresis. In this way, high and low sounds can be discriminated, as well as long ones from short ones and strong ones from weak ones, which is a fundamental prerequisite for enjoying fundamental discourse elements such as intonation, duration, rhythm and accentuation in all its degrees.

Analytical phase includes a considerable number of exercises which, presented gradually and adapted to a subject's ability, aim at steadily acquiring spatial and temporal patterns, as well as obvious somatognosic ones which are essential pillars of learning in all of its form [44].

Sequences of rhythmic beats already presented in syncresis are proposed in a shielded mode so as to stimulate and simultaneously evaluate acoustic attention and the beginning of rhythmic-motor organization. The latter is further trained by presentating rhythmic patterns evoking words with different tonic accent, already proposed in synchresis where, however, they were related to simple bisyllabic words. Now rhythm becomes more complex extending to trisyllabic words (slippery, flat and truncated).

Thoroughly coordinated to the motor area, we go on with the **linguistic area** including activities that involve vowel sound improvement, so that subjects become aware of their distinctive traits by gradually learning to coordinate the organs used for phonation and articulation as well as for respiratory rhythm.

Absolutely in line with the method basic principle that provides always interconnected activities, stimulation of bed-writing leads [45] to a conscious acquisition of single phonic (phonemes) and graphic (graphemes) units as well as vowels and consonants, which are spatialized from appropriately emphasized easy graphic symbols. A subject learns to know even sound slightest differences, articulation [46] and graphics, starting with discriminating vibrant phonemes which have their own sound from the deaf ones which produce only noise [47]. These acquisitions allow a correct decoding and coding of phono-graphic units and, therefore, a chance to combine them correctly, proceeding slowly to initially reading and writing words at high use frequency and then more and more complex and correct from a graphic-spelling perspective [48].

Analysis marks a real turning point in the **cognitive-behavioral area,** because a subject who activates the above mentioned selective attention, obtained by coordinating all learnings, gradually manages to organize mental schemes that can start up a mnemonic process, which is obviously a short-term memory [30]. All this has important effects on behaviour, since the awareness of being able to manage a progressively greater number of learning has a significant influence on interests and self-esteem.

3. Results

3.1. Syncresis

Data highlighted in Table 1 clearly show that subjects' exposure to global stimulations during syncretic phase, sent coordinately and simultaneously to all the aforesaid cerebral areas, according to an inextricable method principle, provides important results in a short time. Starting from the second evaluation already, but even more from the third one, it should be noted that the majority of subjects report positive results in the considered areas related to syncresis. Regarding variables ascribable to cognitive-behavioral area, a supervisory status, which is absent and poor at the beginning, becomes present during following evaluations. It also improves attention capacity in all its aspects: attention level that is mostly low during the first evaluation phase becomes sufficient and good during following evaluations due to carrying out therapeutic interventions; the duration of patients' attention becomes short first, and then it gets prolonged after following stimulations. In line with solicitation simultaneity that characterizes AUGEV method, there are evident improvements in the motor area as well. In particular, an initial detected general dynamic incoordination is completely overcome. Patients who were not able to execute simple orders or who found them difficult to do at first evaluation, are afterwards able to reproduce simple or even complex orders. Subjects show also an improvement in executing simple

Table 1. Observed variables during syncresis.

Variables	*Modes*				*Asymptotic Significance*
Supervisory status	absent	poor	present		0.000
Attention: level	poor	sufficient	good		0.000
Attention: duration	short	prolonged			0.003
General dynamic coordination	absent	limited	present		0.000
Understanding and execution of orders	absent	partial	simple	complex	0.007
Performing simple unshielded rhythmic beats	absent	wrong	correct		0.000
Word rhythm: performing a flat bisyllable	absent	wrong	occasionally correct	correct	0.000
Word rhythm: truncated bisyllable	absent	wrong	occasionally correct	correct	0.000
Oral praxies	absent	lacking	present		0.000
Phono-articulatory praxies	absent	lacking	present		0.000
Pronunciation of vowels	absent	altered	slightly altered	correct	0.000
Execution of graphemes	absent	lacking	good		0.000

unshielded rhythmic beats. A similar positive trend in terms of achieved results following the treatments is recorded in executing measures that reproduce the rhythm of flat and truncated bisyllabic words compared to which, at second evaluation already, the share of those who cannot execute them decreases in favor of an increase of those who perform them wrong firstly, then intermittently correct and completely correct. Regarding the linguistic area, incoordination detected in first evaluations involves organization of verbal and written communication, considered unanimously one of the most complex activities of human mind. Thanks to the application of AUGEV method, almost all subjects are gradually able to recover from initial deficits related to oral and phono-articulatory praxis. Progress of vowel pronunciation is also evident: all subjects, who at the time of their taking in charge, were unable to emit vowels, recovered in following evaluations. Grapheme execution completes the picture of variables related to synchresis, towards which almost all subjects show inadequacies, afterwards recovered during following evaluations.

3.2. First Analysis

Regarding AUGEV method analytical phase, it is quite clear that in the evaluations following the first one subjects report positive percentages in three variables pertaining to three large perceptive areas: visual, acoustic and proprioceptive. Coordination and simultaneity of stimulations in the above-mentioned areas, which are extremely detailed in the analytical phase, have an important impact in the cognitive-behavioral area: attention becomes selective and begins

to address pertinent information, a progress that allows a mnemonic process activation, even if it is still a short-term memory. However, the latter becomes a stable acquisition only in second analysis. In the motor area, segmental coordination, which turns out to be absent or limited at the beginning, is acquired by a good number of subjects who become able to perform motor acts based on models that provide personal body awareness. A significant improvement of motor coordination, acoustic perception and short-term memory is obtained by evaluating simple shielded rhythmic beat executions. The start of rhythmic motor skills is also appreciated in executing rhythmic models related to trisyllabic words: in fact, in the fourth evaluation almost all subjects are able to execute word rhythms with three syllables (slippery, flat or truncated). Another important positive element in analytical path progress is data concerning the phonatory setting [49], which are significant of correct establishment of audio-phonator feedbacks. The analytic ability to manage small muscle areas is also evident in the meaning found in variables related to sound pitch within a fifth (remember that 5 are, generally, the shades within which natural speech moves) and in individual vowel sound refinement. In particular, for vowels a, è, i, ò, u [50] considerable improvements are made in evaluations following the first one, with an increasing incidence of subjects able to emit them in a guided manner first, then on a model basis. Some absolutely reliable difficulties remain in correctly producing the two closed vowels "é" and "ó", as they provide for perceptive discrimination and articulatory control not yet achieved by subjects who are acquiring language. The latter is strongly favored by an increasingly conscious use of bed-writing, which allows fixing sound-acoustic patterns by virtue of a coordinated use of graphics and tact-motors. The results in this area, highlighted in **Table 2**, are also positive: in pronouncing and reading individual alphabetic letters (graphical decoding), in the one concerning a variable combination between consonants and vowels (syllabic decoding), including the more complex consonant-vowel-consonant scheme (pronunciation of caudate syllables and coding of final consonants in syllables), finally in reading true words (lexical decoding) and in writing under phonemic dictation (phoneme-grapheme conversion). Perceptual training on analysis leads a subject to check also minimum differences between very similar phono-graphemes (for example, p-b, f-v, d-t, l-r, c-g): at the fourth evaluation almost all cases are able to decode them correctly. The ability to control graphic stroke improves significantly. Findings show that subjects are progressively acquiring a correct verbo-graphic production.

3.3. Spectrographic Examination: Definition and Results

From the qualitative analysis carried out on examined population, it emerges clearly a positive response of all subjects to stimulations contained in Augev method treatment protocol. However, it was considered proper in phono-linguistic field to confirm qualitative data with quantitative evaluations obtained thanks to voice spectrographic analysis. The spectrographic survey represents AUGEV method further strong point, which proceeds innovatively towards

Table 2. Observed variables during first analysis.

Variables	*Modes*				*Asymptotic Significance*
Visual perception	absent	limited	good	excellent	0.000
Acoustic perception	absent	limited	good	excellent	0.013
Proprioceptive sensitivity	absent	limited	good	excellent	0.01
Selective attention	absent	present			0.000
Short-term memory	absent	present			0.136
Segmental coordination	absent	limited	present		0.000
Performance of simple rhythmic beatings	absent	wrong	correct		0.002
Word rhythm: slippery three-syllable	absent	wrong	occasionally correct	correct	0.006
Word rhythm: flat three-syllable	absent	wrong	occasionally correct	correct	0.000
Word rhythm: truncated three-syllable	absent	wrong	occasionally correct	correct	0.012
Voice setting	undetectable	absent	lacking	present	0.000
Intonation of sounds within a fifth	absent	altered	present		0.000
Vowel pronunciation à	absent	guided	on model: lacking	on model:good	0.002
Vowel pronunciation è	absent	guided	on model: lacking	on model:good	0.012
Vowel pronunciation é	absent	guided	on model: lacking	on model:good	0.118
Vowel pronunciation i	absent	guided	on model: lacking	on model:good	0.039
Vowel pronunciation ò	absent	guided	on model: lacking	on model:good	0.04
Vowel pronunciation ó	absent	guided	on model: lacking	on model:good	0.376
Vowel pronunciation u	absent	guided	on model: lacking	on model:good	0.005
Consonant pronunciation	absent	altered	slightly altered	correct	0.000
Graphematic decoding	altered	partially correct	correct		0.04
Syllabic decoding	altered	partially correct	correct		0.041
Pronunciation of caudate syllables	absent	altered	correct		0.000
Coding of final syllable consonant	altered	partially correct	correct		0.000
Lexical decoding	altered	partially correct	correct		0.04
Phoneme-grapheme conversion	absent	partial	good		0.04
Homographic grapheme decoding	altered	partially correct	correct		0.001
Homogeneous grapheme decoding	altered	partially correct	correct		0.001
Graphic stroke	uncertain	excessively marked	definite		0.006

phono-linguistic evaluation of recording vocal signal data. It is made with a computerized sonograph through which a vocal sample is taken by means of a high sensitivity microphone that records a subject's voice as faithfully as possible. This survey aims at providing objective physical-acoustic and phonetic-acoustic values of voice and language [20]: fundamental frequency, formants, phonatory duration, intensity. In an extremely brief way we report definitions of these parameters:

- fundamental frequency (F_0), or first harmonic, is the lowest frequency among those of single waves that form a complex wave. F_0 measured in Hertz (Hz) is perceived as intonation (acute and severe sounds), the linguistic element that identifies utterance melodic trend;
- formants are frequencies resulting from groups of more intense harmonics, for instance multiple frequencies of F_0. They are also measured in Hz. The first (F_1) and the second formants (F_2) identify individual vowels and are directly implicated in voice resonance mechanism;
- phonatory duration refers to sound emission time, which is exclusively vocalic in our case;
- amplitude is an energy with which a sound wave propagates. Regarding human voice, it is measured in decibel (dB) and is perceived as a sound volume, that is, a quality that distinguishes sounds in weak and strong ones.

We can simply say that sounds generated by a vocal cord vibration (whose frequency is the fundamental one) go into resonance cavities (hypopharynx, oropharynx and rhinopharynx) and here they are amplified by resonance (measurable through the value of formants F_1 and F_2), resulting more intense and acquiring a timbre that characterizes each speaker's voice. Detection and evaluation of vowel signals carried out by a spectrographic examination are indicative of self-monitoring phono-acoustic ability (feed-back) acquired by a subject during an expressive-verbal act. During educational-rehabilitation process each subject performs more spectrographic evaluations, usually coinciding with significant changes that an operator recognizes on a skill/ability level acquired in perception, discrimination and speech sound production. Thanks to these periodic surveys and monitoring spectrographic traces over time, it is possible to target an intervention and verify progressive disappearance of initial anomalies. Referring to the population in our study, it is important to clarify that the majority of subjects could not make this instrumental evaluation from the start, given a total absence of spoken language and, therefore, an inability to emit articulate and finalized sounds. However, it is possible to appreciate in all subjects an acquired ability to emit vocal sounds from the following evaluation already, even if its production still takes place in a guided way in some cases.

These sounds, just sketchy and very inaccurate [51] in the beginning, become more and more defined during evaluation progress and acquire their own individual tone. A confirmation is unequivocally given by comparing the values of F_0, F_1, F_2 and E, measured for each of seven vowels with the reference physiological ones related to a subject's age and sex. In the table below, for each of the 40 cases, values of fundamental frequency (F_0), the first (F_1) and the second formant (F_2) and sound energy (E), recorded in first spectroscopy exam with those detected in the last one, were compared to highlight a sharp tendency to approximate the range that scholars have identified for each vowel as referable to average values falling within the norm.

For the sake of brevity, it was considered appropriate to present only the values measured for vowel "a" (**Table 3**), considered a typical vocal for its pho-

no-articulatory characteristics. In reference with fundamental frequency (F_0), it is possible to see how 29/40 subjects report values falling entirely within reference range in the last evaluation, while 7 of the remaining 11 show how they have started to fall within standard values.

Data related to first (F_1) and to second formant (F_2) are also positive, since respectively 65% and 67.5% of the cases show an improvement of last spectrographic examination compared to the first one with values that get close to the average values measured for vowel "a" (Tables 4-6). These are very interesting

Table 3. Basic frequency (F_0). Case distribution by fundamental vocal frequency (F_0) a.

Cases	Sex	Age	First spectrographic examination	Reference range	Average value reference	Execution 1° exam	Age	Last spectrographic	Reference range	Average value reference	Execution last exam
1	M	6	245	280 - 365	325	guided	12	234.57	170 - 245	210	on model
2	F	4	324	310 - 450	355	on model	14	245	195 - 270	235	on model
3	M	8	172.27	260 - 330	295	guided	10	256.4	195 - 275	235	on model
4	M	13	245	155 - 230	195	on model	18	149.52	100 - 155	125	on model
5	M	6	153.13	280 - 365	325	guided	8	280.12	260 - 330	295	on model
6	M	7	268.9	260 - 330	295	on model	9	272.12	220 - 300	260	on model
7	M	8	402	260 - 330	295	guided	22	115.23	100 - 155	125	on model
8	F	8	190.09	245 - 310	280	on model	10	166.72	225 - 320	265	on model
9	M	8	268.9	260 - 330	295	on model	11	254.54	185 - 260	225	on model
10	M	5	290.13	300 - 390	350	on model	13	191.69	155 - 230	195	on model
11	M	9	239.67	220 - 300	260	on model	10	266.43	195 - 275	235	on model
12	M	5	200.45	300 - 390	350	on model	8	263.53	260 - 330	295	on model
13	M	6	204.17	280 - 365	325	on model	8	197	260 - 330	295	on model
14	M	5	180.69	300 - 390	350	on model	6	167.46	280 - 365	325	on model
15	M	6	212.02	280 - 365	325	guided	12	218.7	170 - 245	210	on model
16	M	9	193.42	220 - 300	260	guided	12	177.37	170 - 245	210	on model
17	M	8	204.17	260 - 330	295	on model	11	218.84	185 - 260	225	on model
18	M	10	147	195 - 275	235	on model	12	221.33	170 - 245	225	on model
19	M	4	172.27	320 - 425	375	on model	15	160.34	130 - 195	155	on model
20	M	5	234.57	300 - 390	350	on model	9	163.45	220 - 300	260	on model
21	M	5	159.78	300 - 390	350	on model	12	134.5	170 - 245	210	on model
22	M	2	230.02	370 - 525	445	guided	4	286.39	320 - 425	375	guided
23	M	12	225	170 - 245	210	on model	13	139.81	155 - 230	195	on model
24	M	5	225	300 - 390	350	on model	12	193.42	170 - 245	210	on model
25	M	8	162.13	260 - 330	295	on model	10	247.96	195 - 275	235	on model
26	F	5	250.57	290 - 425	335	on model	7	261.94	245 - 350	290	on model
27	M	18	120.81	100 - 155	125	on model	19	137.05	100 - 155	125	on model
28	M	4	181.93	320 - 425	375	on model	6	250.22	280 - 365	325	on model

Continued

29	F	7	225.19	245 - 350	290	on model	9	165.52	235 - 335	275	on model
30	M	3	200.45	340 - 460	400	on model	9	265.8	220 - 300	260	on model
31	M	8	248.68	260 - 330	295	on model	9	264.29	220 - 300	260	on model
32	M	10	250.57	195 - 275	235	on model	18	207.43	100 - 155	125	on model
33	F	7	190.09	245 - 350	290	on model	15	236.18	185 - 260	220	on model
34	M	3	282.69	340 - 460	400	on model	10	275.63	195 - 275	235	on model
35	M	8	268.9	260 - 330	295	on model	10	249.91	195 - 275	235	on model
36	M	10	277.9	195 - 275	235	guided	11	245.63	185 - 260	225	on model
37	M	3	168.25	340 - 460	400	on model	4	185.24	320 - 425	375	on model
38	F	5	256.4	290 - 425	335	on model	10	268.9	225 - 320	265	on model
39	M	4	175.3	320 - 425	375	on model	5	150.53	300 - 390	350	on model
40	M	5	275.63	300 - 390	350	on model	10	235.7	195 - 275	235	on model

Table 4. Case distribution by first formant (F_1) vowel a.

Cases	Sex	Age 1°	First spectrographic examination	Reference range	Execution 1° exam	Age last one	Last spectrographic examination	Reference range	Execution last one
1	M	6	976.6	700	guided	12	696.4	700	guided
2	F	4	623.3	700	on model	14	938.8	700	on model
3	M	10	1003	700	guided	10	675.8	700	on model
4	M	13	1067	700	on model	18	775.5	700	on model
5	M	6	995.9	700	guided	8	1037	700	on model
6	M	7	1071	700	on model	9	840.7	700	on model
7	M	8	784	700	guided	22	639	700	on model
8	F	8	1105	700	on model	10	989.6	700	on model
9	M	8	1027	700	on model	11	911.1	700	on model
10	M	5	1463	700	on model	13	870.6	700	on model
11	M	9	982.9	700	on model	10	913.6	700	on model
12	M	5	882.7	700	on model	8	1019	700	on model
13	M	6	944	700	on model	8	802.2	700	on model
14	M	5	632.7	700	on model	6	741.5	700	on model
15	M	6	867.6	700	on model	12	845.9	700	on model
16	M	9	951	700	on model	12	723.2	700	on model
17	M	8	986.3	700	on model	11	860.7	700	on model
18	M	10	773.4	700	on model	12	917.2	700	on model
19	M	4	1030	700	on model	15	1372	700	on model
20	M	5	1297	700	on model	9	993.5	700	on model
21	M	5	1060	700	on model	12	1132	700	on model

Continued

22	M	2	824.1	700	guided	4	1157	700	guided
23	M	12	680.6	700	on model	13	715.8	700	on model
24	M	5	1039	700	on model	12	712.9	700	on model
25	M	8	820.2	700	on model	10	555.6	700	on model
26	F	5	1029	700	on model	7	963.2	700	on model
27	M	18	921.3	700	on model	19	849.1	700	on model
28	M	4	1045	700	on model	6	1036.74	700	on model
29	F	7	1447	700	on model	9	1276	700	on model
30	M	3	1230	700	on model	9	1080	700	on model
31	M	8	750.8	700	on model	9	1306	700	on model
32	M	10	1054	700	on model	18	1130	700	on model
33	F	7	894.5	700	on model	15	1010	700	on model
34	M	3	1093	700	on model	10	1001	700	on model
35	M	8	1055	700	on model	10	998.4	700	on model
36	M	10	352.1	700	guided	11	297.7	700	on model
37	M	3	649.3	700	on model	4	1136	700	on model
38	F	5	1364	700	on model	10	848.1	700	on model
39	M	4	913.7	700	on model	5	1214	700	on model
40	M	5	944.4	700	on model	10	1045	700	on model

Table 5. Case distribution as to second formant (F_2) vowel a.

Cases	Sex	Age	First spectrographic examination	Reference range	Execution 1° exam	Age	Last spectrographic examination	Reference range	Execution last one
1	M	6	1803	1250	guided	12	1424	1250	on model
2	F	4	1470	1250	on model	14	1670	1250	on model
3	M	8	1390	1250	guided	10	1367	1250	on model
4	M	13	1462	1250	on model	18	1433	1250	on model
5	M	6	1391	1250	guided	8	1707	1250	on model
6	M	7	1619	1250	on model	9	1163	1250	on model
7	M	8	1187	1250	guided	22	1682	1250	on model
8	F	8	1979	1250	on model	10	1919	1250	on model
9	M	8	1735	1250	on model	11	1266	1250	on model
10	M	5	2582	1250	on model	13	1319	1250	on model
11	M	9	1436	1250	on model	10	1219	1250	on model
12	M	5	1794	1250	on model	8	1735	1250	on model
13	M	6	1895	1250	on model	8	1253	1250	on model
14	M	5	1507	1250	on model	6	1549	1250	on model

Continued

15	M	6	2325	1250	on model	12	1566	1250	on model
16	M	9	1603	1250	guided	12	1908	1250	on model
17	M	8	1556	1250	on model	11	1828	1250	on model
18	M	10	1851	1250	on model	12	1981	1250	on model
19	M	4	2685	1250	on model	15	2919	1250	on model
20	M	5	2161	1250	on model	9	1387	1250	on model
21	M	5	1864	1250	on model	12	1556	1250	on model
22	M	2	1859	1250	guided	4	1949	1250	guided
23	M	12	1693	1250	on model	13	1456	1250	on model
24	M	5	1745	1250	on model	12	1357	1250	on model
25	M	8	1740	1250	on model	10	1586	1250	on model
26	F	5	1677	1250	on model	7	1864	1250	on model
27	M	18	1633	1250	on model	19	1600	1250	on model
28	M	4	2047	1250	on model	6	1795	1250	on model
29	F	7	1889	1250	on model	9	1664	1250	on model
30	M	3	2007	1250	on model	9	1799	1250	on model
31	M	8	1694	1250	on model	9	1953	1250	on model
32	M	10	1680	1250	on model	18	2949	1250	on model
33	F	7	1935	1250	on model	15	1756	1250	on model
34	M	3	1960	1250	on model	10	1393	1250	on model
35	M	8	1578	1250	on model	10	1493	1250	on model
36	M	10	1388	1250	guided	11	1295	1250	on model
37	M	3	1512	1250	on model	4	1823	1250	on model
38	F	5	1835	1250	on model	10	1832	1250	on model
39	M	4	1770	1250	on model	5	1924	1250	on model
40	M	5	1992	1250	on model	10	1491	1250	on model

Table 6. Case distribution by amplitude (E) Vowel a.

Cases	Sex	Age	First spectrographic examination	Reference range	Execution 1˚exam	Age	Last spectrographic examination	Reference range	Execution last one
1	M	6	53.79	50 - 65	guided	12	64.53	50 - 65	on model
2	F	4	60.28	50 - 65	on model	14	62.85	50 - 65	on model
3	M	8	61.79	50 - 65	guided	10	61.32	50 - 65	on model
4	M	13	62.84	50 - 65	on model	18	58.27	50 - 65	on model
5	M	6	56.84	50 - 65	guided	8	68	50 - 65	on model
6	M	7	59.8	50 - 65	on model	9	67.92	50 - 65	on model
7	M	8	50	50 - 65	guided	22	65.84	50 - 65	on model

Continued

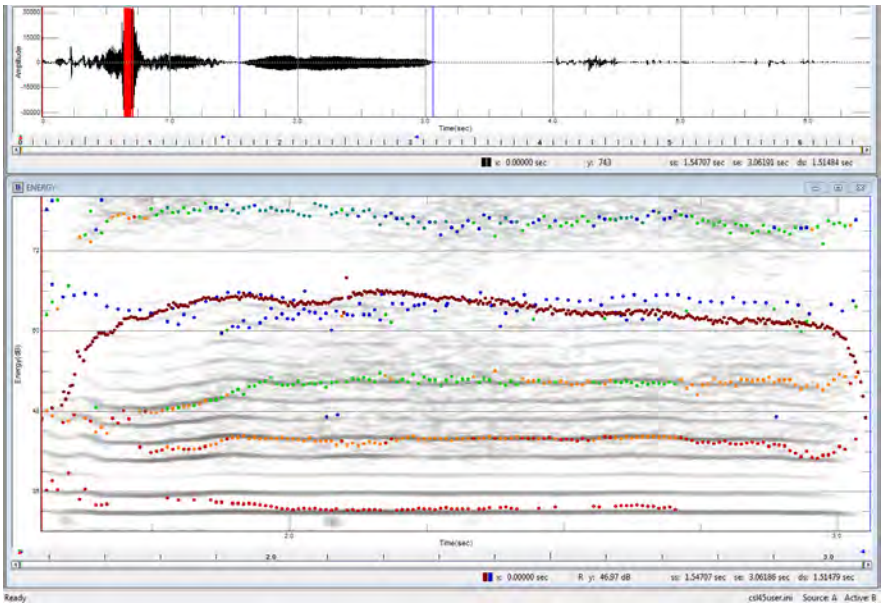
8	F	8	63.74	50 - 65	on model	10	65.81	50 - 65	on model
9	M	8	59.28	50 - 65	on model	11	59.12	50 - 65	on model
10	M	5	60.61	50 - 65	on model	13	65.69	50 - 65	on model
11	M	9	56.41	50 - 65	on model	10	61.36	50 - 65	on model
12	M	5	58.59	50 - 65	on model	8	59.66	50 - 65	on model
13	M	6	74.54	50 - 65	on model	8	59.33	50 - 65	on model
14	M	5	61.39	50 - 65	on model	6	56	50 - 65	on model
15	M	6	66.05	50 - 65	on model	12	62.16	50 - 65	on model
16	M	9	72.95	50 - 65	guided	12	65.47	50 - 65	on model
17	M	8	58.15	50 - 65	on model	11	57.34	50 - 65	on model
18	M	10	62.27	50 - 65	on model	12	57.85	50 - 65	on model
19	M	4	67.2	50 - 65	on model	15	64.67	50 - 65	on model
20	M	5	67.89	50 - 65	on model	9	62.37	50 - 65	on model
21	M	5	69.04	50 - 65	on model	12	63.26	50 - 65	on model
22	M	2	61.98	50 - 65	guided	4	69.3	50 - 65	guided
23	M	12	56.34	50 - 65	on model	13	61.4	50 - 65	on model
24	M	5	62.98	50 - 65	on model	12	61.5	50 - 65	on model
25	M	8	64.39	50 - 65	on model	10	57.81	50 - 65	on model
26	F	5	60.47	50 - 65	on model	7	58.35	50 - 65	on model
27	M	18	70.77	50 - 65	on model	19	62.7	50 - 65	on model
28	M	4	65.49	50 - 65	on model	6	55.06	50 - 65	on model
29	F	7	80.67	50 - 65	on model	9	63.14	50 - 65	on model
30	M	3	70.98	50 - 65	on model	9	64.81	50 - 65	on model
31	M	8	62.85	50 - 65	on model	9	63.09	50 - 65	on model
32	M	10	66.77	50 - 65	on model	18	58.48	50 - 65	on model
33	F	7	71.62	50 - 65	on model	15	64.51	50 - 65	on model
34	M	3	66.73	50 - 65	on model	10	66.41	50 - 65	on model
35	M	8	61.97	50 - 65	on model	10	66.46	50 - 65	on model
36	M	10	68.99	50 - 65	guided	11	53.41	50 - 65	on model
37	M	3	58.49	50 - 65	on model	4	63.82	50 - 65	on model
38	F	5	67.25	50 - 65	on model	10	54.5	50 - 65	on model
39	M	4	73.12	50 - 65	on model	5	64.57	50 - 65	on model
40	M	5	55.35	50 - 65	on model	10	60.64	50 - 65	on model

data, if we consider that 22/40 of the subjects do not have a starting spectrographic evaluation, because they were initially completely unable to emit vocal sounds as already mentioned, whereas 4 of the remaining 18 were able to emit vowel sounds in the initial examination by guided mode only, that is, by phoneme phono-articulatory setting. Referring to what briefly explained in synthetic

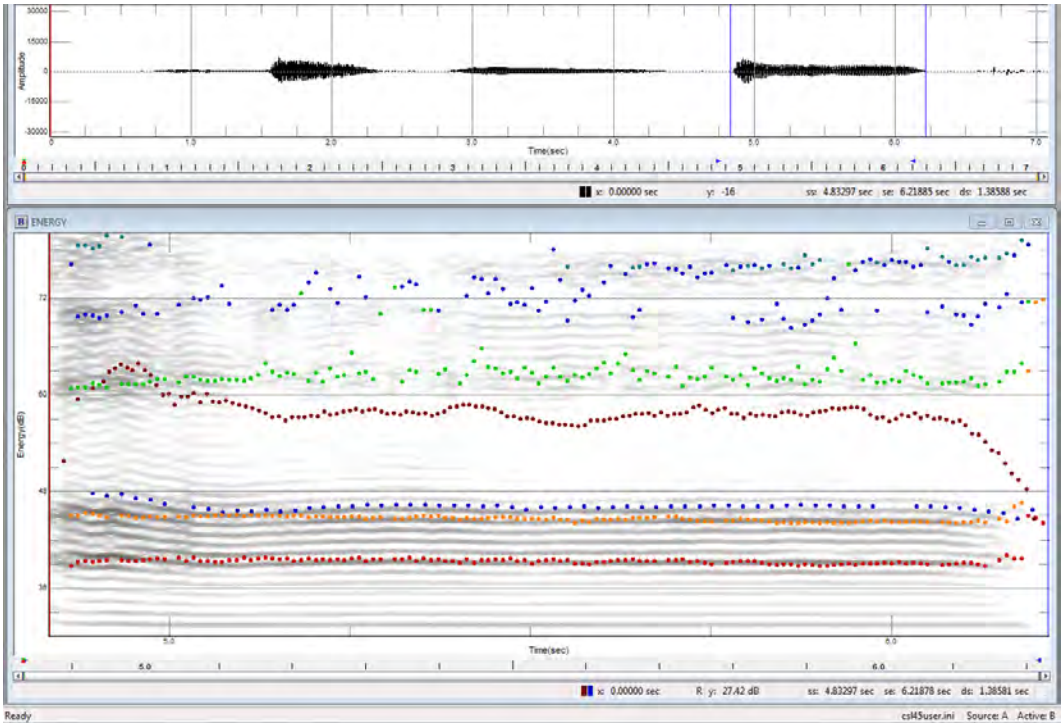
introductory notes about formants and remembering how the height of the first two F_1 and F_2 determines differences among vowels, we can well understand that values of the latter go to approximate reference value as a subject becomes more coordinated in articulating vowel sounds, a skill that acquires completely by completing the analytic phase (at the end of second analysis).

Regarding Energy, almost the totality of study population, that is 36/40 subjects, reports values within reference range, demonstrating a progressive acquisition of coordination and therefore self-control on vowel sound emission.

In order to prove more clearly what has been claimed so far regarding the positive evolution of educational-rehabilitation path implemented by AUGEV method, spectrographic exams of 6 subjects belonging to the population of this study are shown below. An employed method regards a presentation, for each of the 6 cases, of first and last performed examination and a selection of vowel "a" as "typical vowel". It is clear that initial examinations show marked anomalies in path time progressing (represented on the abscissa axis): an harmonic texture is generally not structured yet (**Figure 4(a)**, **Figure 5(a)**, **Figure 7(a)**) or irregular (**Figure 4(a)**, **Figure 5(a)**, **Figure 7(a)**), which is an index of a bad oropharyngeal resonance and, therefore, a missed or incorrect activation of phono-acoustic feedbacks when going back to causes. Obviously, also time trend of frequencies (F_0, F_1, F_2) and amplitude (E) is initially strongly irregular. Values measured by an instrument along with vocal segment to be analyzed are indicated by colored dots, where each color identifies a different parameter: blue color is combined with F_0, red and orange respectively with F_1 and F_2 and brown color with E. In no-pathological conditions, points of the same color are arranged next to each other in an ordered frequency alignment. In the examples shown, it is easy instead to see how the first tests show a markedly anomalous pattern with migrations (**Figures 2(a)-7(a)**), rarefactions (**Figure 5(a)**, **Figure 6(a)**) and/or frequent

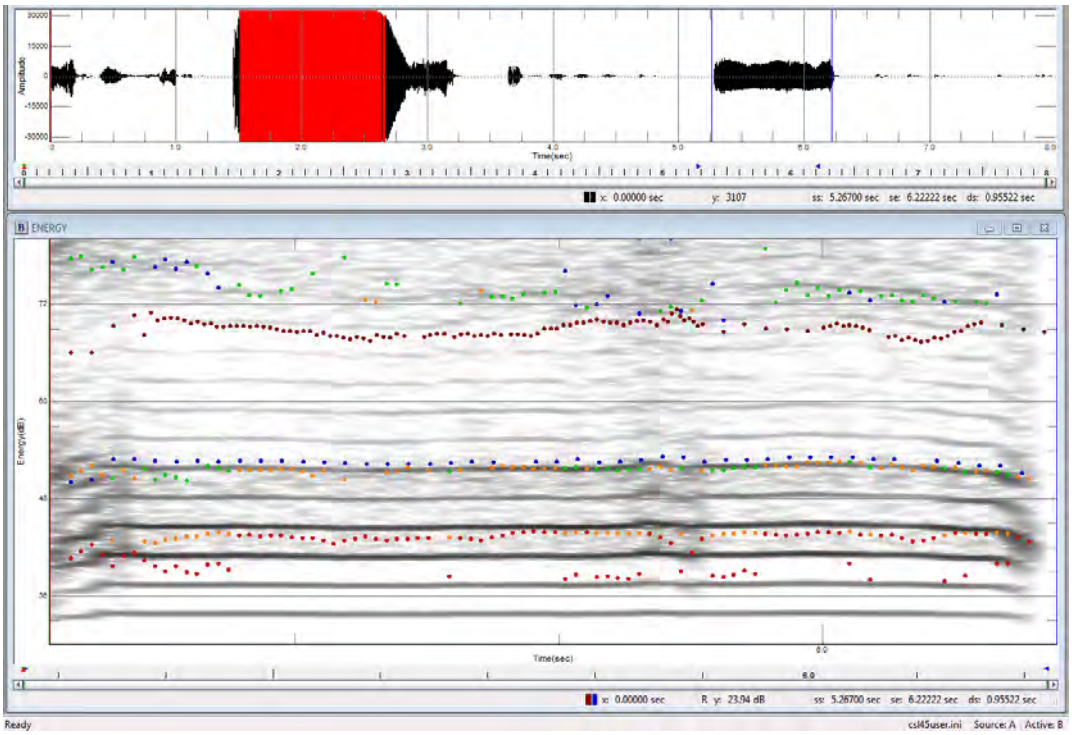


(a)

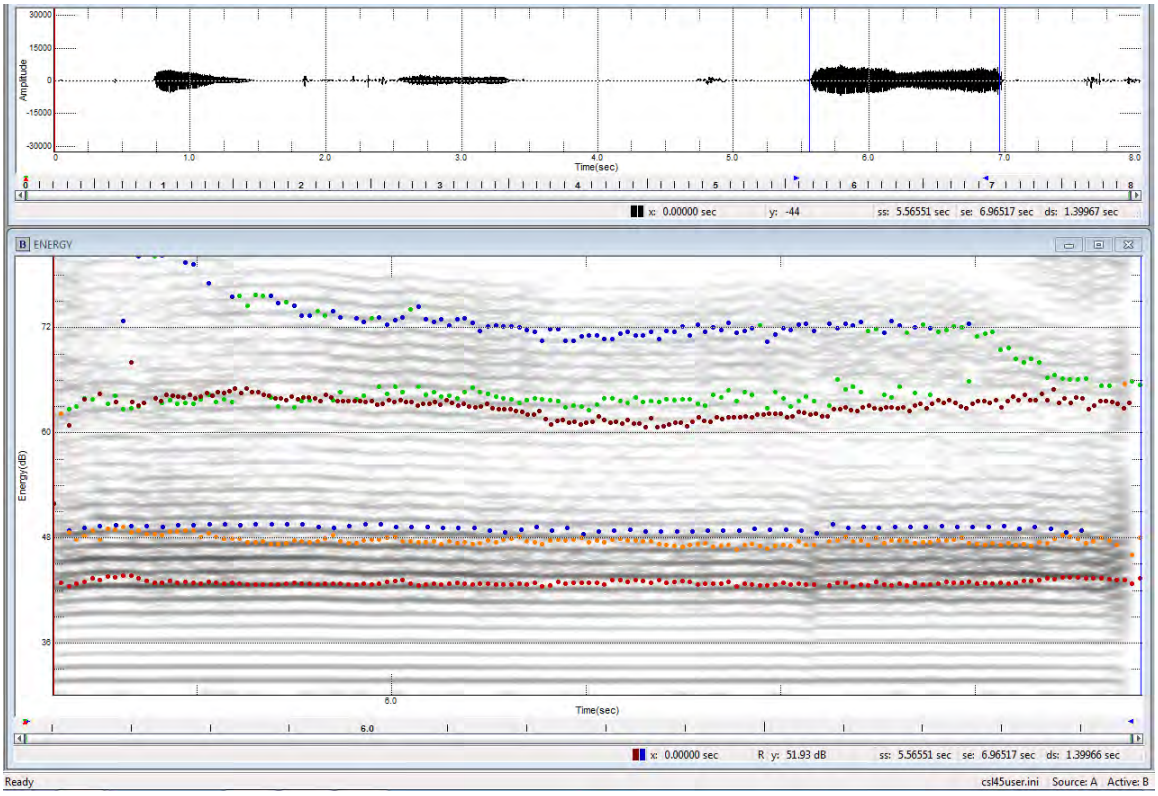


(b)

Figure 2. (a) Spectral examination of the vocal signal. ***Legend of all the figures beneath.*** Symbology of the phonetic-acoustic parameters detected in the spectrographic examination: ●●●●●●●●●●● = Fundamental Frequency (Fo), measured in Hz; ●●●●●●●●●●● = First Formant (F_1), measured in Hz; ●●●●●●●●●●● = Second Formantt (F_2), misurata in Hz; ●●●●●●●●●●● = Energy (E), misurata in dB; (b) Spectral examination of the vocal signal.

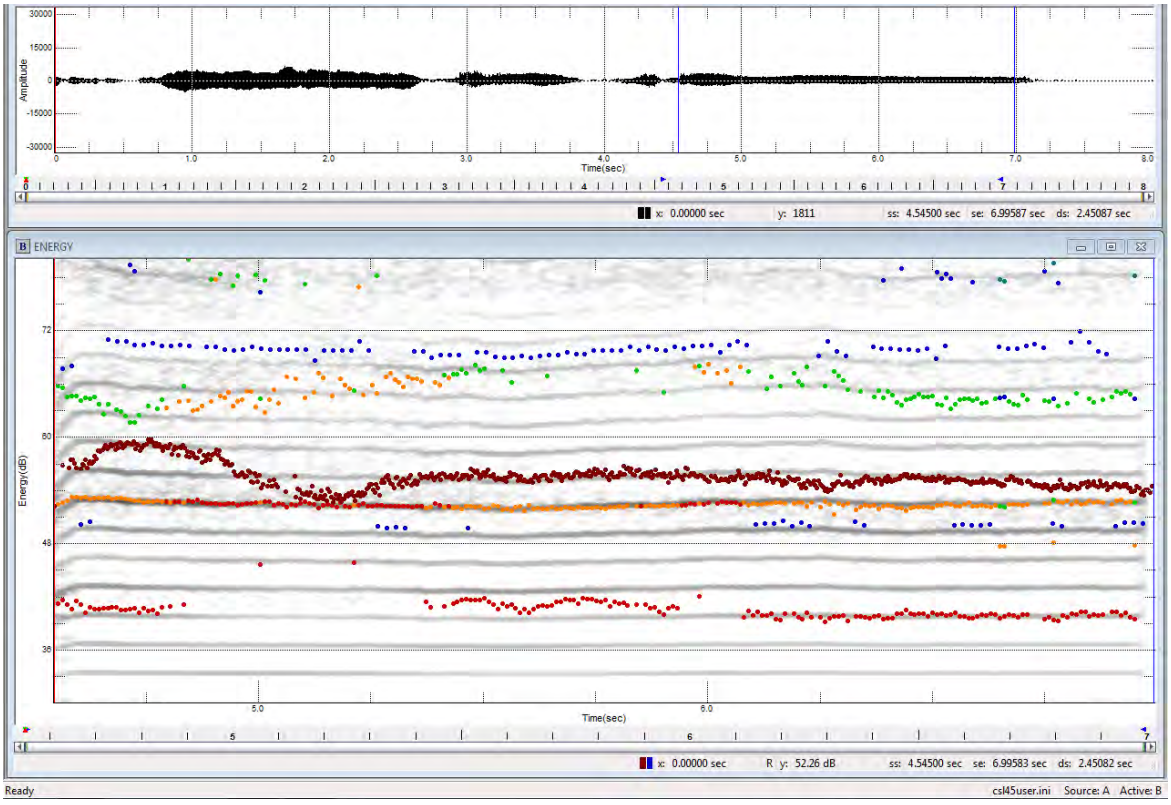


(a)

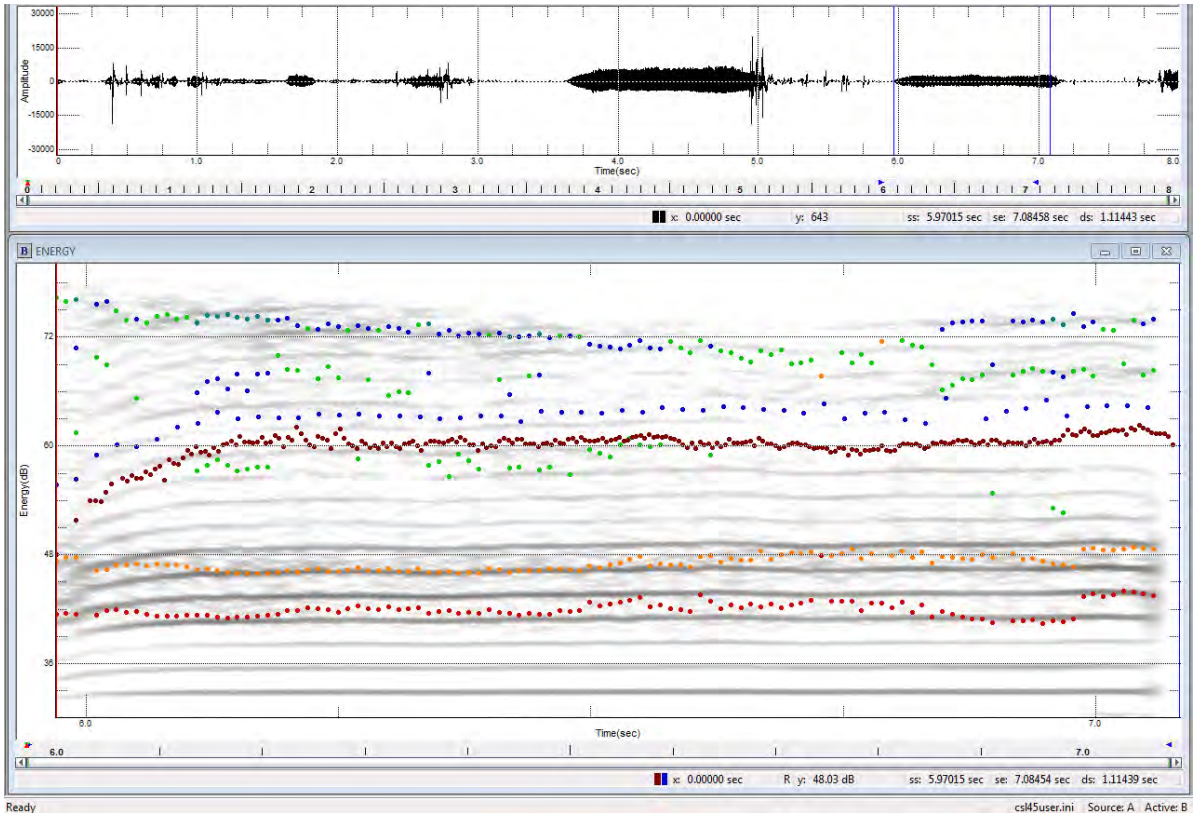


(b)

Figure 3. (a) Spectral examination of the vocal signal; (b) Spectral examination of the vocal signal.

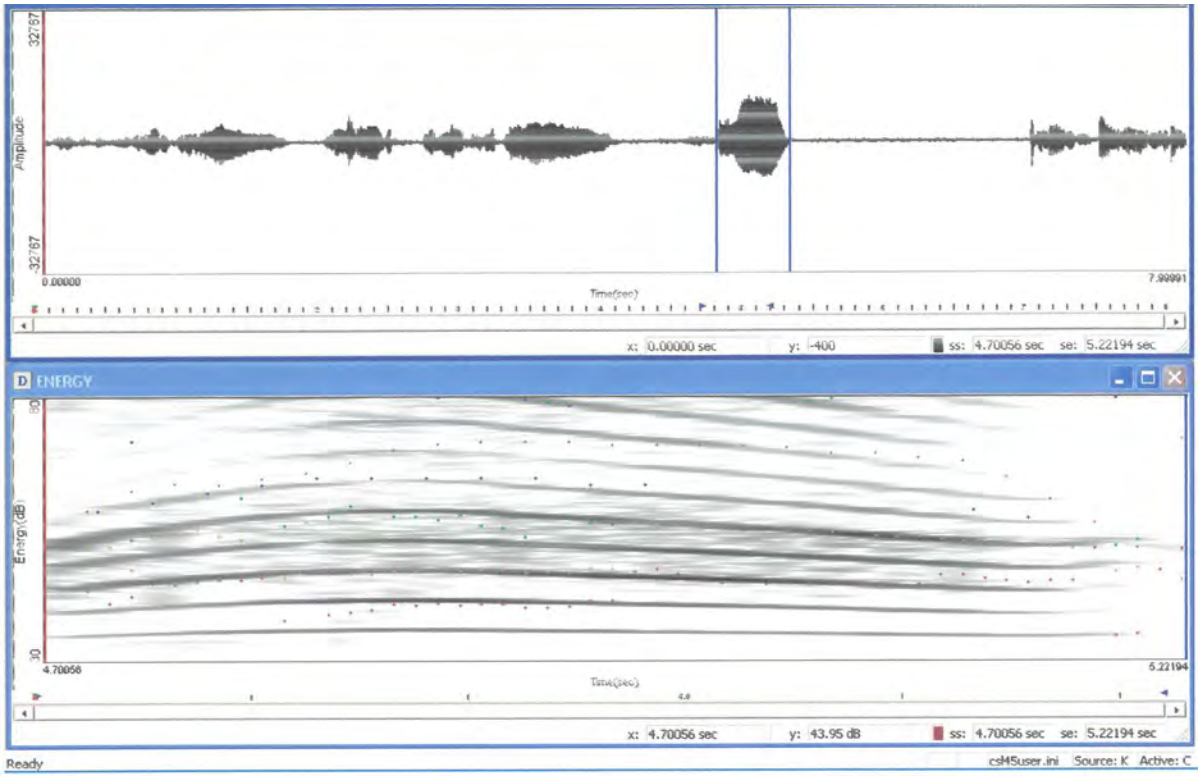


(a)

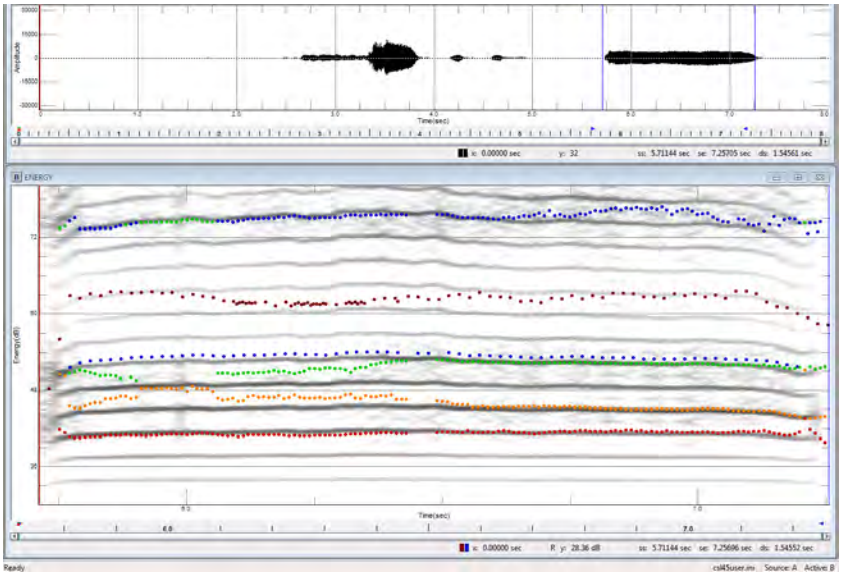


(b)

Figure 4. (a) Spectral examination of the vocal signal; (b) Spectral examination of the vocal signal.

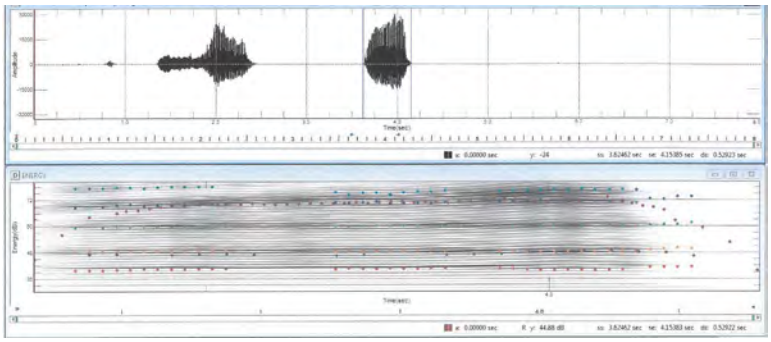


(a)

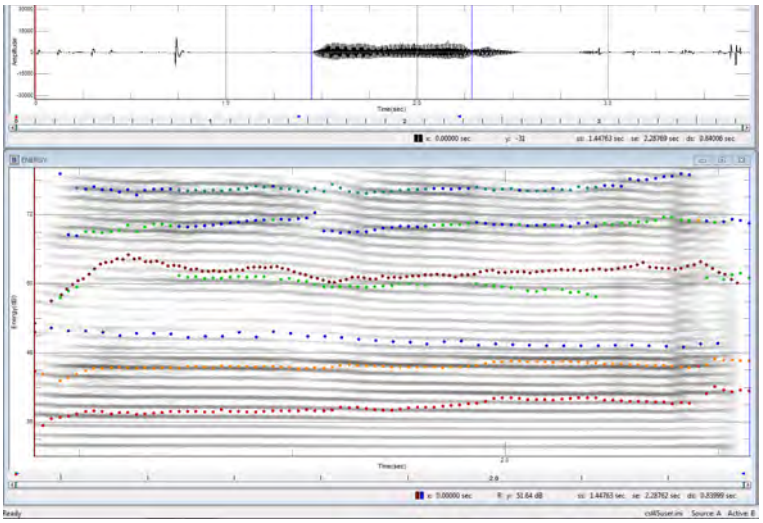


(b)

Figure 5. (a) Spectral examination of the vocal signal; (b) Spectral examination of the vocal signal.

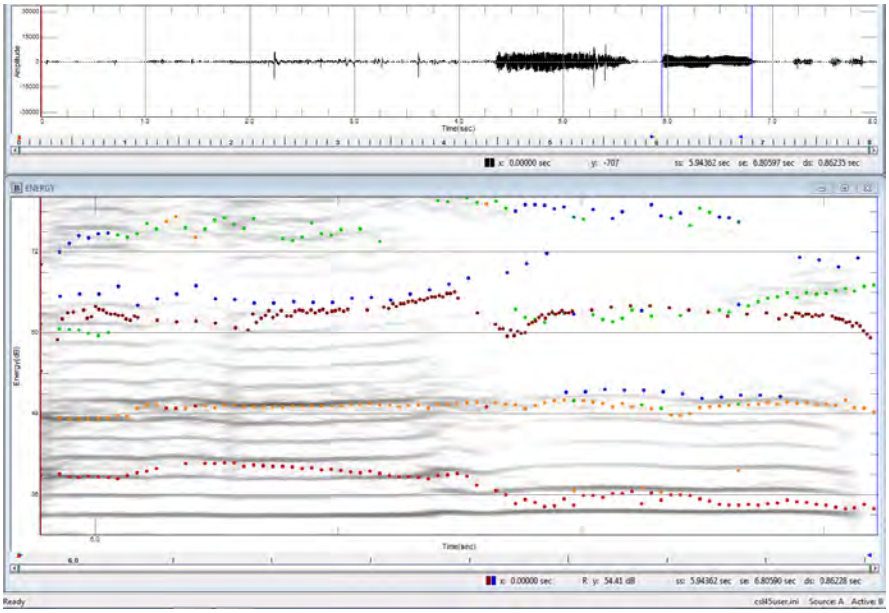


(a)

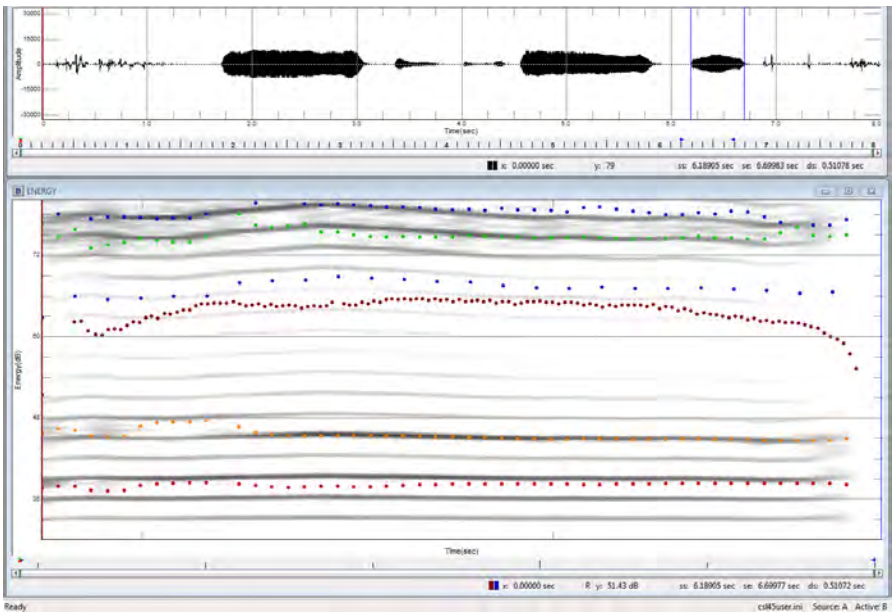


(b)

Figure 6. (a) Spectral examination of the vocal signal. (b) Spectral examination of the vocal signal.



(a)



(b)

Figure 7. (a) Spectral examination of the vocal signal; (b) Spectral examination of the vocal signal.

intrusions in an harmonic texture (**Figure 2(a)**, **Figures 4(a)-7(a)**). In a spectrographic framework, an aperiodic signal (noise) is often present (**Figures 2(a)-6(a)**), sometimes very strongly, which at high frequencies is to be mostly related to insufficient tension and cordial adduction, with a consequent fugatory air leak (blown voice) and at low frequencies it is mainly due to an irregular vibration of strings, due to their excessive adduction and rigidity. Phonatory attack is irregular (**Figures 2(a)-6(a)**) and often the presence of diplofony and/or bitonality is indicated on the diagram. However, this is indicative of a subject's

inability to control individual phono-articulatory productions, a difficulty also explained by the irregular intensity curve (E). This situation is clearly modified in each subject's last spectrographic examination: harmonic texture is now well defined (**Figure 2(b)**, **Figure 4(b)**, **Figure 5(b)**) and it is not "polluted" by an aperiodic signal (noise) (**Figure 2(b)**, **Figures 4(b)-6(b)**) and/or sub-harmonics (responsible for diplophony) (**Figure 4(b)**, **Figure 6(b)**). Individual frequencies (F_0, F_1 and F_2) are now aligned and phonatory intensity curve (E) has also been normalized (**Figures 4(b)-6(b)**). In the last exam, phonatory attack is partially or completely presented as a regularized examination (**Figures 4(b)-6(b)**) and is now generally soft.

Conflicts of Interest

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

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Postoperative Therapeutic Effect of ACL Reconstruction at Different Periods

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Abstract

Objective: To analyze postoperative therapeutic effects of patients with fractured anterior cruciate ligament (ACL) that underwent autologous tendon reconstruction at early and late period. Methods: A total of 60 patients underwent autologous tendon reconstruction were enrolled and retrospectively analyzed via arthroscopes from December, 2015 to December, 2017 in our hospital, in which 30 patients treated with ACL reconstruction within 6 weeks of injury were selected as the early reconstruction group (Group A), and the other 30 cases with ACL reconstruction between 6 weeks and 6 months were as late reconstruction group (Group B); the therapeutic effect of early and late ACL reconstruction was analyzed by recording and comparing of several indexes, such as knee lysholm score, knee IKDC score, intraoperative hemorrhage, operation time, pre- and post-operative range of motion (ROM) of the knee, etc. Results: The pre- and post-operative lysholm scores and IKDC scores were compared between the two groups, without statistically significant results ($P > 0.05$). The knee ROM scores of the late reconstruction group were higher than those of the early group ($P < 0.05$), and the intraoperative blood loss in the late stage was less than that in the early group ($P < 0.05$), which exhibits that the short-term clinical efficacy of early and late arthroscopic autologous tendon reconstruction for knee ACL injury was similar, but the late reconstruction group was with less intraoperative bleeding, and better post-operative joint mobility recovery; in conclusion, it is recommended that patients can be operated between 6 weeks and 6 months after injury.

Keywords

Arthroscopes, Anterior Cruciate Ligament Reconstruction

1. Introduction

ACL is a main structure preventing anterior tibial movement, and ACL injury

refers to the rupture of ACL due to intense exercise or other external factors, resulting in instability of knee joint structure. In recent years, with the elevation of traffic accidents in China and the development of competitive sports, the incidence of ACL injury increases year by year. After ACL injury, the knee weakened, which seriously impacts on the patient's motor function; usually, it cannot heal itself; if treated late, the function of the knee joint will be in danger. At present, the most common and effective method is arthroscopic ACL reconstruction, but there still remains controversy over the best time to operate after injury, and some reported that delayed reconstruction of ACL will lead to an increase of the incidence of meniscus and cartilage injury as well as muscle strength loss. The incidence of knee joint osteoarthritis increases to about 15% - 20% after ACL tearing [1], and will induce 10% to 50% of patients with varying degrees of meniscus tearing when the ACL is torn [2] [3] [4]. In contrast, early ACL reconstruction can lead to joint fibrosis and joint stiffness, affecting later knee motion function recovery. Therefore, the best operation time of ACL reconstruction through clinical retrospective analysis was discussed in this paper.

2. Research Subjects

2.1. Data and Methods

Totally, 60 patients with autologous tendon reconstruction in our hospital in December 2017 were enrolled and underwent arthroscopes for retrospective analysis. Inclusion criteria: 1) preoperative MRI diagnosed of ACL rupture and further diagnosed of ACL fracture in intraoperative knee arthroscopy; 2) single knee joint injury, the offisde knee joint is normal; 3) cooperation of postoperative rehabilitation; 4) postoperative follow-up over 12 months; 5) patients aged 20 - 50. Exclusion criteria: 1) patients combined with other knee joint ligament rupture; 2) combined with lower limb fracture or severe soft tissue injury; 3) patients with history of knee surgery; 4) patients who could not cooperate with the completion of rehabilitation after surgery; 5) less than 12 months of follow-up time, or incomplete follow-up.

2.2. Patient Grouping

All eligible patients were numbered, and each group was randomly selected from 30 patients. The patients were divided into 2 groups by the operation time after the injury patients applied ACL reconstruction within 6 weeks of injury were as the early group (Group A), and the other with ACL reconstruction between 6 weeks and 6 months were as late group (Group B); then the two groups of patients with knee lysholm score, knee LKDC score, knee activity, intraoperative bleeding amount, as well as clinical indexes, such as operation time and thigh circumference margin were compared with, and all the patients were informed consent to experiment and treatment.

2.3. Basic Situation of the Patient

There were 30 cases of early reconstruction in two groups, including 18 males,

12 females, 8 cases of meniscus injury (26.7%) with average age of 34.4 ± 3.6 years, involving 15 cases of traffic accidents, 10 sports injury and others 5 cases. In the late reconstruction group, there were 30 cases, including 17 males, 13 females, of which 10 meniscus injury (33.3%) with average age of 36.2 ± 3.8 years, the cause of injury: 18 traffic accidents, 8 sports injury, others 4 cases; and no significant statistical difference in age and sex between the two groups ($P > 0.05$).

2.4. Patient Informed Consent

This study was approved by the Medical Ethics Committee of the hospital. All patients signed informed consent before surgery.

3. Therapeutic Method

3.1. Surgical Methods

All patients were applied epidural anesthesia, and completely operated by senior surgeons in the same group, after successful anesthesia, the patient was in prostration with a pneumatic tourniquet on the thigh of the affected limb, then routine disinfection, paving, connecting the arthroscopic system and dialogued successfully, elevating the influenced limbs, expelling blood with repellent belt, tourniquet inflation, intraoperative pressure maintained 55 Kpa. The affected limb knees 90 degrees, with the patellar ligament next to do 0.5 cm straight incision to the joint sac, then rinse liquid (0.9% saline 6000 ml) perfusion joint cavity; the planning system cleared the field of operation, explored anterior, posterior cruciate ligament, medial and lateral menisci, and diagnosed and repaired or removed the damaged menisci (see **Figure 1**). On the medial side of the tibial nodule of the affected knee, about 3 - 4 cm incision was made, and the femoral thin muscle and semitendinosus were cut and dissociated in turn, the tendon was removed and woven, the prepared ligament was stacked into 4 bundles; the tibial end and femur diameter were measured with the sleeve; the value was recorded, and the ligament was wound with saline gauze for preparation. The ACL locator locates the posterior cruciate ligament intercondylar stop point (see **Figure 2**), drilling into the guide needle and expanding the bone tunnel next to the tibial nodule, the position of the guide needle can be seen under the scope, and then the guide needle is positioned and the bone tunnel is expanded with the posterior lateral condyle of the femur, and the position of the bone tunnel can be seen under the scope, and the braided ligament will be connected to the locking belt loop (see **Figure 3**). The femur side is fixed with a loop titanium plate, the tibia side with interfacial screws, the knee joint of the patients is repeatedly activated to observe whether there is intercondylar fossa, if there is, applying intercondylar fossa plasty; the front and rear drawer experiments are negative, the lateral stress test is negative, the knee joint is stable, the wound is stitched by layer and the gauze bandage is pressurized, recorded the transoperative bleeding amount and returned to the ward.

The surgical procedure is as shown in **Figures 1-4**.

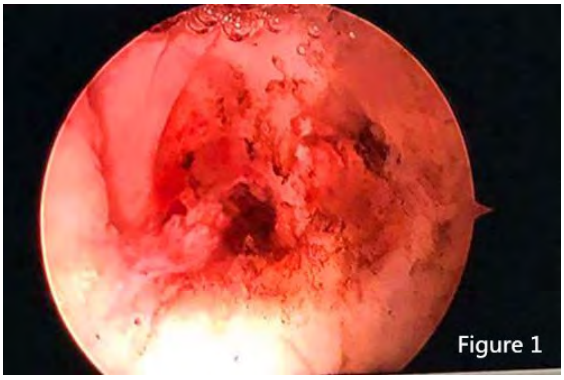

Figure 1. The anterior cruciate ligament rupture.

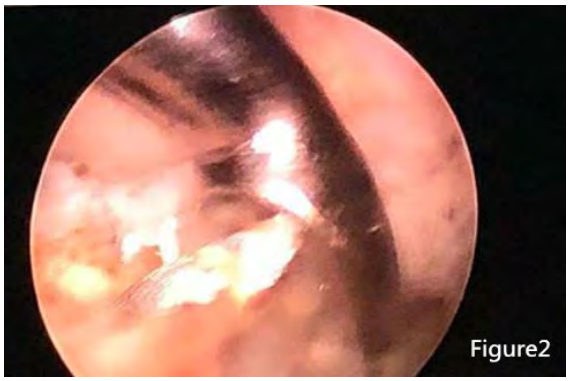

Figure 2. Anterior cruciate ligament humerus stop positioning.

Figure 3. Implanted reconstruction ligament.

Figure 4. Check implant ligament stability.

3.2. Postoperative Rehabilitation Program

Inform patient of postoperative rehabilitation plan, please Rehabilitation Department Physician cooperates in guiding the patient for rehabilitation training:

On the first 1 - 2 days after operation, the patient began to exercise the toes and ankles under the guidance of a rehabilitation doctor (20 activities every half hour).

From 3 days to 4 weeks after surgery, the muscle strength of the muscles around the knee joint was gradually exercised under the protection of the knee brace (0˚ - 90˚), and the ankle joint was active. Muscle exercises mainly exercise quadriceps and hamstrings, patients on their own muscle contraction and relaxation alternately.

4 - 6 weeks after the operation: The affected limb was gradually loaded under the protection of a brace; the knee joint movement exercise was started. 6 weeks later, the knee motion reached 120˚.

7 - 12 weeks after surgery: Remove the brace and start walking slowly and squatting.

12 weeks later: Gradually resume daily work and start moderate exercise, but avoid strenuous exercise.

4. Evaluation Index

4.1. Record Indicator

The operative time, intraoperative blood loss, IKDC score, lysholm score, and range of motion of the knee joint before and after arthroscopic reconstruction of the anterior cruciate ligament with autologous tendon were recorded.

4.2. Joint Stability Examination

Anterior drawer test, Lachman test under local anesthesia.

5. Statistical Analysis

Statistical analysis was performed by SPSS 17.0 software (IBM Corporation, USA). The operative time, intraoperative blood loss, knee Lysholm score, IKDC score, and knee joint mobility were compared between the two groups. The results were expressed as mean ± standard deviation ($x \pm s$)'s formal representation, the data between groups are represented by independent samples t Test for comparative analysis to $P < 0.05$ indicated that the difference was statistically significant, and gender, cause of injury, etc. were compared by chi-square test for difference.

6. Results

6.1. Perioperative Index

Intraoperative blood loss, operative time, knee motion, preoperative and postoperative 3 month thigh circumference difference comparing **Table 1** below, the

Table 1. Comparison of general conditions between the two groups of patients during perioperative period.

	Group A	Group B	t	p
volume of bleeding (ml)	76.38 ± 10.59	68.57 ± 8.28	3.4	0.01
time of surgery (min)	61.28 ± 3.54	59.73 ± 3.10	1.92	0.58
preoperative knee mobility	104.23 ± 6.45	104.07 ± 4.03	0.12	0.91
knee joint motion 3 months after operation	124.80 ± 3.54	126.90 ± 1.90	3.21	0.02
preoperative thigh circumference	2.01 ± 0.67	1.78 ± 0.60	1.48	0.14
thigh circumference 3 months after surgery	1.52 ± 0.58	1.31 ± 0.46	1.73	0.09

difference in operative time and thigh circumference between the two groups (P average > 0.05), the difference was not statistically significant, but the amount of intraoperative blood loss was lower in the late reconstruction group than in the early reconstruction group, and the knee joint mobility was higher in the late group than in the early group at 3 months after surgery (P < 0.05).

6.2. Lysholm Score and IKDC Score

The Lysholm scores and IKDC scores of the two groups before surgery, 3 months after surgery, and 12 months after surgery are shown in Table 2 and Table 3 (P all > 0.05) the difference was not statistically significant.

As shown in the above table, the results of the preoperative and postoperative comparisons between the two groups of patients suggest that the intraoperative blood loss in the late reconstruction group was lower than that in the early reconstruction group (P < 0.05), and the knee joint mobility in the late group was higher than that in the early group (P < 0.05). The Lysholm score and IKDC score were compared between the two groups before surgery, 3 months after surgery, and 12 months after surgery (P > 0.05), the difference was not statistically significant. There were no postoperative complications such as joint infection and redness in both groups. One patient in the late stage group was found to have the stump attached to the posterior cruciate ligament after anterior cruciate ligament rupture.

7. Discussion

The anterior cruciate ligament (ACL) is an important structure that controls the forward stability and rotational stability of the knee joint. It causes anterior instability and rotational instability of the knee joint after injury [5] [6] [7]. The instability of the knee joint after ACL rupture not only affects daily activities and sports, but also causes damage to the soft tissues of the knee joint and changes in the force lines of the lower extremities, which in turn leads to secondary meniscal injury and synovitis. It has been found that earlier surgery can reduce the

Table 2. Comparison of Lysholm scores before and after treatment in two groups of patients.

Lysholm score				
	Group A	Group B	t	p
before reconstruction	47.73 ± 8.65	49.76 ± 7.39	1.06	0.29
3 months after reconstruction	87.73 ± 3.57	88.56 ± 2.52	1.14	0.25
12 months after reconstruction	93.17 ± 1.72	92.71 ± 2.04	0.99	0.32

Table 3. Comparison of IKDC scores before and after treatment in two groups of patients.

IKDC score				
	Group A	Group B	t	p
before reconstruction	52.53 ± 5.97	56.95 ± 6.02	3.06	0.78
3 months after reconstruction	87.90 ± 2.97	87.59 ± 2.39	0.49	0.62
12 months after reconstruction	92.83 ± 3.00	93.22 ± 1.87	0.66	0.50

occurrence of inflammation and further reduce the probability of knee osteoarthritis [8]. Many scholars believe that when ACL rupture occurs, ACL reconstruction should be given in time to reduce the occurrence of secondary meniscal injury, cartilage degenerative changes and chronic synovitis and other complications [9] [10] [11].

In this study, we compared the clinical efficacy of arthroscopic autologous tendon reconstruction surgery for ACL rupture in patients with early and late post-injury, and found that patients in the late reconstruction group had a better recovery of joint mobility than the early group ($P < 0.05$). Laird *et al.* [12] [13] The study pointed out that when the human body is injured, the body will stimulate the corresponding inflammatory response to resist the damage suffered by the body, and the continuous high-intensity inflammatory response will cause the body to feel pain and affect postoperative recovery. Another scholar in the study of ACL reconstruction patients with postoperative pain and swelling factors, pointed out that ACL rupture early ACL reconstruction patients, reconstruction surgery intensified the original injury [14] [15]. It can be speculated that early ACL reconstruction surgery may further stimulate and exacerbate the original unresolved inflammatory response, which in turn results in higher postoperative knee motion in the late reconstruction group.

Additionally, in clinical practice, we found that patients in the early reconstruction group had more intraoperative blood loss than those in the late reconstruction group ($P < 0.05$). Hemorrhage in the joint cavity of patients in the early reconstruction group affected the operative field, resulting in prolonged operative time, increased surgical risk, and patients were more prone to knee joint adhesions after early surgery, and severely affected the recovery of knee joint function.

This study found that although the early and late reconstruction groups had different advantages and disadvantages during the perioperative period, the knee function of both groups could be restored to normal after ACL reconstruction and postoperative rehabilitation. Lysholm scores and IKDC scores before, 3, and 12 months after surgery in both groups in this study (P average > 0.05). The difference was not statistically significant, indicating that there was no significant difference in postoperative knee function between the two groups.

MRI is the most accurate imaging method for clinical diagnosis of ACL injury. It has the advantages of non-invasiveness, small radiation, etc. It can detect combined injuries such as bone contusion and meniscus injury in time. The accuracy of MRI in the diagnosis of ACL injury is 90% - 100%. In this study, all patients in the early group underwent MRI after injury. In the late group, some patients did not undergo MRI in time after injury, so ACL and meniscus injuries were not diagnosed in time. In this study, one patient in the late group had ACL rupture followed by attachment to the posterior cruciate ligament, which was easily missed during the examination. Therefore, knee arthroscopy should be alert to the possibility of intrasynovial rupture or reattachment of the broken end, we must use the hook carefully repeated exploration in order to confirm the diagnosis.

Of course, there are still many deficiencies in this study, such as the inclusion of a small number of comparative samples, and the lack of comparative analysis of postoperative long-term efficacy, etc., some patients in the late group did not perform MRI in a timely manner, resulting in the failure to further analyze the meniscus loss and other influencing factors; in the future will be further included in more patients for long-term follow-up, and further observation of whether the merger of other intra-articular injuries affect the patient's recovery.

8. Conclusion

In summary, early and late arthroscopic autologous tendon reconstruction surgery for knee ACL injury has similar clinical outcomes. However, patients with late reconstructive surgery have less intraoperative blood loss and higher postoperative knee motion. Therefore, from the aspects of postoperative recovery and efficacy, we recommend that these patients undergo ACL reconstruction surgery from 6 weeks to 6 months after injury.

Conflicts of Interest

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

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Advances in Research on Immunological Checkpoint Inhibitors in Immunotherapy of Liver Cancer

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Abstract

The current treatments of liver cancer in China are mainly comprehensive treatment and systematic treatment, with poor therapeutic effect and high recurrence rate and metastasis rate. The existence of immunosuppressive microenvironment is an important reason for liver tumor cells to escape from the host immune system, and also an important basis for the occurrence and development of liver cancer. With the recent transformation of the target of tumor therapy from tumor cells to tumor cell immune microenvironment, immunotherapy has emerged quietly. It is a new strategy for the treatment of hepatocellular carcinoma to improve the immune attack on tumor cells by changing the immunosuppressive environment of hepatocellular carcinoma cells. Immune checkpoint is the main mechanism by which liver cancer cells escape the host immune system. PD-1/PDL-1 and CTLA-4 are targeted immunocheckpoint inhibitors, which have shown good therapeutic effects and application prospects in the clinical treatment of HCC. This article reviews the latest advances in immunocheckpoint inhibitors in the immunotherapy of hepatocellular carcinoma.

Keywords

Liver Cancer, Immunotherapy, Immunosuppressive Microenvironment, Immune Checkpoint Inhibitor, PD-1/PDL-1, CTLA-4

1. Introduction

China is a large country with hepatitis B, and half of the world's liver cancer also occurs in China [1]. Because of the concealment of its pathogenesis, liver cancer is mostly found in the late stage. The current treatments for liver cancer include

radical surgical resection, liver transplantation, radiofrequency ablation, TACE, radiotherapy and chemotherapy, and molecular targeted therapy, but the treatment effect is not satisfactory [2]. Due to the early diagnosis concept and the continuous development of systemic treatment, the prognosis of liver cancer has been greatly improved compared with 10 years ago. The 5-year survival rate of radical resection of liver cancer reached 70% [3], but the recurrence rate and metastasis rate of liver cancer still have not improved significantly. The clarification of the tumor immune microenvironment and the mechanism of immunosuppression point make the rise of immunotherapy in the field of cancer treatment, and at the same time give a new treatment strategy for liver cancer.

The normal adaptive immunity and innate immune system of the human body can recognize and attack liver cancer cells at any time. Immune cells or tumor cells in the liver cancer microenvironment have high expression of inhibitory co-stimulatory molecules, that is, immune checkpoints, leading to the inactivation of anti-tumor T lymphocytes. An immunosuppressive microenvironment is formed [4], which leads to immune escape of tumor cells and further tumor progression and metastasis. The mechanism of immunotherapy is activation of specific T lymphocytes, activation and enhancement of anti-tumor immune response in patients, targeted attack and clearance of tumor cells. It mainly includes adoptive immunotherapy, tumor vaccine and checkpoint suppression, among which some checkpoint inhibitors have shown good clinical efficacy, and some checkpoint inhibitors have been approved for clinical treatment in the United States and Europe. Here, the author mainly reviews the latest development of immunological checkpoint inhibitors in immunotherapy.

Among the current clinically significant results are programmed death protein-1 (PD-1)/programmed death protein ligand-1 (PDL-1) and cytotoxic T lymphocyte-associated antigen (CTLA-4) inhibitors.

2. PD-1/PDL-1

PD-1 (programmed death 1) is a kind of important immunosuppressive molecules, which is a membrane protein of 268 amino acid residues. Also known as CD279, it induces immune suppression and promotes the immune response of tumor cells to escape cytotoxic T cells. PD-1 is mainly expressed on T cells, B cells and natural killer cells. The ligands for PD-1 include PDL-1 and PDL-2. PDL-1 is also known as B7-H1 or CD274, and PDL-2 is also known as B7-H2 or CD273, and their regulation is different. Natural killer cells (NK) or activated T cells induce PDL-1 expression in activated hematopoietic cells and endothelial cells by secreting interferon (IFN)-γ. PDL-2 is more likely to be induced by interleukin (IL)-4 than IFN-γ, which is expressed on the surface of activated dendritic cells (DCs) and macrophages.

PD-1/PDL-1 signaling pathway plays an important role in tumor immune escape. PD-1 functions in the effector phase of T cell activation. It inhibits T cell immune activity and promotes tumor growth by binding PDL-1. Therefore,

blocking the binding of PD-1 and PDL-1 can reactivate the immune activity of T cells and enhance the killing effect of the patient's immune system on tumor cells.

PD-1/PDL-1 antibody, also known as PD-1/PDL-1 inhibitor, whose mechanism is as follows: T cells recognize the antigen MHC on the surface of tumor cells, MHC stimulates T cell activation, and activates T cells to synthesize cytokinins. T cells that are activated for a long time produce PD-1, and cytokinins induce tumors. The cells produce PDL-1, and PD-1 on the surface of T cells binds to PDL-1 on the surface of tumor cells, thereby inhibiting T cell proliferation and differentiation, leading to decreased T cell function and even apoptosis [5], which ultimately causes tumor cells to escape the immune system. The attack, the tumor cells survive, forming a microenvironment of tumor immunity, in which the tumor cells survive and progress. In the presence of PD-1 inhibitors or PDL-1 inhibitors, PD-1 and PDL-1 cannot bind to produce inhibitory effects on T cells. Continuous activation of T cells destroys the immunosuppressive microenvironment for the survival of tumor cells and produces a strong immune effect on tumor cells, thereby killing them (**Figure 1**).

2.1. PD-1 Inhibitors

Currently, PD-1 inhibitors mainly include Nivolumab [6] [7] and Pembrolizumab [8], which are used for the treatment of non-small cell lung cancer, malignant melanoma, gastric cancer, liver cancer, colorectal cancer and other tumors [9]. Hepatocarcinoma has a high degree of immunosuppression in the microenvironment. Among them, Nivolumab has a significant effect on liver cancer. It was approved by the US Food and Drug Administration (FDA) as a second-line

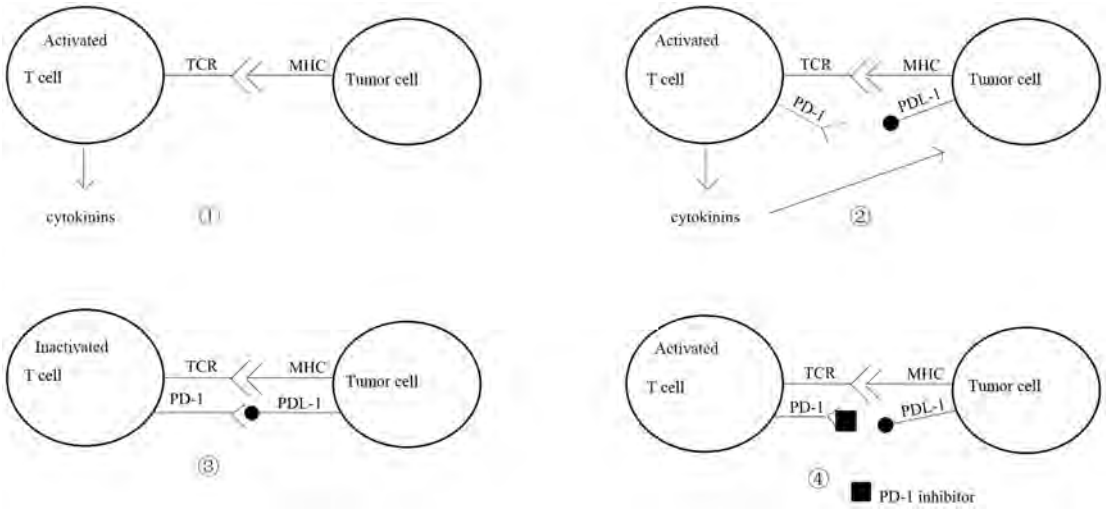

Figure 1. (1) T cells identify tumor cell surface antigen MHC, thus becoming activated T cells. Activated T cells produce cytokinin; (2) Activated T cells produce PD-1, at the same time, cytokinin induces tumor cells to produce PDL-1; (3) The combination of PD-1 and PDL-1 inhibits the activation of T cells, thus tumor cells survive. (4) When PD-1 inhibitors combined with PD-1, PD-1 and PDL-1 could not be combined to inhibit T cells, T cells continued to activate and kill tumor cells.

treatment for advanced liver cancer in 2017. In some studies, Nivolumab was used to treat patients with advanced liver cancer, with a disease control rate of 81.8% and an objective remission rate of 63.6%. This study included a total of 11 patients, with the lack of large sample trials, but it also suggested that Nivolumab may have a good benefit in the treatment of advanced liver cancer [10]. In a trial using Nivolumab (Checkmate-040) [11], 48 patients were enrolled in stage I, with a low dose of Nivolumab (less than 3 mg/kg) with an objective response rate of 15% and an overall survival of 15 months; Phase II included 214 patients, treated with Nivolumab (3 mg/kg) until the disease progressed, 2 of them achieved complete remission, 33 achieved partial remission, and the duration of complete remission and partial remission was 14 to 17 months and 8 In the month, all patients enrolled in this stage had an overall survival of 82.5% and 70.8% at 6 and 9 months, an objective response rate of 16%, and a disease control rate of 68%. Phase III of the study (CheckMate-459) compared the efficacy of sorafenibmonotherapy in patients with liver cancer and liver cancer patients who received Nivolumab after treatment with sorafenib, which showed a significant increase in survival and survival.

Pembrolizumab is another PD-1 inhibitor. It has been reported that patients with liver cancer have been treated with Pembrolizumab for 8 months after failure of sorafenib treatment, showing good tolerance and no significant adverse reactions [12]. A phase II trial (KEYNOTE-224) [13] in the United States for the use of Pembrolizumabmonotherapy in patients with liver cancer showed nearly the same data and efficacy as Nivolumab. In addition, there are many trials in the world about Pembrolizumabmonotherapy and combination therapy, and it is believed that the results will definitely bring new dawn to the treatment of liver cancer.

2.2. PDL-1 Inhibitor

Currently commonly used PDL-1 inhibitors are Avelumab, Durvalumab and Atezolizumab. At the 2017 American Society of Clinical Oncology meeting, a trial of Durvalumab was published [14]: Objective remission rate after 40 patients with advanced hepatocellular carcinoma who failed to receive Duvalumab (10 mg/kg) after treatment with sorafenib At 10%, the overall survival is 13.2 months. In the treatment of advanced liver cancer, Durvalumab showed better efficacy. Expect more clinical trials and data to better use PDL-1 inhibitors.

3. CTLA-4

Cytotoxic T lymphocyte-associated antigen-4 (CTLA-4), also known as CD152, is a leukocyte differentiation antigen and a transmembrane receptor on T cells. CTLA-4 is a key inhibitory receptor that affects T cell function, and is mainly expressed on the surface of activated CD4+ T cells, CD8+ T cells and Treg cells. CTLA-4 is involved in the negative regulation of T cell activation, inactivating T cells, and thus tumor cells survive and progress.

The mechanism of action of CTLA-4 antibody is as follows: T cells require two signaling pathways to be simultaneously activated, and antigen presenting cells provide B7 and MHC ligands, which bind to CD28 and TCR on the surface of T cells, respectively, and T cells are activated, thereby killing tumors cell. When T cells are over-activated, T cells express CTLA-4 protein themselves, CTLA-4 competes with CD28 for binding to B7, and CTLA-4 binds to B7, which blocks CD28-B7 signaling pathway, thereby inactivating T cells. The cells survive. Tumor cells use this negative regulation feature to induce T cells to express a large amount of CTLA-4, compete with CD28, and reduce T cell activity, so that tumor cells escape the immune system attack. CTLA-4 antibody can bind to CTLA-4 expressed by T cells, so that CD28 can re-engage with B7, the signal pathway is restarted, T cells can be reactivated, the immunosuppressive microenvironment is broken, and the body's immunity to tumor cells is improved.

The CTLA-4 antibodies currently approved for the treatment of tumors on the market are mainly Tremelimumab and Ipilimumab. Tremelimumab is a human IgG2 monoclonal antibody that blocks CTLA-4. A small sample of viral-related liver cancer patients showed clinical trials using Tremelimumabmonotherapy with a partial response rate of 17.6%, a disease control rate of 76.4%, and a tumor progression time of 6.48 months. The study also found a significant reduction in hepatitis viral load in patients treated with Tremelimumab [15]. This suggests that Tremelimumab may have better antiviral and antitumor effects and requires a larger sample of clinical trials to further confirm its efficacy and safety. Compared with monotherapy, studies have shown that combination therapy, such as radiofrequency ablation or TACE, may benefit more [16]. Clinical trials of Nivolumab + Ipilimumab in combination with liver cancer are also underway.

4. Combination of PD-1 Inhibitor and CTLA-4 Inhibitor

Clinical trials of PD-1 inhibitors combined with CTLA-4 inhibitors for advanced liver cancer are in progress. A trial of advanced melanoma showed that the combination of Nivolumab + Ipilimumab has a higher objective response rate and higher progression-free survival than monotherapy, indicating that the combination therapy may have a more complete therapeutic effect [17].

5. Immunological Checkpoint Inhibitors Combined with Traditional Treatment Methods

Immunological examination inhibitors are combined with existing traditional treatment methods, including radiofrequency ablation, transcatheter arterial chemoembolization, surgical resection, radiation therapy, and molecular targeted therapy. By combining the immunosuppressive microenvironment that destroys tumor cell survival, inducing local inflammation and releasing new antigens to activate the immune system and improve the efficacy of immunotherapy, there may be better and faster results. Studies have used CTLA-4 antibody

as a follow-up adjuvant therapy in patients with advanced liver cancer after TACE or radiofrequency ablation, prolonging patient survival [18]. This combination also increases the number of CD 3+ and CD 8+ cells in untreated lesions. These findings demonstrate that immunological checkpoint inhibitors can be combined with hepatic artery embolization chemotherapy or as an adjuvant therapy after surgical resection or radiofrequency ablation. A clinical trial of a combination of rivastatinib and Pembrolizumab in the treatment of liver cancer showed a higher rate of tumor remission [19]. In 2017, the American Society of Clinical Oncology (ASCO) reported that this combination therapy has a 50% - 70% response rate and a lasting drug effect in the treatment of solid tumors [20]. Therefore, traditional topical therapy combined with immunosuppressive agents such as PD-1, PDL-1 and CTLA-4 may be superior to traditional treatment, which requires a large number of clinical trials to further verify.

6. Conclusion

Liver cancer is a highly immunosuppressive disease. Traditional treatment methods have a high recurrence rate and cannot achieve satisfactory benefits. The emergence of immunotherapy has brought a new perspective to the treatment of liver cancer. In response to the immunosuppressive microenvironment of liver cancer, immunological checkpoint inhibitors reactivate the patient's own immune activity, destroy the immunosuppressive microenvironment, improve the patient's anti-tumor ability, and even completely eliminate tumor cells. PD-1/PDL-1 inhibitors and CTLA-4 inhibitors have achieved good results in most clinical trials. Patients have longer survival and reduced treatment-related adverse reactions, but immunotherapy for liver cancer still needs a multicenter, large sample clinical trial to confirm its effectiveness and safety. The immune mechanism needs to be further clarified. Immunological checkpoint inhibitors also require our further exploration and development, and drug-related adverse reactions also require clinical trials to validate and evaluate. The safety and efficacy of immunological checkpoint inhibitors in combination with other therapies need to be further explored. At present, the treatment of liver cancer is still based on traditional treatment. The combination of immunological checkpoint inhibitors and traditional treatment may completely cure liver cancer, which in turn will change the treatment of liver cancer. Immunotherapy has shown unparalleled therapeutic prospects and is expected to cure liver cancer in the future, thus becoming the first-line treatment for liver cancer treatment.

Conflicts of Interest

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

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Abbreviation Note List

HCC	hepatocarcinoma
PD-1	programmed death-1
PDL-1	programmed cell death 1 ligand 1
PDL-2	programmed cell death 1 ligand 2
CTLA-4	cytotoxic T lymphocyte-associated antigen-4
TACE	transcatheter arterial chemoembolization
CD279	cluster of differentiation 279
CD274	cluster of differentiation 274
CD273	cluster of differentiation 273
CD152	cluster of differentiation 152
CD28	cluster of differentiation 28
B7	costimulatory molecule B7
B7-H1	B7 homolog 1
B7-H2	B7 homolog 2
DC	dendritic cells
MHC	major histocompatibility complex

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Value of Thromboelastography in Judging Abnormal Coagulation Function in Patients with Early Hemorrhagic Shock

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Abstract

Objective: To detect the changes of coagulation function in patients with early hemorrhagic shock by thromboelastography (TEG). **Methods:** TEG was performed in 50 patients with early hemorrhagic shock and surgical indications. The TEG parameters were compared with 50 healthy people. The coagulation and fibrinolysis in patients with early hemorrhagic shock were observed. **Results:** In terms of coagulation parameters, the R value decreased, the α angle increased, and the K value and MA value did not change significantly in patients with early hemorrhagic shock. Fibrinolytic aspects: EPL, LY30 observations have no significant changes compared to normal values. **Conclusion:** The plasma coagulation factor activity is increased in patients with early hemorrhagic shock; the fibrin level is increased; the blood is in a hypercoagulable state; and the fibrinolysis function is not changed. The timely detection of TEG can be used for coagulation function monitoring and blood transfusion therapy in patients with surgical hemorrhagic shock. It provides an important basis for preventing the formation of deep vein thrombosis.

Keywords

Thromboelastography, Early Hemorrhagic Shock, Coagulation Function, Fibrinolytic System, Deep Venous Thrombosis

1. Introduction

Hemorrhagic shock and coagulopathy caused by various causes during surgical perioperative period are serious threats to patients' life safety. Hemorrhagic shock is a common emergency in surgery. When the effective blood volume of the body is drastically reduced, the coagulation function and blood state will change accordingly. Studies have shown that patients with traumatic dysfunc-

tion cause a mortality rate of 25% to 40% when admitted to hospital [1]. At present, clinically routine coagulation parameters such as prothrombin time (PT) and activated partial thrombin time (APTT) can only detect the activity and function of blood coagulation factors in the absence of platelets, reflecting a certain stage of the coagulation process or some kind of blood coagulation product [2]. The thromboelastograph is an analyzer that monitors the coagulation process from the entire dynamic process of platelet aggregation, coagulation, fibrinolysis, etc. It was invented by the German Harter in 1948. The principle is based on the final result of the blood coagulation process to form a blood clot, and the physical characteristics of the blood clot (blood clot strength and stability) determine whether it has normal coagulation function. The thromboelastogram (TEG) is a graphical display of the complete process of coagulation initiation to clot formation and fibrinolysis. Compared with conventional detection methods, TEG is faster and more accurate. In this paper, TEG detection is used to determine the perioperative coagulation function and fibrinolysis status in patients with early hemorrhagic shock, which provides an important basis for blood transfusion therapy and prevention of deep vein thrombosis in patients with hemorrhagic shock.

2. Subjects and Methods

2.1. Object and Grouping

Control group: 50 people with normal physical examination and normal coagulation function, 27 males and 23 females; experimental group: 50 patients with hemorrhagic shock treated in The Central Hospital of Xiaogan from December 2016 to November 2018, all undergoing surgical treatment (10 cases of chest trauma, 11 cases of abdominal trauma, 2 cases of chest and abdomen combined injury, 3 cases of open head injury, 5 cases of multiple body injuries, 19 cases of open fracture and pelvic fracture), including 34 males and 16 females. Sixteen patients, aged 6 to 74 years, with a median of 56 years, did not take antiplatelet drugs in all cases. Exclusion criteria: 1) history of primary thrombocytopenia; 2) history of blood; 3) less blood loss (less than 800 ml), less trauma, failure to meet early hemorrhagic shock criteria; 4) lungs Disease, hemolysis, and heart failure. The diagnostic criteria for early hemorrhagic shock are: 1) There is a cause of shock. 2) Pulse fine speed, more than 100 times/minute. 3) Systolic blood pressure is lower than 90 mmHg, or pulse pressure difference is less than 20 mmHg. 4) Within 6 hours after trauma. 5) Blood loss is not less than 800 ml. This research was approved by the Medical Ethics Committee of our hospital. All patients signed an informed consent form.

2.2. Test Methods

All patients considering early hemorrhagic shock were tested for TEG within 6 hours after trauma and within half an hour after admission, and 50 patients with healthy controls were tested for TEG.

2.2.1. Coagulation Function Parameter

1) R value: The time required for coagulation to form the first obvious thrombus, usually 4 to 9 minutes, mainly reflecting the interaction between all relevant coagulation factors involved in the coagulation process; application of anticoagulant or lack of coagulation factor. When the value of R is prolonged, the value of R is shortened when the blood is hypercoagulable [3]. 2) K value: The time from the first obvious thrombus formation to the time when the blood clot reaches a certain level (MA amplitude 20 mm), the reference range is 1 - 3 min, which mainly reflects the action of fibrinogen; 3) α angle: refers to from R The point is the maximum tangent of the arc and forms an angle with the horizontal line, reflecting the rate of blood clot formation from the thrombus, the normal range is 53˚ - 72˚; 4) MA value: the maximum intensity of thrombus, mainly reflecting platelets and fibrin The function, the normal range is 50 - 70 mm.

2.2.2. Fibrinolysis Function Parameter

1) EPL: predict the percentage of blood clots to be dissolved within 30 min after the MA value is determined, the normal range is 0% - 15%; 2) LY30: MA determines the degree of blood clot dissolution after 30 min, reflecting the fibrinolysis; the normal range is 0% - 8.0%.

2.3. Assess the Risk of Venous Thrombosis after Surgery

Evaluation sheet of risk factors for deep venous thrombosis of lower limbs was used to assess the risk of thrombogenesis after surgery. The higher the score, the greater the risk of thrombosis.

2.4. Statistical Methods

The control group and the experimental group were tested for TEG parameters. The measurement data were expressed as mean ± standard deviation. Two independent samples were performed using SPSS 17.0 statistical software package. $P < 0.05$ was considered statistically significant.

3. Results

1) In terms of coagulation parameters, the R value decreased and the α angle increased in patients with early hemorrhagic shock. The difference was statistically significant. There was no significant change in K value and MA value, indicating that the patient's plasma coagulation factor activity increased, fibrin level increased, and blood was in a hypercoagulable state (**Table 1**).

2) In terms of fibrinolysis, the EPL and LY30 observations in patients with early hemorrhagic shock did not change significantly compared with the normal values, indicating that there was no abnormality in fibrinolytic function in patients with early hemorrhagic shock (**Table 2**).

3) Since the high risk of thrombosis after surgery, we use the Autar Form to assess the risk. It was invented by Autar, which was proved useful.

Table 1. Coagulation function parameter change (n = 50, $\bar{x}$ ± s).

	R (min)	K (min)	αangle (˚)	MA (mm)
Normal	5.34 ± 0.80	1.83 ± 0.45	64.59 ± 4.65	58.51 ± 4.06
shock	4.06 ± 1.13*	1.78 ± 1.07	69.07 ± 8.07*	59.91 ± 10.04

Table 2. Fibrinolysis function parameter change (n = 50, $\bar{x}$ ± s).

	EPL (%)	LY30 (%)
Normal	1.63 ± 2.84	0.70 ± 1.43
shock	1.18 ± 2.57	0.72 ± 1.92

Remark: Compared with the normal group, *P < 0.05.

4. Discussion

4.1. Coagulation Mechanism in Patients with Early Hemorrhagic Shock

The normal coagulation system includes the exogenous coagulation system and the endogenous coagulation system. The main role of the coagulation process in the initiation of coagulation is the exogenous coagulation system. When the wound causes acute hemorrhage, tissue factor release, activation of coagulation factor VII initiates the exogenous coagulation process, and activates FXI, FVIII, and FV through a small amount of thrombin generated after activation, and activates the endogenous coagulation system to produce a high concentration. Thrombin promotes fibrin formation through a series of cascades.

4.2. TEG

TEG can monitor the whole process of blood coagulation, synthesizes plasma components and cellular components, and considers the effects of quantity and function on blood clot formation [4]. Due to the value of TEG in the monitoring of coagulation function, it has been widely used in the monitoring of coagulation status during surgical perioperative period, to assess the coagulation function of critically ill or surgical patients, guide treatment and provide reference indicators. The coagulation function of patients with surgical hemorrhagic shock changes significantly. Early monitoring of coagulation status in patients with hemorrhagic shock has important reference value for surgical treatment and prevention of postoperative complications in patients with hemorrhagic shock.

4.3. Coagulation

4.3.1. R Value

The R-value thromboelastogram reflects the activity of the clotting factor. This study showed that the R value of patients with early hemorrhagic shock was lower than the normal value (the difference was significant), indicating that the clotting factor activity increased in patients with hemorrhagic shock, and the infusion in shock. In the treatment, blood volume should be supplemented quickly. If blood transfusion is needed, the concentrated red blood cells should

be infused. If the blood loss is large, infusion of plasma rich in blood coagulation factors should be considered. Studies have shown that if the R value is greater than 10 min, it indicates that the clotting factor is significantly reduced, and fresh frozen plasma (15 mL/kg) can be input [5].

4.3.2. K Value and Alpha Angle

K values were used to assess the rate at which the blood clot reached a certain intensity (20 mm amplitude), and the alpha angle was used to assess the rate of fibrin formation, and the two provided the same information, both affected by fibrinogen. The angle determines the rate at which blood clots form. This study showed that the angle of α in patients with early hemorrhagic shock was higher than the normal value (the difference was significant), and there was no significant difference in K value, indicating that fibrinogen increased and the formation rate of blood clot was accelerated in hemorrhagic shock, suggesting that suggesting that after relieving the cause of bleeding, low molecular weight heparin anticoagulant therapy can be applied.

4.3.3. MA

MA was used to assess the intensity of blood clots. Due to platelet count and function, MA value was associated with platelet action, and elevated MA value suggested that blood was hypercoagulable [6]. Studies have shown that the MA value and the probability of thrombosis have higher sensitivity and specificity, the MA value increases, and the probability of thrombosis increases significantly [7]. Another study found that trauma patients with MA > 65 mm, the chance of pulmonary embolism is 3.5 times that of other patients, can guide the prevention of anticoagulant therapy [8]. This study showed that the MA value of patients with early hemorrhagic shock increased slightly (the difference was not significant), reflecting that there was no significant difference in overall platelet function before and after early hemorrhagic shock, suggesting that patients with early hemorrhagic shock do not need to transfuse platelets.

4.4. Fibrinolytic Function

The regulation of the fibrinolytic system and the coagulation system does not result in the formation of effective hemostasis due to hyperfibrinolysis, and also avoids excessively low fibrinolysis, thereby forming excessive and excessive thrombus and causing unnecessary blood vessel embolism. This study showed that EPL in patients with early hemorrhagic shock was lower than normal, and LY30 was slightly higher than normal, indicating that patients with early hemorrhagic shock had mild hyperfibrino function, but the difference was not statistically significant.

4.5. Risk Factors for Deep Venous Thrombosis of Lower Extremities

The risk assessment form for deep vein thrombosis developed by Autar is applicable to all bedridden patients [9]. Most patients with surgical hemorrhagic

shock were mainly bedridden in the early postoperative period. The risk factors for lower extremity deep venous thrombosis were scored in 50 patients with hemorrhagic shock. ≤10 points is divided into low-risk, 11 - 14 points is classified as medium-risk, and ≥15 points is classified as high-risk, including 4 low-risk patients, 5 intermediate-risk patients, and 41 high-risk patients. It indicates that patients with surgical hemorrhagic shock have high risk factors of deep venous thrombosis of lower extremity in the early postoperative period, and the risk of deep vein thrombosis is increased. On the one hand, due to limited mobility of patients after trauma, they are in bed for a long time, and the venous return flow is slow. In particular, patients with lower extremity surgery; on the other hand, through the changes in the R and α angles of the thromboelastogram, the blood is in a hypercoagulable state, the rate of formation of blood clots increases, and the risk of venous thrombosis increases. Studies have shown that the hypercoagulable state of TEG is associated with deep vein thrombosis in patients with trauma [10], so TEG provides a basis for early prevention of deep vein thrombosis in patients with surgical hemorrhagic shock.

In summary, patients with early hemorrhagic shock have a significant change in blood status and coagulation function compared with normal body due to the rapid loss of blood volume, activation of the coagulation system. In addition, the traumatic blood loss itself causes the loss of coagulation factors, coupled with the compensatory transfer of body fluids, and the subsequent active rehydration causes the dilution of coagulation factors, eventually leading to coagulation disorders [11]. The traditional coagulation function test index only reflects one aspect of coagulation function, cannot monitor the function of platelet and fibrinogen, evaluate the true state of coagulation, or clarify the real-time coagulation level to predict the potential bleeding and thrombosis risk [12]. TEG can reflect the whole process of blood clot formation to dissolution, namely the speed, final strength and stability of blood clot formation, and dynamically reflect the fibrinolysis process, which can help us visually and accurately determine the blood coagulation of patients with hemorrhagic shock. Fibrinolysis function changes [13]. TEG quickly adjusts the coagulation function, which in turn prompts the patient to inject blood component treatment, thus effectively adjusting the patient's coagulation function [14]. At the same time, it can accurately analyze the factors of coagulopathy in hospitalized patients, which is beneficial to reduce the use of clinical blood products and avoid blind blood transfusion [15]. Through the analysis of TEG, we can see that the R value of patients with early hemorrhage is lower than normal, and the angle of α is higher than normal, indicating that the activity of coagulation factor is increased, the fibrinogen is elevated, and the formation of blood clot is formed in patients with early hemorrhagic shock. The rate is accelerated, the blood is in a hypercoagulable state, and the blood volume should be actively supplemented, and the cause of shock should be relieved by surgery in time. For patients with shock who need blood transfusion, infusion of homologous red blood cells should be preferred because plasma is rich in clotting factors, and at this time, patients have higher clotting factor ac-

tivity. Infusion of plasma will aggravate the patient's hypercoagulable state, and if necessary, infusion of plasma and Cold precipitation, etc. Due to increased clotting factor activity, increased fibrinogen, and hypercoagulable state in patients with hemorrhagic shock, the risk of deep venous thrombosis in the lower extremities increases. Especially for patients after orthopedic surgery, long-term bed rest also increases the risk of venous thrombosis. The thromboelastogram can be treated with different anticoagulant treatment according to the change of index, thus further reducing the probability of deep venous thrombosis after orthopedic surgery [16]. Clinical studies have shown that actively improving blood hypercoagulability after surgery can effectively prevent the occurrence of deep venous thrombosis of lower extremities, and the use of low molecular weight heparin anticoagulation has no clinical significance [17]. Therefore, after the operation to relieve the cause of hemorrhagic shock, preventive measures should be taken early in the postoperative period, and if necessary, anticoagulation with low molecular weight heparin should be used to reduce the risk of postoperative deep vein thrombosis. The thromboelastogram has its advantages in judging abnormal coagulation function in patients with hemorrhagic shock, but it also has limitations, and cannot completely replace the traditional coagulation function detection method. First of all, TEG is an in vitro testing program, so the detection environment is still different from the actual environment of the organism. Second, TEG detects the body's overall coagulation function, but sometimes it cannot be used to distinguish abnormalities in a certain coagulation process. Third, there is currently no standardized operation and evaluation guideline. The quality control of TEG is not ideal. So the combination of the two is more conducive to hemorrhagic shock and other critically ill patients.

Conflicts of Interest

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

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Oral Health Status and Gingival Response to Three Different Restorative Materials among Saudi Patients: A Clinical & Histopathological Study

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Abstract

Background: The correlation between oral health and dental restoration is fundamental. For the gingival and periodontal tissues to stay healthy, dental restoration should be in regularity with the surrounding tissues. This study aims to assess the oral health status and histopathological gingival response to three different restorative materials among Saudi patients. **Methods:** The study groups consist of 240 patients (50% males and 50% females), aged 18 - 45, with inclusion and exclusion criteria in the study. Participants are divided into three equal groups: those with composite resin restorations, those with amalgam restorations and those with glass ionomer restorations. Biopsies were taken from adjacent gingival tissues. Clinical parameters were determined by: plaque index (PLI), gingival index (GI) and clinical attachment loss (CAL). All data were collected and evaluated by through statistical analysis. **Results:** The clinical findings of the current study revealed that amalgam restorations produce a higher means of PLI, GI and CAL compared with composite resin restorations and glass ionomer restorations, but not insignificant levels, except CAL ($p = 0.004^*$). As for histopathological findings, there were significant differences in gingival tissue response to amalgam restorations, composite resin restorations and glass ionomer cement fillings, where there were statistically significant differences in numbers of chronic inflammatory cells ($p < 0.001$). **Conclusion:** At the end of the present study, we concluded that the amalgam restorations are less biocompatible compared to composite resin restorations and glass ionomer restorations.

Keywords

Gingival Response, Histopathological Study, Oral Health Status

1. Introduction

Gingival health and its maintenance are essential conditions for oral health. According to several studies conducted on human, there were unwanted gingival response and attachment loss adjacent to some dental restorations [1] [2] [3]. Consequently, the margins of dental restorations should be a fit correlation with adjacent gingival tissues, because the open margins and rough dental restorations facilitate plaque accumulation and development of gingival and periodontal diseases [4].

Nevertheless, some clinical and histological researches indicate that the extension of sub-gingival dental restoration may cause unwanted tissue impacts, even in good plaque controlled patients [5] [6]. Therefore, it's important to state that the mechanical and physical characteristics are considered to be a basic condition for dental restoration materials, quality assessment, in addition to gingival tissues biological response [7]. With regard to the biological assessment, the dental restorative materials that aren't triggering destructive responses in the adjacent gingival tissues are acceptable materials [8].

Biologically, composite resin fillings comprise reactive chemicals liberated into the oral and gingival tissues, and are more toxic through and promptly after 24 h of polymerization [9]. However, the effect of composite filling on gingival tissue per se may be not destructive effect and the adhesive characteristics of bacterial plaque may have more impact, according to the studies of Larato (1972), Dunkin & Chambers (1983) where they found gingivitis adjacent to composite resin restorations and the adjacent gingival tissue of non-restored teeth was not inflamed [10] [11]. Furthermore, many previous studies displayed that the accumulation of bacterial plaque on composite resin restorations is more than polished amalgam restorations [12] [13] [14].

Dental amalgam restoration is composed of mercury, silver, tin and copper with other metallic elements to improve mechanical and physical characteristics [15]. Lorscheider and his coworkers (1995) indicated that the main source of mercury in humans was the dental amalgam restoration. They have showed that this evidence doesn't confirm the toxicity of dental amalgam due to mercury [16].

Glass-ionomer restorations are a type of dental materials recognized as an acid-base dental filling depending on the reaction of polymeric acids with powdered glasses [17]. Biocompatibility of traditional glass ionomer restorations is acceptable [18]. There were many studies conducted on cultured cells which displayed that the light activated glass ionomer restorations had poor biocompatibility and greater cytotoxicity than the traditional glass ionomer restorations

[19]. To assess the biocompatibility of dental restoration materials, a series of tests must be done, including *in-vitro* examinations for their cytotoxicity in the adjacent gingival tissues [20]. In fact, there is restricted data on the clinical and histopathological gingival response and oral health status among Saudi patients being treated with three different restorative materials. So, the current study was designed.

2. Subjects & Methods

This prospective clinical study carried out on 240 patients (50% males and 50% females), aged 18 - 45. The patients are selected from the outpatient clinics of Periodontics and Community Dental Sciences Department (PCS), College of Dentistry, King Khalid University from August 2017 - February 2018. All the patients in the present study were in a good oral health and under the maintenance phase of periodontal therapy. Furthermore, they were without any systemic diseases and did not receive any antibiotics since six months.

The study was explained to the patients and a written consent, according to the applied protocol of the Scientific Research Committee, College of Dentistry, King Khalid University, was obtained. All participants filled the systemic and oral status form.

The inclusion criteria of the patient selection was based on evaluating the gingival tissues adjacent to three dental restorations, macrofilled filler composite resin restorations, amalgam restorations and glass ionomer restorations that were done dental restorative specialists before three months. These restorations extended into sub-gingival areas (class II & class V fillings) and needed correction after surgical crown lengthening by gingivectomy to obtain the specific histological samples from the adjacent gingival tissues of dental restorations (**Figure 1**).

Accordingly, the patients in the current study were divided into three equal groups (n = 80), group (I) included 430 restored teeth with composite resin restorations and group (II) included 410 restored teeth with amalgam restorations and group (III) included 420 restored teeth with glass ionomer restorations.

The clinical examination of dental restorations carried out by observation and the use of the explorer to assess the surface and margins of dental restorations in addition to using William's periodontal probe to evaluate periodontal clinical parameters. The periodontal parameters included plaque index (PLI, 0 - 3) [21], gingival index (GI, 0 - 3) [22] and clinical attachment loss (CAL).

The gingival biopsies 3 mm(from the dental restorations adjacent gingival margin)were taken under local anesthesia by sharp dissections (Bard-Parker blades no. 15) and they were put into 50% formoalcohol bottles (50 ml alcohol and 50 ml 10% formalin) for fixation into 24 hours (Histowax, Histolab, Gotenborg, Sweden) (**Figure 2**).

Samples were sent to the histopathological lab and the investigations were done after preparation of slides by the standard histological technique with hematoxylin and eosin stains (model 6062, SLEE, Mainz, Germany).

Figure 1. Clinical photograph of restorations extended into sub-gingival areas on #25, 26 & 27.

Figure 2. Clinical surgical crown lengthening for restorative purposes #14 & #15.

The histopathological investigation of all samples was conducted by a bifocal light microscope (Olympus B × 51, Olympus Corp, Tokyo, Japan) at X200 original magnification to evaluate gingival tissue reaction. The inflammatory response of gingival tissues, adjacent to dental restoration materials, was evaluated quantitatively under the microscope. The number of chronic inflammatory cells recorded as follows: no inflammation (no or few inflammatory cells); 1) mild inflammation (25 inflammatory cells). 2) moderate inflammation (increased reaction zone, 25 - 125 inflammatory cells). 3) severe inflammation (focal areas of necrosis, 125 inflammatory cells) [23].

The data were collected and assessed with statistical analysis by SPSS (SPSS Inc., Chicago, IL, USA) 21.0 statistical software. The results revealed by the assessment of mean ± standard deviation (SD) and there were statistically significant differences in clinical findings of the current study ($p < 0.05$).

3. Results

Two hundred and forty patients have completed this study without any compli-

cations related to the surgical procedures during crown lengthening to obtain the histological samples. The age and distribution of patients in the present study summarized in Table 1 and Figure 3 where 32% of patients included in group I and 35% in group II, moreover 33% in group III while the mean age and standard deviation of the group I, II and III were 29 ± 1.36, 31 ± 1.14 and 30 ± 1.52 respectively. Table 2, Figure 4 and Figure 5 reveal the clinical findings and number of chronic inflammatory cells of the present study where the mean of PLI, GI, and CAL of group II is the highest compared to group I and III. Moreover, the mean of chronic inflammatory cells number of group II is the highest compared to group I and III. That may be due to the roughness of amalgam restorations surfaces which facilitate bacterial plaque accumulation. Furthermore, in Table 2 and Figure 4 the mean of PLI, GI and CAL of group I is more than the mean of PLI, GI, and CAL of group III that may be attributed to the reaction of adjacent gingival tissues to composite resin restorations or deficiency in polishing of composite resin restorations particularly in the cervical and interproximal areas. Consequently, there were significant differences in all clinical parameters but without statistical significance differences except CAL where there were statistically significant differences in CAL in the comparison between the groups of this study ($p < 0.05$).

In the histopathological study of biopsy specimens of the present study, there were differences found in the comparison between groups I, II and III. The microscopic examination of biopsies revealed inflammatory response consisting of mild to moderate chronic inflammatory cell infiltration and mild to moderate dilated blood vessels in group I. Furthermore, moderate chronic inflammatory

Table 1. The mean and distribution of age.

Groups	Rang of age	Mean and ±(SD)*	
I	19 - 35	29 ± 1.36	
II	18 - 45	31 ± 1.14	0.453††
II	19 - 41	30 ± 1.52	

SD: Standard deviation. ††No statistically significant differences ($p > 0.05$).

Table 2. Mean and standard deviation (±SD) of the results findings.

	Clinical findings			Histopathological findings	
Groups	PLI**	GI***	CAL****	Number of chronic inflammatory cells	Inflammatory response score
I	1.4 ± 0.55	1.7 ± 0.7	2.3 ± 0.91	26.66 ± 4.26	2
II	1.6 ± 0.71	1.9 ± 0.62	2.9 ± 1.1	38.84 ± 2.65	2
III	1.3 ± 0.48	1.6 ± 0.67	2.1 ± 0.81	14.58 ± 1.2	1
P. Value	0.14	0.21	0.004‡	$p \leq 0.001$‡	-

**Plaque index; ***Gingival index; ****Clinical attachment loss. ‡statistically significant differences ($p < 0.05$).

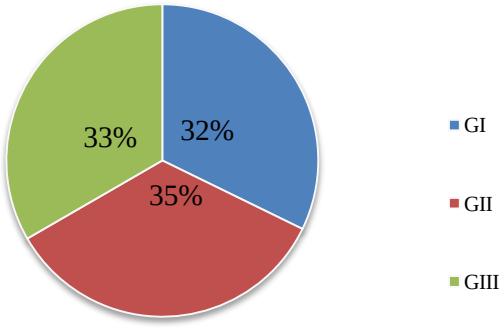

Figure 3. The mean and distribution of age.

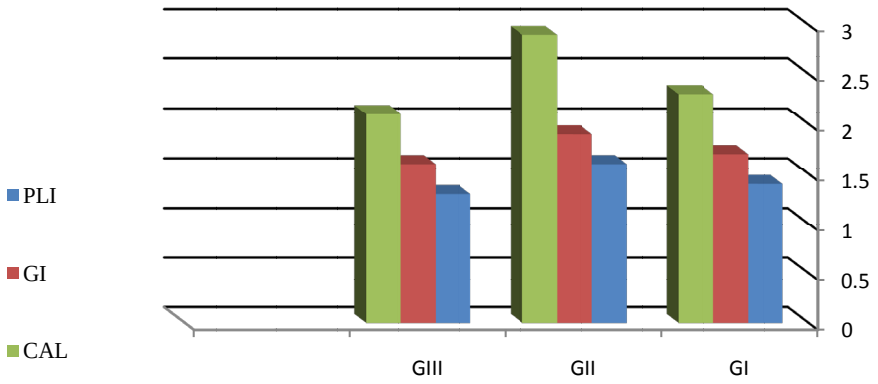

Figure 4. Clinical findings.

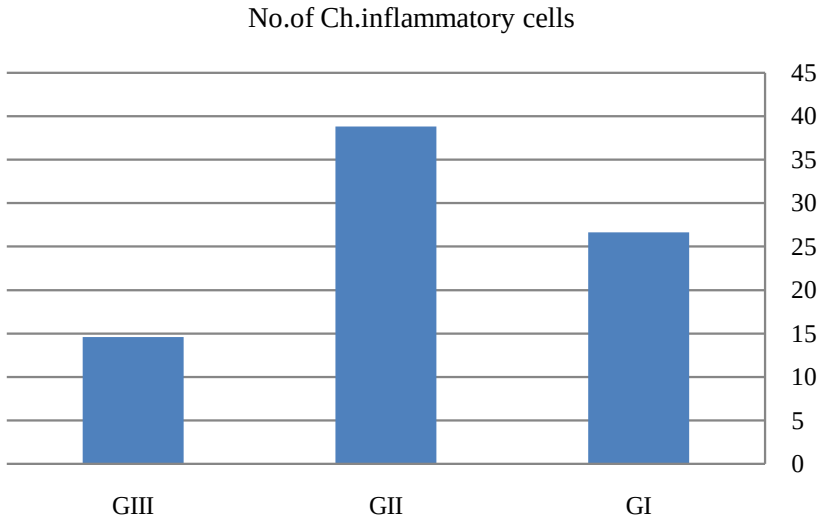

Figure 5. Inflammatory response assessment.

cell infiltration and moderate dilated blood vessels in group II, while it was normal to mild chronic inflammatory cell infiltration and mild dilated blood vessels in group III.

Generally, there were minor pathological changes in the adjacent gingival tissues of dental restorations. These pathological changes were mild to moderate in the samples of group I and moderate in group II, while these changes were nor-

mal to mild in group III.

Most of the biopsies of group I displayed mild to moderate epithelial hyperplasia and mild to moderate acanthotic change and mild to moderate inflammatory epithelial hyperplasia. Furthermore, moderate epithelial hyperplasia, moderate acanthotic changed and moderate inflammatory epithelial hyperplasia in group II, while these changes were normal to mild epithelial hyperplasia, normal to mild acanthotic changed and normal to mild inflammatory epithelial hyperplasia in group III (Figures 6-8).

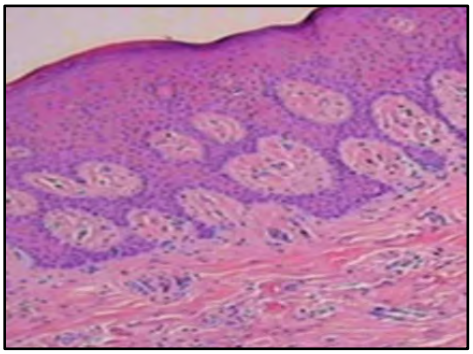

Figure 6. The biopsy of gingival adjacent of composite resin restoration displayed (stratified squamous epithelium with moderate chronic inflammatory cells.

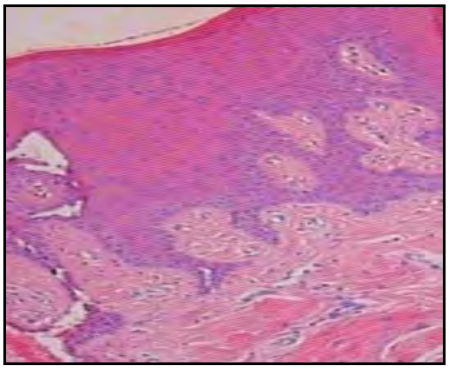

Figure 7. The biopsy of gingival adjacent of amalgam restoration displayed hyperplastic stratified squamous epithelium and chronic inflammatory cells.

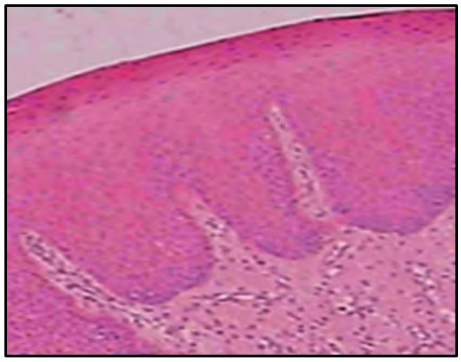

Figure 8. The biopsy of gingival adjacent of glass ionomer restoration displayed normal gingival tissue showing long rete pegs and mild chronic inflammatory cells.

4. Discussion

The potentially harmful impact of dental restorative materials on the gingival tissues has been the object of various clinical and histological studies [24]. According to (Leyhausen, 1998) study, there are possible impacts of dental restorative materials on oral and gingival tissues in different methods, particularly by the releasing water-soluble elements in saliva and by direct reaction with periodontal tissues [25]. Consequently, there are criteria for the selection of dental restoration materials for use in humans. It includes evaluation of four points as: the experimental evaluation, the assessment of their local reaction, the identification of the possible clinical hazard to save the patients and evaluation of the systemic side effects [26].

In Saudi Arabia, there are few studies conducted for assessment of the clinical and histopathological effects of dental restorative filling materials on the adjacent gingival tissues and oral health. This study is from the recent studies in Saudi Arabia that included the comparison between the effects of three dental restorative material fillings on gingival tissues and oral health. Within the last 20 years, composite resin restorations and glass ionomer restorations have been considered as restorative materials to the achievement of esthetic objectives in dental restoration procedures [27]. According to the data of earlier epidemiological studies, there were adverse effects of inadequate dental restorations such as margins shortage and rough surface on gingival tissues as a result of an increase of plaque retention and accumulation, where they found that the more severity of gingival disease in the areas of plaque formation and mechanical irritation [28] [29].

In the present study, primary examination positively displayed inflammation in gingival tissues adjacent to composite resin restorations, amalgam restorations and glass ionomer restorations may refer to the presence of some characteristics of these three dental restorative materials that are responsible for harmful effects on the gingival health status, due to their ability to keep of plaque consequently hinder plaque control.

It should be noted, and according to the studies of App (1961) and Trott & Sherkat (1964), there were significant differences in PLI, GI and CAL, in the comparison between group (I), which included control group and group (II) patients who are treated by amalgam dental restorations where PLI, GI and CAL were more in group (II) than group (I) [30] [31].

In the study of van Dijken JWV and Sjostrom S (1991), they have compared between one-year-old Class V, composite resin restorations, glass ionomer restorations and enamel surfaces. There was an increase in the degree of gingivitis adjacent to the resin composite resin restorations more than glass ionomer restorations and enamel surfaces without statistical significant differences, corresponding to the results of the present study [32]. Furthermore, correspond with the results of an earlier study which revealed that the fluoride-containing and leaching materials of glass ionomer restorations have inhibitory effects on the

growth of oral microorganisms [33].

Many of earlier researches agree with the clinical findings of the current study like the studies of Peumans *et al.* (1998) [34] and Paolantonio *et al.* (2004) [35], where they found the adverse effects of composite resin restorations on oral health and an increase in these adverse effects in amalgam restorations due to the nature of their surfaces. In the present study, it's found that the oral hygiene status correlated with the degree of PLI being higher with moderate oral hygiene adjacent to amalgam and composite resin restorations compared to glass ionomer restorations.

As it's known, the products of bacterial induce the inflammatory reaction of gingival tissues and their immune response then clinical attachment loss and bone loss due to the destructive effects of microbial plaque [36]. That is a confirmation of the results of the present study where it's found an increase in PLI, GI and CAL adjacent of class II fillings of composite resin restorations, amalgam restorations, and glass ionomer restorations, but the increase of these clinical parameters were in the adjacent areas of amalgam restorations more than composite resin restorations and glass-ionomer restorations.

The histopathological examination of 3 months results showed that moderate inflammatory reactions appeared in the sub-epithelial tissues of group I and group II, while there was mild inflammation reaction in the sub-epithelial tissues of group III. The persistence of a chronic inflammatory response to the composite resin restorations of this study are attributed to the continued breakdown or release of irritant products from the restorations, is similar to the results of Geurtsen (1998) [37] study, where Geurtsen found that there were gingival inflammation in histopathological samples due to release different products from a composite resin within 24 hours after polymerization.

Although in the current study, necrosis was not revealed in the composite resin restorations group, inflammatory responses may be due to the cytotoxicity of the components of this material. This finding agrees with the results of Geurtsen (2000) [38]. According to an earlier study which was done to evaluate the effect of amalgam restorations on the epithelial tissue in the oral mucosa, there were severe inflammation and tissue necrosis that attributed to the release of silver amalgam and more than 70% Hg0 vapor in the first day of dental restoration [39] [40].

These results correspond to the results of this study where it was found there is an increase in the numbers of chronic inflammatory cells in samples of group II more than group I and group III. In the study of Ziff MF (1992) [41] [42], there was a correlation between dental amalgam and oral lichen planus among some cases as allergic reactions to mercury and after the removal of amalgam, there were an improvement and remission of the lesions. These histological findings are in agreement with the histological results of this study, where the biopsies of group II patients displayed epithelial hyperplasia, acanthotic changed and inflammatory epithelial hyperplasia.

Finally, most of the published researches of the biological effects, evaluation of

glass ionomer restorations, revealed that these dental restorative materials were lower in cytotoxicity compared to the other dental restorative materials [43]. These reports are in agreement with the results of the current study where the gingival samples of glass ionomer restorations had the lowest severity of inflammation and, there were inflammatory cells infiltration and edema formation.

5. Conclusion

Depending on the inflammatory responses of the adjacent gingiva and despite the limitations in the current study, the researchers conclude that clinical and histopathological findings of the dental restorative materials in the present study do not exactly reveal their deleterious effect on oral health and periodontal tissues, but they comprise a preliminary phase in the assessment of their irritant effects.

6. Strength and Limitations

To our knowledge, no study has been done on oral health status and gingival response to three different restorative materials among Saudi patients in Aseer region. The strength of this study includes revealing if there is a correlation between severity of periodontal diseases and type of dental restorative material or there is no correlation, which is considered the gold standard to evaluate the biocompatibility of these materials.

The present study had many limitations. First, although all patients were receiving oral hygiene instructions and professional plaque control during the first visit before the surgical procedures, most of them have not responded to our instructions. Consequently, that caused delays healing in some cases after the operation. Second, the difficulty of using the cytotoxicity testing and cells culturing for evaluating the biocompatibility of the dental restorative materials due to the clinical and histological study cannot produce evidence of any significant correlation between cytotoxicity of the dental restorative material and periodontal tissue destruction; however, the results of the present study support the possibility of a causal relation.

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Conflicts of Interest

There are no conflicts of interest.

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The Common Causes of Irritable Bowel Syndrome (IBS) in Northern Saudi Arabia

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Abstract

Background: Several psychological factors have been linked to the etiology of irritable bowel syndrome (IBS). The aim of the present study was to assess the burden of psychological factors (anxiety, depression, and working status) in the etiology of IBS in Northern Saudi Arabia. **Methodology:** Data regarding IBS were attained from 930 Saudi volunteers existing in the city of Hail, Northern Saudi Arabia. A purposeful questionnaire was developed and used to obtain the required data. Each questionnaire was completed by a medical student in the course of the interview. **Results:** IBS symptoms were recognized in 46% of the study population of whom 38% were males and 62% were females. The risk of anxiety as a risk for IBS was statistically significant. The relative risk and 95% confidence interval (95% CI) = RR (95% CI) = 1.4801 (1.2608 to 1.7376), $P < 0.0001$. The risk of emotional stress as a risk for IBS was statistically significant. The relative risk and 95% confidence interval (95% CI) = RR (95% CI) = 1.5337 (1.2918 to 1.8211), $P < 0.0001$. **Conclusion:** IBS and IBS related symptoms are prevalent in Northern Saudi Arabia. IBS symptoms are significantly associated with anxiety, depression and to a lesser extent may be linked to occupation and daily working hours.

Keywords

Irritable Bowel Syndrome, Anxiety, Depression, Emotional Stress, Working Hours, Saudi Arabia

1. Introduction

Irritable bowel syndrome (IBS) is a chronic disorder that can considerably decrease the quality of life and work efficiency [1]. IBS is a public medical complaint that significantly alters the patient quality of life and makes a series of diagnostic and treatment challenges [2]. IBS upsets 7% to 21% of the universal population. The prevalence of IBS fluctuates amongst nations, as well as criteria

used to describe its manifestation. Females are at somewhat greater risk for IBS than males [3]. In Saudi Arabia, studies conducted on medical students and interns in Jeddah reported a prevalence of IBS of 31.8% [4].

The diagnosis of IBS depends on the documentation of characteristic symptoms and the barring of other organic illnesses. Managing of patients with IBS is enhanced by a personalized, complete way that holds dietary, lifestyle, medical, and behavioral interventions [1]. Investigation regularity in patients with IBS is intensely connected to demographic and clinical characteristics, mainly comorbid conditions associated with IBS. The existence of shared overlapping comorbid conditions should upsurge clinicians' sureness in making the diagnosis of IBS, thus limiting redundant investigation and decreasing healthcare expenditures [5].

Psychological factors have been conspicuously involved in the causativeness as well as upkeep of IBS. The high prevalence of psychiatric comorbidities such as anxiety and depression in IBS delivers evidence in consideration of appropriate screening for these conditions in gastrointestinal clinics. Identification and treatment for these comorbidities can enhance the quality of life as well as whole consequences [6]. For patients with IBS, mental illness, mainly depression and/or anxiety, leads to an additional subordinate quality of life [7]. As several studies reported that IBS is associated with increased psychological distress and mental comorbidity, like major depressive disorder and generalized anxiety disorder [8], our aim in the present study was to assess the burden of psychological factors (anxiety, depression, and working periods) in the etiology of IBS in Northern Saudi Arabia.

2. Materials and Methods

In this community based cross-sectional survey, data about IBS were obtained from 930 Saudi volunteers living in the city of Hail, Northern Saudi Arabia. Participants were randomly selected by simple random regardless of age, gender, education level, occupation. Randomization was done separately for each gender (taking numbers of respondents as, 1, 3, 5, 7, etc.). About 1300 persons were recruited and 930 (71.5%) persons have responded.

Data were collected during the period from October 2018 to January 2019.

A purposeful questionnaire was designed and used for obtaining the necessary data. Each questionnaire was filled by a medical student during the interview. The following information was obtained from each participant: age, sex, and education level, anxiety, anxiety frequency, depression, depression frequency, emotional stress, and working hour*s.*

IBS symptoms were identified based on Rome III criteria.

2.1. Data Analysis

Statistical Package for Social Sciences (version 16) was used for analysis and to perform a Pearson Chi-square test for statistical significance (P value). The 95% confidence level and confidence intervals were used. A p value less than 0.05 was

considered statistically significant.

2.2. Ethical Consent

Each participant was asked to sign a written ethical consent during the questionnaire's interview. The informed ethical consent form was designed and approved by the ethical committee of the College of Medicine (University of Hail, Saudi Arabia) Research Board.

3. Results

The present study, involved 930 Saudi volunteers, their ages ranging from 18 to 78 years with a mean age of 34 ± 13.7 years. Out of 930 participants, 395/930 (42%) were males and 535/930 (58%) females. Greatest numbers of participants were found at the age groups 21 - 29 (n = 360), ≥50 (n = 157), and 40 - 49 years (n = 151). Males were predominantly seen at the age groups ≥50 (n = 115), 40 - 49 (n = 97) and 21-29 years (n = 92). Females were predominantly at 21 - 29 (n = 268), ≤20 (n = 108), and 30 - 39 years (n = 63), as indicated in Table 1, Figure 1.

The majority of the study population were found with university level of education (n = 523), and secondary education (n = 245), as shown in Table 1, Figure 1.

IBS symptoms were identified in 46% of the study population of whom (38%) were males and (62%) were females.

Anxiety was stated by 514 participants of whom 283 (55%) were found with IBS symptoms. The risk of anxiety as a risk for IBS was statistically significant. The relative risk and 95% confidence interval (95% CI) = RR (95% CI) = 1.4801 (1.2608 to 1.7376), P < 0.0001. Most patients experienced anxiety once daily 164/252 (65%) and the remaining 35% reported anxiety 2 to 3 times daily, as indicated in Table 2, Figure 2.

Table 1. Distribution of the study population by gender, age, and education.

Variable	Males	Females	Total
Age			
≤20 years	13	108	121
21 - 29	92	268	360
30 - 39	78	63	141
40 - 49	97	54	151
≥50	115	42	157
Total	395	535	930
Education			
Illiterate	33	27	60
Basic	27	38	65
Secondary	125	120	245
University	199	324	523
Post-university	11	26	37
Total	395	535	930

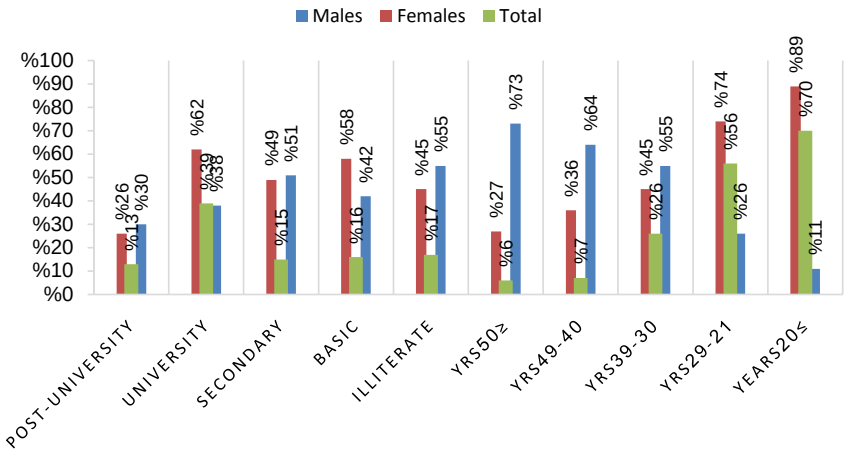

Figure 1. Description of the study population by gender, age, and education.

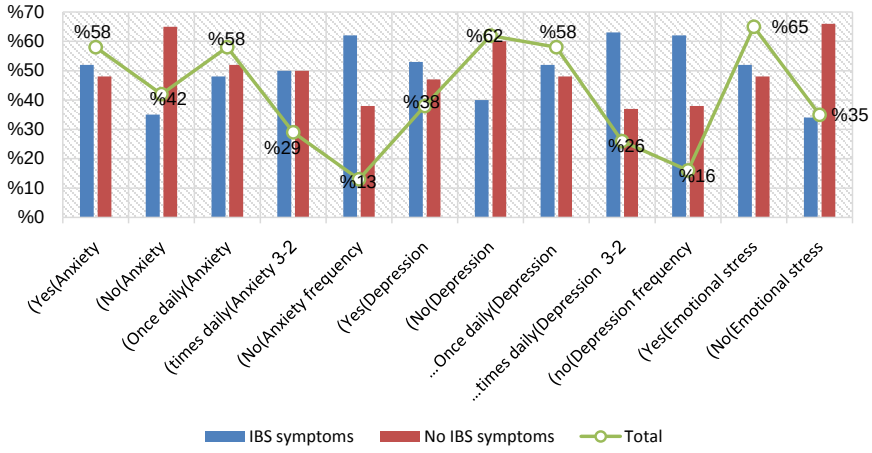

Figure 2. IBS symptoms by psychological causes.

Table 2. Distribution of the study population by IBS symptoms and psychological causes.

Variable	IBS symptoms	No IBS symptoms	Total
Anxiety			
Yes	283	258	541
No	129	236	365
Total	412	494	906
Anxiety frequency			
Once daily	164	159	343
2 - 3 times daily	88	86	174
No	48	29	77
Total	320	274	594
Depression			
Yes	177	160	337
No	223	329	552
Total	400	489	889

Continued

Depression frequency			
Once daily	116	115	223
2 - 3 times a day	62	37	99
no	39	24	63
Total	217	176	393
Emotional stress			
Yes	310	287	597
No	108	211	319
Total	418	498	916

Depression was indicated by 337 participants of whom 177 (52.5%) were found with IBS symptoms. The risk of depression as a risk for IBS was statistically significant. The RR (95% CI) = 1.3001 (1.1264 to 1.5006), P = 0.0003. Most patients experienced depression once daily 116/178 (65%) and the remaining 35% reported depression 2 to 3 times daily, as indicated in Table 2, Figure 2.

Emotional stress was stated by 597 participants of whom 310 (52%) were found with IBS symptoms. The risk of emotional stress as a risk for IBS was statistically significant. The relative risk and 95% confidence interval (95% CI) = RR (95% CI) = 1.5337 (1.2918 to 1.8211), P < 0.0001, as indicated in Table 2, Figure 2.

IBS symptoms were identified in 96/167 (57.5%), 45/81 (55.6%), 94/261 (36%), 144/328 (44%), 21/36 (58.3%) and 17/41 (41.5%) of the jobless, employers, self-employed, governmental jobs, students, and business, respectively, as indicated in Table 3, Figure 3.

With regard to the working hours, the majority of IBS symptoms were encountered among those working 6 - 8 hours/day followed by 4 - 6 hours, constituting 353/728 (48.5%) and 212/728 (29%), in this order. However, within the entire working hour's groups, the proportions of IBS increased with increasing of working hours, but it didn't show any statistically significant differences, as shown in Table 3, Figure 3.

4. Discussion

The burden of IBS is increasing in Saudi Arabia amongst different population settings, which might be associated with daily life tension. The prevalence of anxiety and depression and other psychological factors represent major IBS predictors in line with socioeconomic characteristics of the Saudi community.

The present study highlighted the roles of anxiety, depression, working hours, and occupation in the etiology of IBS. The study included diverse population settings in term of age, sex, education, and occupation. IBS symptoms were identified in 46% of the study population of whom (38%) were males and (62%) were females. Several published data indicated that IBS is a significant problem

Table 3. Distribution of the study population by IBS symptoms, occupation and working hours.

Variable	IBS symptoms	No IBS symptoms	Total
Occupation			
Jobless	96	71	167
Employer	45	36	81
Self-employed	94	167	261
Governmental jobs	144	184	328
Students	21	15	36
Business	17	24	41
Total	417	497	914
Working hours			
<4 hours/day	40	35	75
4 - 6	115	97	212
6 - 8	114	239	353
8 - 10	32	32	64
>10 hours	10	11	24
Total	311	414	728

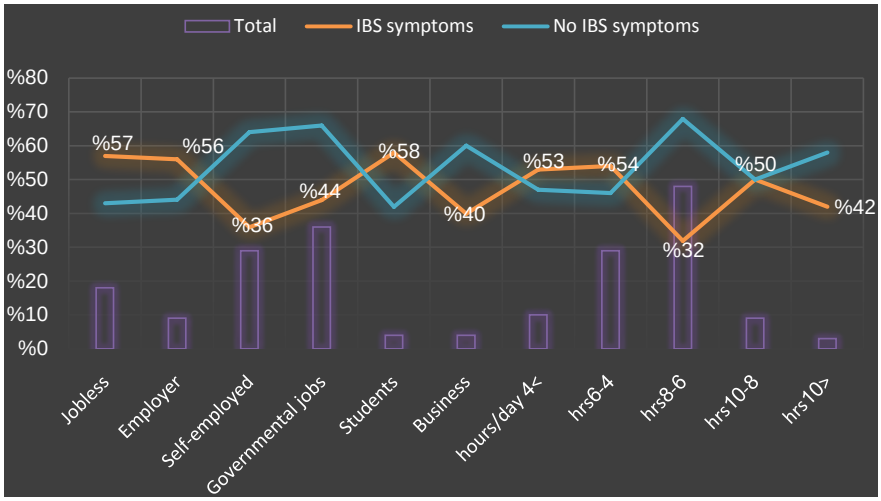

Figure 3. IBS symptoms by occupation and working hours.

among females compared to males. Female sex predisposes children and adolescents to develop IBS [9]. The reported prevalence rates of IBS among Saudi medical students and nurses were ranging from 14.4% [10] to 31.8% [11]. However, the high percentage of IBS in the present series may be attributed to the fact that, the present study considered any IBS related symptoms.

The findings of the present study showed that anxiety a strong risk for IBS. The RR (95% CI) = 1.4801 (1.2608 to 1.7376), $P < 0.0001$. Moreover, depression was also statistically significant risk associated with IBS. The RR (95% CI) =

1.3001 (1.1264 to 1.5006), P = 0.0003. In a study from Saudi Arabia to determine the prevalence, severity, and predictors of IBS among nurses, found that morbid anxiety is one of the major predictors of IBS [10]. A study from Saudi Arabia reported a high prevalence of IBS existing among medical students and interns. Female gender, morbid anxiety, living in the school dormitory, emotional stress, and higher educational level (grade) were the predictors of IBS [11]. Another study investigated medical students provided evidence that as medical students of the higher year of their under graduation were having a higher level of anxiety which leads to IBS [12]. In a systemic review involved 16 studies related to IBS, the prevalence of IBS among medical students ranged from 9.3% to 35.5%. The relatively high prevalence among medical students may be attributed to their special stressful learning environment. Some studies found that female gender, family history of IBS, psychiatric stress, anxiety, depression, infections, dietary factors, and sleep disorders were associated with IBS [13]. Moreover, in the present study, the frequencies of anxiety and depression were relatively lower (once per day), which may indicate relatively moderate IBS symptoms.

The risk of emotional stress as a risk for IBS was statistically significant. The relative risk and 95% confidence interval (95% CI) = RR (95% CI) = 1.5337 (1.2918 to 1.8211), P < 0.0001. Our emotional situation can have several magnitudes on our somatic health and well-being. Negative emotions such as anxiety play a chief role in gut functioning because of the bidirectional communications between the gut and brain, known as, the brain-gut axis [14]. In a study examined the responses to emotional stress in IBS patients, it delivers evidence that there is a definite change in stress responses in IBS patients, but no total overstated stress response [15]. The biopsychosocial model applied to the understanding of IBS pathophysiology proposed that psychosocial factors, interacting with peripheral/central neuroendocrine and immune alterations, may encourage symptoms of IBS, modify symptom severity, influence illness experience and quality of life, and disturbing outcome. An earlier study has proposed that negative emotions and attitudes have harmful effects on health, and a number of behavioral and biological mechanisms could trigger these links [16]. However, the prevalence of psychiatric conditions in IBS patients differs in diverse cultures [17].

In the present study, IBS symptoms were frequently seen in all occupational settings. However, some of these occupations are stressful. Stress has been involved as contributing to the initiation and exacerbation of bowel and discomfort symptoms in patients with IBS [18]. The Pressure Management Indicator (PMI) is a validated questionnaire to analyze all aspects of occupational stress-a model encompassing causes of stress, the mean of coping, the personality, and the consequential effects of the communication between these 3 components. The level of occupational stress was higher in IBS patients compared to healthy subjects (socio-professional stress effects were lower in IBS patients) and associated with IL-6 levels [19]. IBS was more common in healthcare professionals than in the control group. Healthcare workers are more disposed to IBS because

of their stressful working environment [20]. Well-being at work has been revealed to be predisposed by job features and personal variances in coping styles. Workplace anxieties, intrinsic and extrinsic effort, and negative coping and attributional behaviors were connected to high levels of depression and anxiety and low job satisfaction [21].

In the present study, higher proportions of IBS symptoms were observed among those with prolonged working hours or those with shorter working hours. There is a lack of data regarding this issue, which can be an aspect for future research.

The limitation of the present study includes its cross sectional setting as well as utility of only parts of the IBS related risk factors.

5. Conclusion

IBS and IBS related symptoms are prevalent in Northern Saudi Arabia. IBS symptoms are significantly associated with anxiety, depression and to a lesser extent may be linked to occupation and daily working hours. More studies in this context are rendered important to provide sufficient evidence for intervention and control.

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Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

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