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Evaluation of the Diagnostic Value of Digital Rectal Examination for Lymph Node Metastasis in Mid-Low Rectal Cancer

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Abstract

Background: NCCN's guidelines for the diagnosis and treatment of rectal cancer suggest that accurate preoperative clinical staging of rectal cancer is very important. Reliable preoperative evaluation is the key to the development of surgical protocols, in order to investigate the diagnostic value of digital rectal diagnosis for lymph node metastasis of middle and low rectal cancer. ***Methods***: We prospectively performed digital rectal examination in 258 patients with mid-low rectal cancer before operation, to analyze the distance from the lower margin of the tumor to the margin of the anus, the diameter of the invasion of the intestinal wall of the tumor, the accuracy between the general type and depth of invasion of the tumor and the pathological results of the postoperative specimen, and the predictability of the lymph node metastasis rate of the rectal digital examination. ***Results***: The results of the analysis showed that the above indicators and postoperative pathological findings have high accuracy. ***Conclusions***: It is concluded that accurate and detailed digital rectal examination before operation can predict lymph node metastasis rate of mid-low rectal cancer at a higher level and accurately.

Keywords

Digital Rectal Examination, Rectal Cancer, Mid-Low, Lymphatic Metastasis

1. Introduction

The use of total mesorectal resection (TME) has become increasingly widespread, leading to a dramatic decrease in the prevalence of local recurrence of rectal cancer from 38% to less than 10% [1]. Even with TME, however, the presence of a tumor or malignant node within 1 mm of the CRM remains an impor-

tant predisposing factor for local recurrence [2]. NCCN's guidelines for the diagnosis and treatment of rectal cancer believe that accurate preoperative clinical staging of rectal cancer is very important. Preoperative simultaneous neoadjuvant therapy is the mode of treatment for stage II, III colorectal cancer patients [3]. The determination of the best surgical procedure for rectal cancer depends on an accurate preoperative assessment of the local progression and distant metastasis of rectal cancer. With the development of neoadjuvant therapy and surgical technique, the recurrence rate is obviously reduced, and the survival rate is now over 70% [4]. Randomized trials have shown that combined preoperative radiation therapy—TME reduces the prevalence of local recurrence from 8% to 2% and is superior to postoperative radiation therapy alone [5] [6]. Therefore, reliable preoperative evaluation is crucial to the surgical plan. There are many imaging methods for preoperative clinical staging of rectal cancer, including MRI, PET, and CT [7]. However, the accuracy of imaging depends on the experience of the radiologist and there are significant internal observer differences [8] [9]. Endoscopic ultrasound (EUS) is reported to be a more accurate staging method [9] [10]. However, not all studies have confirmed the superiority of the United States [11]. Imaging studies rely mainly on lymph node size to assess lymph node metastases. The accuracy of simply determining lymph node metastasis based on lymph node size is still low. This is mainly because imaging does not easily identify reactive growth and lymph node metastasis [12]. The results showed that the accuracy of EUS, CT and MRI in lymph node metastasis was only 62% - 87%, 22% - 73% and 39% - 75% [13]. Overall, image judgment is a process of visual perception and requires considerable experience.

The digital rectal examination can not only determine the presence of mid-low rectal cancer, but also can further understand the position, size, texture, degree of involvement and relationship of prostate, urethra, vagina and uterus. A total of 258 patients with low rectal cancer were enrolled in this study. The accuracy of palpation for preoperative assessment of lymph node metastasis in low-grade rectal cancer was assessed by digital rectal examination.

2. Material and Methods

2.1. Patient Characteristics

From January 2005 to December 2015, 258 cases of rectal cancer in general surgery department of Yanbian University affiliated Hospital were collected. Each patient was confirmed by fiberoptic colonoscopy and biopsy and surgically resected. This study excluded patients whose lesions could not be resected and whose preoperative anal finger examination was more than 8 cm from the anal margin. The study was approved by the Ethics Committee of Yanbian University affiliated Hospital. There were 97 males and 161 females, with an average age of 66 ± 3.1 years, the youngest age being 29 years and the maximum age 84 years. Digital rectal examination mainly assessed the distance from the lower margin of the tumor to the anal margin, the length of the diameter of the infiltrating intes-

tinal wall, the gross pathological type, and the depth of the invasion. The patient is placed in the chest and knee position, Place the non-examining hand on the patient's right pelvic bone to provide counter-traction. Place your lubricated index finger on to the anus, pointing anteriorly and apply gentle pressure to the midline of the anus. Slowly enter the anus as you maintain pressure. After a few seconds, the anal sphincter should relax, allowing the digit to be advanced further into the rectum. Sweep your finger in a clockwise and then anti-clockwise manner to assess the entire circumference of the rectum. Feel for masses within the rectal wall (noting the approximate size, consistency and location—anterior, posterior, right or left lateral walls), note the approximate distance from the anal verge. If necessary, the patient squats, and increases abdominal pressure. The depth of invasion is as follows: intramucous carcinoma, soft lesion, no contact with hard parts, excellent mobility, almost not fixed in the rectal wall, free movement, difficult to distinguish from adenoma, a part of the tumor is hard and tough to infiltrate into the submucous layer. Submucosal carcinoma: because of the proliferation of submucosal fibrous tissue, compared with mucosal carcinoma, the texture becomes hard and tough, and the mobility is almost the same as mucosal carcinoma, moving with the mucosa, not with the intestinal wall. Carcinoma that infiltrates deep muscle layer: the quality is hard; the activity is restricted to some extent; the intestinal wall moves with the tumor. Immersion of deep muscle layer into extra intestinal fat: further reduction of activity. When adhesions infiltrate into other organs (prostate, vagina, presacral, etc.), tumor fixation and loss of activity. The specimens were examined by H-E staining under light microscope.

2.2. Surgical Technique

All patients who were included in this study underwent curative resection for their primary tumors, according to surgical oncological principles, and total mesorectal excision was performed by experienced surgical experts. All regional lymph nodes were dissected, including IMA lymph nodes. The inferior mesenteric vein was ligated and divided. Distal surgical margins of >5 cm were achieved for tumors located above the peritoneal reflection, and surgical margins were >2 cm for tumors located below the peritoneal reflection. Lateral pelvic lymph node dissection was not performed routinely in the surgical procedure. The primary tumor and all dissected lymph node specimens were stained with hematoxylin and eosin and evaluated by experienced pathologists.

2.3. Statistical Analysis

Statistical analysis was performed using the SPSS 17.0. With lymph node metastasis as an end event, single factor and multiple factors Logistic regression model is established. We used x^2 tests to analyze the lymph node metastasis related factors and used multiariable Logistic regression analysis to analyze the single factor analysis meaningful variables.

3. Results

A total of 4357 lymph nodes were detected in 258 patients with rectal cancer, with an average of 16.90 lymph nodes per case. The number of lymph nodes detected in each patient was greater than or equal to 12 cases. There were 92 patients with lymph node metastasis. For the distance from the lower margin of rectal tumor to the anal margin, the circumference, gross type and depth of invasion, the accuracy of rectal finger examination is shown in Tables 1-4. Univariate analysis showed that there was no significant difference between lymph node metastasis and the distance from the lower margin of the tumor to the anal margin, but there have significant difference between lymph node metastasis and circumference, gross types as well as depth of infiltration (Tables 5-8). Multivariate analysis showed that gross type and depth of invasion were independent factors affecting lymph node metastasis (Table 9).

Table 1. Comparison of the accuracy rate of digitalexamination and postoperative pathology: the anal margin to the lower margin of the tumor.

	3 cm	4 cm	5 cm	6 cm	7 cm	8 cm
DE (n)	38	45	61	43	39	32
PPJ (n)	36	40	53	34	30	22
Accuracy (%)	94.74	88.89	86.89	79.07	76.92	68.75

DE: Digital examination; PPJ: postoperative pathological judgment.

Table 2. Comparison of the accuracy rate of digital examination and postoperative pathology: the circulus degree.

	1/4 ≥ T	2/4 ≥ T > 1/4	3/4 ≥ T > 2/4	T > 3/4
DE (n)	59	65	66	68
PPJ (n)	51	55	55	58
Accuracy (%)	86.44	84.61	83.33	85.29

DE: Digital examination; PPJ: postoperative pathological judgment.

Table 3. Comparison of the accuracy rate of digital examination and postoperative pathology: gross pathologic type.

	UT	IDU	IU	ID
DE (n)	52	85	78	43
PPJ (n)	44	73	68	36
Accuracy (%)	84.62	85.88	87.18	83.72

DE: Digital examination; PPJ: postoperative pathological judgment; UT: uplift type; IDU: local defined ulcer; IU: Infiltrating ulcer; ID: Infiltrating diffuse.

Table 4. Comparison of the accuracy rate of digital examination and postoperative pathology: for the infiltration depth.

	M&S	ML	IWO	IV
DE (n)	16	42	157	43
PPJ (n)	13	37	139	36
Accuracy (%)	81.25	88.10	88.54	83.72

DE: Digital examination; PPJ: postoperative pathological judgment; M&S: mucosa and submucosa; ML: muscular layer; IWO: Intestinal wall outside; IV: *infringe viscera*.

Table 5. The Digital examination vspostoperative specimens of lymph node metastasis compared in the distance from rectal cancer's inferior border to anal.

	n	Digital examination						Postoperative pathologic examination					
		3 cm	4 cm	5 cm	6 cm	7 cm	8 cm	3 cm	4 cm	5 cm	6 cm	7 cm	8 cm
LN (+)	92	12	14	24	14	16	12	11	15	25	15	16	10
LN (−)	166	26	31	37	29	23	20	27	31	37	32	24	15
x^2 tests		$x^2 = 1.854$ $p > 0.05$						$x^2 = 2.032$ $p > 0.05$					

LN: lymph node.

Table 6. The Digital examination vs postoperative specimens of lymph node metastasis compared in circulus degree.

	n	Digital examination				Postoperative pathologic examination			
		1/4 ≥ T	2/4 ≥ T > 1/4	3/4 ≥ T > 2/4	T > 3/4	1/4 ≥ T	2/4 ≥ T > 1/4	3/4 ≥ T > 2/4	T > 3/4
LN (+)	92	10	19	28	35	9	19	31	33
LN (−)	166	49	46	38	33	47	51	38	30
x^2 tests		$x^2 = 3.839$, $p < 0.05$				$x^2 = 3.695$, $p < 0.05$i			

LN: lymph node.

Table 7. The Digital examination vspostoperative specimens of lymph node metastasis compared in gross pathologic type.

	n	Digital examination				Postoperative pathologic examination			
		UT	IDU	IU	IDUT	UT	IDU	IU	IDUT
LN (+)	92	10	19	26	37	8	19	27	38
LN (−)	166	42	66	52	6	40	67	56	3
x^2 tests		$x^2 = 6.651$, $p < 0.01$				$x^2 = 7.572$, $p < 0.01$			

UT: uplift type; IDU: local defined ulcer; IU: Infiltrating ulcer; ID: Infiltrating diffuse. *LN*: *lymph node*.

Table 8. The Digital examination vspostoperative specimens of lymph node metastasis compared in infiltration depth.

	n	Digital examination				Postoperative pathologic examination			
		M&S	ML	IWO	IV	M&S	ML	IWO	IV
LN (+)	92	0	6	43	43	0	11	34	47
LN (−)	166	16	36	114	0	15	36	115	0
x^2 tests		$x^2 = 14.354$, $p < 0.01$				$x^2 = 16.586$, $p < 0.01$			

M&S: mucosa and submucosa; ML: muscular layer; IWO: Intestinal wall outside; IV: infringe viscera; LN: lymph *node.*

Table 9. Lymph node metastasis multi-factor analyzed with rectal cancer characteristics through digital examination.

Variate	PRC	SE	RR	p-value
circulus degree	0.261	0.112	1.282	0.094
macroscopic pathology	0.232	0.107	1.677	0.035
infiltration depth	0.367	0.106	1.358	0.011

PRC: partial regression coefficient; SE: standard error; RR: relative risk.

4. Discussions

Most rectal cancer occurs in the lower rectum, and about 80% of them are located below the peritoneal reflex plane, within the range of digital rectal examination. Through digital rectal examination, on the one hand, rectal cancer can be diagnosed and misdiagnosis can be avoided. On the other hand, the degree of progression of rectal cancer can be assessed initially to provide further guidance for further examination. Correct digital rectal examination, in addition to being able to assess the distance from the lower edge of the tumor to the anal margin, the invasion circumference of the intestinal wall of the tumor, the general type, but also indirectly determine the depth of tumor invasion, with or without intestinal obstruction and lesions outside the rectal wall. In this study, we chose a rectal cancer within 8 cm from the lower edge of the tumor to the anal margin. The results showed that the distance from the lower edge of the tumor to the anal margin determined by digital rectal examination was compared with the results of postoperative pathological examination. The accuracy rate was 68.75% to 94.74%. The farther the distance from the anal margin was, the greater the error was. The reason for this may be, that the rectum is not perpendicular, and that the sacrum depression is curved and can be extended after surgery, so that the tumor is farther away from the anal margin.

As long as you take proper and careful fingertip palpation, you should have a higher accuracy rate in the invasion circumference of the intestinal wall and the gross pathological type of tumor. The accuracy rate was 83.33% - 86.44% and 83.72% - 87.18% respectively in our study. In imaging, localized lesions are indistinguishable from fibrosis and tumor invasion. Although the diagnosis of ad-

vanced T3 tumors is relatively easy, the distinction between T2 tumors and early T3 tumors requires considerable experience and high-quality images [10]. As the invasion of the intestinal wall increases, the chance of tumor metastasis increases. Tumor growth not only grows along the surface of the intestinal wall, but also penetrates into the intestinal wall. Therefore, the larger the diameter of the tumor, its depth will inevitably increase, and the chance of invading lymph nodes will increase. Different biological characteristics of rectal cancer have different growth patterns and invasiveness, and have different effects on lymph node metastasis. The intestinal muscularis and serosal layer play a role in the resistance to cancer cell invasion. As the tumor infiltrates deep into the intestinal wall and outside the intestinal wall, the larger the contact area with the lymphatic vessels, the greater the chance of lymph node metastasis. Depth of tumor invasion outside the muscularispropria is not considered in TNM staging; however, it has substantial clinical significance. The American Joint Committee on Cancer criteria for the staging of rectal cancer has been modified to incorporate depth of invasion outside the muscularispropria. The majority (80%) of rectal tumors are stage T3 lesions that form a heterogeneous group, with 5-year survival rates varying based on the depth of tumor invasion outside the muscularispropria. The cancer-specific survival rate drops from 85% to 54%, independent of nodal involvement, when the depth of tumor invasion outside the muscularispropria exceeds 5 mm [14]. In the subgroup of superficial tumors, EUS may be more accurate in deciding whether the tumour has penetrated the rectal wall [15], EUS is far from being ideal in identifying regional lymph node metastases. The ability of differentiating tumor invasion range was poor [16]. In addition, the examination of patients with intestinal stenosis or high rectal tumors was significantly restricted [17]. By palpation at the fingertips, the accuracy we perceive was 81.25% - 88.54%.

Because of the application of modern advanced examination equipment, many doctors ignore digital rectal examination in preoperative evaluation of rectal cancer value. They think rectal finger diagnosis is of little significance before operation. Accurately assessing lymph node metastasis before surgery is directly related to the development of treatment plans and the choice of surgical procedures, as well as preconditioning, and it is important to improve the quality of the patient's life [18]. Our univariate analysis showed that the invasion circumference of the intestinal wall of the tumor, the gross pathological type, and the depth of invasion were all related to the positive rate of lymph nodes, but further multivariate analysis showed that the gross pathological types and depth of invasion were two important factors affecting lymph node metastasis.

5. Conclusion

In conclusion, by correct and detailed digital rectal examination before surgery, palpation through your fingertips, you will perceive the high accuracy of lymph node metastasis in rectal cancer. It is necessary to combine the palpation of fin-

gertips with the visual inspection of imaging to perceive the preoperative staging of low and middle rectal cancer. Although the limitation of this study is that surgeons who perform preoperative anal finger examinations require clinically experienced, longer index fingers.

Conflicts of Interest

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

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The Influence of Insole with Metatarsal Retro-Capital on Posture, Plantar Pressure and Body Segments Positions in Runners

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Abstract

Objectives. The aim of this study was to investigate the effects of orthopaedic soles on the body posture. *Methods.* Forty-eight runners (21 men and 28 women) maintained a standing-up position on both feet with bare feet with neutral soles and orthopedic soles which contained bilaterally a podiatrist element of 3 mm height behind the metatarsal heads (Metatarsal Retro Capital Bar, MRCB). Stabilometric, plantar pressure and kinematic data in the sagittal plane on both sides were measured at 40 and 60 Hz, respectively. The position of the center of pressure on the anteroposterior axis (Y_{CoP}), the forefoot plantar pressure (FPP) and the anteroposterior position of the knee (Y_k), the hip (Y_H), the shoulder (Y_S) and the ears (Y_E) with respect to the vertical axis passing through the joint of the ankle were determined for each experimental condition. *Findings.* The addition of a MRCB orthopedic element induced in backward displacement of CoP, hip, shoulder and ears ($p < 0.01$). Y_{CoP} and FPP changes were significantly correlated with Y_H, Y_S and Y_E changes ($p < 0.01$). *Conclusion.* These results suggest that the addition of an orthopedic element located behind the metatarsal heads influences the overall position of the body and can help podiatrist in the care of their patients.

Keywords

Posture, Pressure, Insoles, Thin Plantar Stimulation, Podiatry

1. Introduction

The postural system which participated to the body balance control, acts like a reversed pendulum around a fixed point located at the ankle [1]. Many mechanoreceptors of the foot's sole participate in the control of the balance [2]. Most of the rapidly adapting Pacini's receptors are located in the front of the foot at the metatarsal heads, whereas the slowly adaptive receptors are mainly located on the medial and lateral sides of the foot. Changes in proprioceptive and mechanical information's on the foot may lead to postural adaptations [3] [4]. General or partial anesthesia of the feet can cause, for example, a displacement of the Center of Pressure (CoP) of the body in the antero-posterior and/or medio-lateral direction while maintaining the standing position [5].

Several studies have investigated the effects of changes in feet sensory input on body posture. Mechanical vibrations applied on the anterior plant of the foot or on the muscles tendons of leg's posterior compartment induced a displacement of CoP to the back [6] [7]. In contrary, a stimulation of the posterior plant of the foot or muscles tendons of the leg's anterior compartment enhanced a CoP displacement towards the front. These results show that the origin of proprioceptive information influences the adaptation of the body to mechanical vibrations. The CoP moves in the same direction of muscular stimulation whereas a plantar stimulation causes a CoP motion to the opposite direction. The resulting cutaneous stimulation gives the body information of an excess of pressure that causes an opposite reaction to release the area. During the stimulation of the forefoot, the soleus was activated initially to move the CoP to the back. The main antagonist muscle, *i.e.*, the tibialis anterior, is then activated to control this movement and prevent the subject from falling back [8].

The use of orthopedic elements under the sole modifies the proprioceptive information from the mechanoreceptors and can cause a displacement of the CoP while maintaining the standing posture. The addition of a 3 mm element under the internal or external part of the plantar arch of one of the two feet moves the CoP to the opposite side [9]. The two-sided placement of this orthopedic element causes the CoP to move to the back [10] and can stabilize postural balance [11]. This change is more important when the two elements are placed on the anterior part of the feet [12], because it contains most fast-acting mechanoreceptors [2], and is comparable to the one observed during stimulation of the anterior plant of the foot by mechanical vibrations [6].

The addition of elements behind the Metatarsal Retro Capital Bar (MRCB) allows to reduce the pressure under the forefoot [13], and thus allows to better distribute it between the forefoot and the rearfoot [14]. Like to cutaneous vibration stimulation, this orthopedic element could have the same effect by increasing the pressure behind the metatarsal heads induce by the relief. If the body reacts in the same way by moving backwards, then the plantar pressure under the feet will be reduced. During running, MRCB elements would help to support

the feet at the end of the run where the pressure is more important under the front feet. The main clinical application of this element is the reduction of pressure under the fronts that can be interesting in sport podiatry to reduce the risk of injury in this area [14] and thus decreasing the risk of metatarsal pain or stress fracture [15]. This better distribution could result in a change on the overall body posture, manifested by a displacement in the antero-posterior axis of the overlying's joints. It has been shown that the bilaterally use of orthopedic elements under the sole of the foot induced changes in the position of the ankles, knees, pelvis and trunk joint in the frontal plane, while maintaining standing position on one foot [16] [17] or during walking [18] [19] [20]. Stimulation of the planar sole via vibratory stimulation [6] [8] or podiatry elements [10] [12] influences the globality of the subject by having an effect on the oculomotor muscles [10] especially through the intermediary of the muscular chains [8]. However, to our knowledge, no studies have evaluated the influence of MRCB element on the overall position of the body.

The aim of this study is to evaluate the effects of wearing orthopedic soles equipped with MRCB elements on the position in the sagittal plane of the CoP and of the overlying's joints. We hypothesize that the addition of MRCB elements induce backward movements of the CoP and all overlying's joints while standing position.

2. Methods

2.1. Population

Forty-eight regular runners, practicing minimum twice a week (27 men and 21 women) who had no medical and/or surgical history, during the last five years, took part in this study (33.3 ± 10.2 years, 172 ± 9.9 cm, 66.8 ± 15.9 kg). After being orally informed and in writing of the experimental protocol, all the participants signed the consent form in accordance with the Helsinki declaration on biomedical research.

2.2. Stabilometric and Plantar Pressure Measurements

The position of the CoP and the plantar pressure under each foot were measured at a sampling frequency of 40 Hz by a Fusyo stabilometric platform (Medicapteurs®, Balma, France).

The average position on the antero-posterior axis of the global CoP (Y_{CoP}) and of the CoP under right foot (Y_{RF}) and left foot (Y_{LF}) were measured in cm with respect to platform point of reference (O, X, Y). Data were analyzed by Fusyo Software (Medicapteurs®, Balma, France).

The average forefoot plantar pressure (FPP) under each foot was calculated for each experimental condition. The median line of the feet, dividing forward and backward, is calculated as half the distance between the most anterior and posterior points of each foot. The values on both sides were averaged and expressed as a percentage of body weight.

2.3. Kinetics Parameters

The positions on the sagittal plane of the joints of the knee, hip, shoulder and the head were recorded on either side by two High-Definition cameras (image resolution: 1290 × 1080 pixels; Go Pro Hero 4®, San Mateo, USA) at a frequency of 60 Hz. The cameras were placed on each side, one meter from the platform, in the extension of its center, and raised from the ground by one meter. The synchronization between the data of the platform and the cameras was allowed by a light diode placed on the platform and visible from the cameras. The joints centers were previously identified and marked by circular black adhesive circles of 12 mm diameter placed for the ankle, on the lateral malleolus; for the knee, at the level of the lateral tuberosity of the lateral femoral epicondylus; for the hip, on the femoral's greater trochanter; for the shoulder, on the major tubercles humeral; and for the head, on the tragus of the ears.

The kinematic data were processed by the Kinovea® software (version 0.8.24). The anterior-posterior position of the knee joint (Y_K), the hips (Y_H), the shoulders (Y_S) and the head (Y_E) were measured in cm with respect to the axis passing through the lateral malleolus. The values on both sides were averaged.

2.4. Plantar Stimulation

The orthopedic soles of each subject contained a MRCB element of 3 mm thickness made of Ethyl Vinyl Acetate (EVA) of hardness 70 shore A (Eloi, Nogent-sur-Marne, France). These elements were placed behind the metatarsal heads by an experienced podiatrist as a function of the individual footprint [12] [21].

2.5. Procedure

The participants were placed barefoot onplatform. Feet were oriented on either side of the transverse axis of the platform at an angle of 30˚, the heels separated of 4 cm and the patients were positioned facing a wall at a distance of 90 cm. The runners had to remain as immobile as possible for 51.2 seconds. Satbilometric, plantar pressure and kinematic were synchronize and collected during this time. Parameters were collected in two sensory conditions: in neutral condition using normal soles (N)) and with podiatric stimulation (MRCB condition).

After one passage of accommodation, the subjects made one passage by condition. The two conditions were randomized for all the participants and separated by one minute of passive recovery.

2.6. Statistical Analysis

Since all data (stabilometric, plantar pressure and kinematic on each side) did not follow the normal distribution (Shapiro-Wilk). The effect of the use of orthopedic soles on stabilometric (Y_{CoP}, Y_{RF}, Y_{LF}), plantar pressure and kinematics variables (Y_K, Y_H, Y_S, Y_E) was tested using the nonparametric Wilcoxon test performed on rows. Spearman test was used to determine the degree of linear relationship between the stabilometric, plantar pressure and kinematic variables. The level of significance for all tests was set to $p < 0.05$.

3. Results

Statistical analysis shows a significant backward displacement 20% of global CoP in the MRCB condition relative to the control condition ($p < 0.01$) (Figure 1(a)). However, no significant differences have been found between the position of CoP of each foot (Y_{RF}, Y_{RL}). FPP was 15% lower in the MRCB condition than in the control condition ($p < 0.01$) (Figure 1(b)).

The anteroposterior position of the hip (Y_H), the shoulder (Y_S) and the head (Y_E) in relation to the ankle joint was significantly reduced with the use of the orthopedic soles by 9%, 11% and 7% respectively ($p < 0.01$) (Figure 2). The anteroposterior position of the knee was not significantly different between the two experimental conditions.

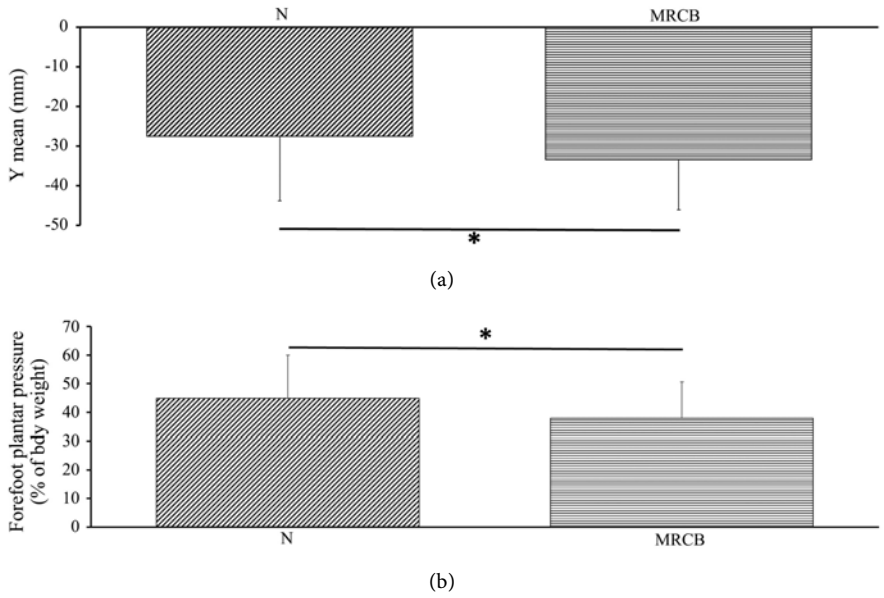

Figure 1. Average position of the COP (a) and plantar pressure under the forefoot (b) with the wearing of the neutral sole (N) and the orthopaedic sole (MRCB) (*: $p < 0.01$).

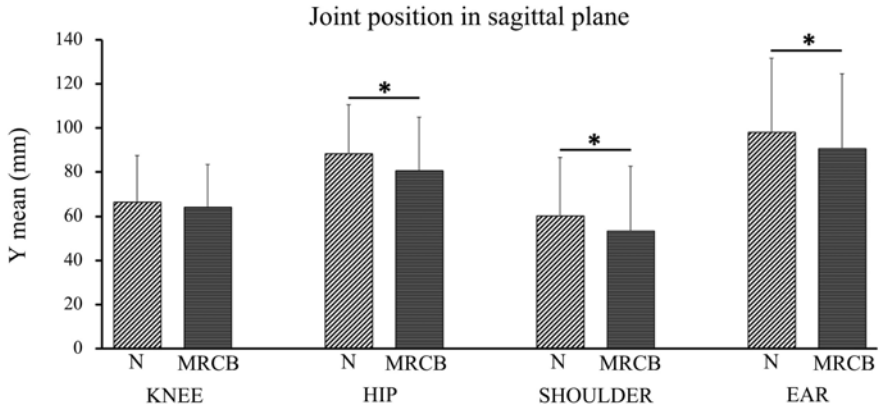

Figure 2. Position of the joints of the knee, hip, shoulder and head with respect to the ankle in the sagittal plane with the wearing of the neutral sole (N) and the orthopaedic sole (MRCB) (*: $p < 0.01$).

Spearman tests revealed a weak relationship between FPP and Y_E ($r = 0.47$, $p < 0.01$); moderate relationships between Y_{COP} and Y_E ($r = 0.61$, $p < 0.01$), between Y_{CoP} and Y_S ($r = 0.67$; $p < 0.01$), between Y_{CoP} and FPP ($r = 0.69$, $p < 0.01$), between FPP and Y_S ($r = 0.70$, $p < 0.01$), between FPP and Y_H ($R = 0.72$, $p < 0.01$); and a strong relationship between Y_{COP} and Y_H ($r = 0.85$, $p < 0.01$). The link between the other variables was not significant.

4. Discussion

The aim of this study was to evaluate the effect of orthopedic elements placed behind the metatarsal heads (MRCB) on the displacement of the center of pressure and on the anteroposterior position of joints overlying the ankle while maintaining the standing posture. Our results showed that the bilaterally use of MRCB elements induces significant backward displacement of the center of pressure and of hip, shoulder and head joints without having any influence on the knee. A decrease a forefoot plantar pression with MRCB is also shown in this study.

Thus this result completes the previous study who found the same results on plantar pressures with vibration [6] and with a podiatric wedge [10] [12] [14]. Thus, the work of the MRCB increases the pressure behind the metatarsal heads thus simulating for the body an earlier imbalance that it seeks to compensate backwards. This conclusion is similar to the vibration tests performed by Kavounoudias *et al.* [6] where the previous vibration's stimulation simulated an excess of pressure in this area. The body replaces its segments to the rear causing a decline in CoP and decreasing the plantar pressures under the front feet.

The backward displacement of the CoP was also observed after vibration's stimulation of the anterior part of the foot [8], and was ever reported with the use of MRCB elements [12]. The backward movement of the pelvic, scapular and head belts observed with the MRCB elements are agree with the reversed pendulum mechanism described previously [1] but without effects to the knee, showing its ability to adapt between the ankle and hip, essential in most sports activities.

However, most podiatrist recommend increasing the height of the heel to decrease the work of the posterior muscle chain. Our results differ somewhat from this theoretical concept since the addition of a MRBC element under the anterior part of the foot seems to decrease the activity this muscular chain regard to the backward displacement of the hip, shoulder joints and head. The effects of this sole's element show here a posterior displacement of the center of pressure, which during the maintenance of the upright posture modifies the point of application of the force while creating a posterior displacement of the hip, the shoulders and the head decreasing the work of the posterior muscle chain. If the knee does not move with respect to the flat sole, while the entire upper part moves backwards, shows that he has undergone some adaptation (flessum?) giving him some freedom. Thus, if the hip goes backwards and the knee does not

move with respect to the axis of the camera, this suggests that it undergoes a different angulation that can be at the origin of a flessum of adaptation. However, this decline in the hip, does not cause a change in the knee that keeps a possible adaptation between the ankle and hip. The freedom left to the knee is a key element of this study especially in the sport where it is a factor of absorption and adaptability.

The overall backward body displacement when using MRCB insoles results in a significant decrease in plantar pressure under the forefoot. Moreover, the reduction of the plantar pressure is correlated with the displacement of the hip, the shoulder and the head. Similar correlations between plantar pressure and the positions of the ankle and knee during the use of external element have been also observed in dynamic walking conditions [20]. The work of the knee in the sagittal plane with a MRCB type element induces low intensity movements (Genu flessum and recurvatum) more in connection with an adaptation between the ankle and the hip.

4.1. Practical Application

According to our results, the use of MRCB orthopedic soles seems to be interesting for persons who suffer from recurrent metatarsal pain such as diabetic patients, but also for the elderly who are more prone to the risk of falling forward [22]. Foot injuries, including stress fractures of the metatarsal heads, represent a large part (15%) of the all injuries observed after a long distance running race, *i.e.* a marathon [15] [23] [24]. The appearance of these injuries is seeming to be related to the increase of the ground reaction force under the front feet. Previous studies showed that the plantar pressure under the forefoot increased after a running race [15] [25] or after an exhaustive laboratory running exercise [24] [26] [27]. During running, this element would reduce the zones of pressure under the forefoot that are more important at the end of marathon and could limit injury such as metatarsal pain and stress fracture [15]. This element can be used in prevention or treatment in all people who remain standing for a long time in static (military, factory operator, …) or who moves a lot daily (postman, waiter, …) for work and who may have sore feet. The daily use of this type of orthopedic soles would allow to continue the patient treatment over the long term, which is reduced or mostly stopped after the classic program of functional rehabilitation used in physiotherapy.

4.2. Limits of the Study, Perspectives, Conclusion

Results of this study must be interpreted with caution because they have been obtained in a static position, whereas humans being spend majority of daily time moving and walking. Moreover, data were analyzed only in the sagittal plane. We used a simple protocol to get as close as possible to observations made during a podiatry consultation. Thus, in the future we could do a 3D analysis of the foot to note if this element modifies its structure, especially in dynamics. Some

studies shown that bilateral internal orthopedic elements could reduce the ankle adduction moment, knee and hip [17] [18] [19] [20], which may be relevant in the context of osteoarthritic diseases [17] or in the patellofemoral syndromes [18]. Therefore, it would be interesting to evaluate the effect of MRCB elements on plantar pressures and positions of knee, hip, shoulder and head joints during walking and running. Future studies should to measure the electromyography activity of the muscles of the anterior and posterior body chains in order to quantify their work when using MRCB elements.

5. Conclusion

To conclude, this study has shown that the addition of orthopedic elements placed behind the metatarsal heads under each foot results in backward movements of the center of pressure and the overlying ankle joints, except the knee. These changes induced a lower plantar pressure under the forefoot. This orthopedic tool could have an impact on rehabilitation and muscular work from a medical point of view in sports performance.

Conflicts of Interest

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

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Correlation between Serotonin Transporter Promoter Gene Polymorphism and PTSD in Children

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Abstract

Objective: To study the association between post-traumatic stress disorder (PTSD) and serotonin transporter promoter (5-HTTLPR) gene polymorphism in Han children in Hainan; to explore the genetic mechanism of PTSD in children. **Methods:** 50 patients with post-traumatic stress disorder and healthy children in Han nationality in Hainan were selected. Detection of 5-HTTLPR gene polymorphism by polymerase chain reaction (PCR) and amplified fragment length polymorphism, the genotype and allele frequencies were analyzed using a case-control association analysis method. **Results:** There were 4, 14 and 32 cases of LL, SL and SS in the post-traumatic stress disorder group of Hainan Han children, and 13, 20 and 17 cases in the control group. From the perspective of gene frequency, the L gene of post-traumatic stress disorder appeared 22.0%, and S appeared 78.0%. In the control group, L appeared 46.0%, and S appeared 54.0%. There were significant differences in genotype and gene frequency ($P < 0.01$). **Conclusion:** The 5-HTTLPR gene polymorphism in Hainan Han children may be associated with post-traumatic stress disorder.

Keywords

Post-Traumatic Stress Disorder, Genetic Polymorphism, A Serotonin Transporter Promoter, Genetics

1. Introduction

Children in the fields of psychiatry, pediatrics, child care and education have

conducted extensive research on the causes of children with PTSD, involved in various fields such as genetics, immunology, virology, neurobiology and psychosocial. Among them, the research on genetics has become an important research direction in the current psychiatric community [1]. In recent years, natural disasters and man-made disasters have occurred frequently, and the incidence of post-traumatic stress disorder (PTSD) in children has increased significantly [2]. The main symptoms of PTSD are: repeated traumatic experience (flashback), traumatic situations involuntarily emerged; second, continuous avoidance and stimulation related to traumatic events; third, sustained alertness [3]. Therefore, exploring the mechanism of occurrence of PTSD in children is very necessary for its prevention and treatment. The serotonin transporter (5-HTTLPR) is distributed on the presynaptic membrane of 5-HT neurons, which plays an important role in the reabsorption of 5-HT neurotransmitters in the synaptic cleft, 5-HT system functional status [4]. In recent years, studies have shown that dysfunction of the serotonin system plays a role in the development of children with PTSD. Therefore, the 5-HTTLPR gene is an important candidate gene for PTSD in children [5]. This study also further explored the correlation between the genotype and allele frequency of 5-HTTLPR in the PTSD group and the control group of Han children in Hainan. It provides a scientific basis for the clinical diagnosis of children with PTSD and provides a scientific basis for the genetics of PTSD in children.

2. Objects and Methods

2.1. Object

All cases were from December 2016 to December 2017. The investigation was conducted in the psychological clinic of Lin Gao County People's Hospital of Hainan Province and Hainan Provincial People's Hospital for the diagnosis of PTSD Han children. **The PTSD Diagnostic Scale and the diagnostic criteria for PTSD in the US Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) have been used.**

Inclusion criteria: 1 age is 4 to 12 years old; 2 right hand; 3 Comply with the diagnostic criteria for PTSD in the US Diagnostic and Statistical Manual of Mental Disorders (DSM-IV). Exclusion criteria: Associated with mental retardation, personality disorder, material dependence or alcohol dependence. Volunteer to participate in the study and to obtain informed consent (child or his father, mother). The study group consisted of 26 males and 24 females with an average age of 6.26 ± 2.40 years. The control group consisted of 27 males and 23 females with an average age of 5.92 ± 2.98 years. There was no significant difference in gender and age between the two groups ($P > 0.05$).

2.2. Methods

Genomic DNA was extracted by a conventional phenol chloride method. The PCR primers are as follows: positive 5'-GGCGTTGCCGCTCTGAATGC-3, Re-

verse 5'-GAGGGACTGAGCTGGACAACCAC-3, using TaKaRaEx from Bio-Engineering (Dalian) Co., Ltd. The PCR product was subjected to vertical electrophoresis on a 6% non-denaturing polyacrylamide gel. After ethidium bromide (EB) staining, the electrophoresis images of each sample were detected by an ultraviolet gel analyzer to determine the genotype.

2.3. Statistical Analysis

Data analysis was performed using SPSS 13.0 statistical software. Methods include: Hardy-Weinberg (H-W) coincidence test, frequency analysis, analysis of variance, t test, and χ^2 test.

3. Results

There was no significant difference in the sex ratio, age and education between the study group and the control group ($P > 0.05$, Table 1).

Hardy-Weinberg's Law of Genetic Balance Test. The Hardy-Weinberg's law of genetic equilibrium tests that the gene distribution of 5-HTTLPR conforms to the law of genetic balance and is representative of the population (Table 2).

Compared with the genotype and allele of the PTSD group and the control group, the 5-HTTLPR gene showed 4, 14, and 32 cases of LL, SL, and SS in the post-traumatic stress disorder group, respectively, and 13, 20, and 17 cases in the control group. From the perspective of gene frequency, the L gene of post-traumatic stress disorder appeared 22.0%, and S appeared 78.0%. In the control group, L appeared 46.0%, and S appeared 54.0%, there were significant differences in genotype and gene frequency between the two groups ($P < 0.01$, Table 3).

Table 1. Comparison of basic situation between PISD group and control group.

Group	gender		Age (year old)
	male	female	
PTSD group	26	24	6.26 ± 2.40
Control group	27	23	5.92 ± 2.98
X^2 or t	0.067		0.487
P	0.795		0.314

▪ by X^2 test ▲ by t test. The healthy control group is a hospital-school joint health check-up child, which is randomly enrolled, and there is no significant difference in gender, age, etc.

Table 2. 5-HTTLPR gene distribution Hardy-wcinbcrg genetic equilibrium law test.

Group	genotype			X^2	P
	LL	SL	SS		
PTSD group	4	14	32	1.696	0.193
Control group	13	20	17	1.899	0.168

Table 3. Comparison of genotypes and alleles between PISD group and control group (n = 50, %).

Group	Genotype frequency (%)			Allele frequency (%)	
	LL	SL	SS	L	S
PTSD group	4 (8.0)	14 (28.0)	32 (64.0)	22 (22.0)	78 (78.0)
Control group	13 (26.0)	20 (40.0)	17 (34.0)	46 (46.0)	54 (54.0)
X^2		10.415		12.834	
P		0.017		0.0002	

4. Discussion

With the rapid development of modern society, the radius of children's activities has expanded, and the use of various vehicles has become more and more frequent. The acute trauma caused by traffic accidents has gradually become a risk factor threatening people's lives and health [6]. A car accident (or witness to a car accident) as a serious, sudden stressful life event can lead to a strong psychological and physical dual stress response in the injured [7]. The stress response caused by this unconventional emergency causes the injured person to cause different degrees of physiological damage on the body, and also causes a series of physiological, psychological and behavioral changes and degrees under the action of the traumatic stress source. Different psychological stress states [8]. A car accident is sudden, unbearable or catastrophic. The physical and psychological impact on the patient is very direct and significant, and often produces a strong psychological stress response, affecting the treatment effect and prognosis.

Post-traumatic stress disorder is a delayed and long-lasting mental disorder caused by unusual, threatening psychological trauma. Specific symptoms of PTSD include re-experience, avoidance, and increased alertness following traumatic events. The diagnostic criteria must include a specific number of each of the three types of symptoms: re-experience, avoidance, and alertness. A large number of studies have confirmed that [9] children with PTSD have obvious family aggregation and genetic predisposition. With the rapid development of molecular genetics and molecular biology technology, many susceptibility genes related to the pathogenesis of PTSD have been identified. Among them, the HTSD gene is closely related to PTSD, but the research conclusions are not the same. Studies have shown that [10], The TDT analysis of the PTSD core family found that the 5-HTT promoter region (5-HTTLPR) S allele was preferentially transmitted to the children, and the 5-HTT gene intron VNTR polymorphism was not significantly associated with PTSD; Two-point haploid TDT analysis showed significant differences in 5-HTTLPR and VNTR allele transmission, and the study found that the [11] L allele was preferentially transmitted to children, The core family TDT study further found no difference in 5-HTTLPR allele

transmission, but was related to the severity of social disorders, in the severely disordered individuals, the S allele is preferentially transmitted, and L allele delivery is superior in individuals with mild to moderate disease, suggesting that the 5-HTTLPR allele itself does not determine the susceptibility of PTSD, which may be related to the severity of social disorders. Cao Yuping *et al.* [12] reported the transmission imbalance of 5-HTTLPR and the second intron VNTR haplotype, but 5-HTTLPR as an independent marker did not have a transmission imbalance. In summary, the 5-HTT gene remains a candidate gene for PTSD. Studies have shown that 5-HTR2A is highly densely distributed in the frontal cortex, and the frontal cortex is closely related to cognitive function, suggesting that 5-HTR2A may be the main receptor link in children with autism 5-HTT neurological abnormalities. It is hypothesized that [13], individual differences in susceptibility to PTSD in children may be related to differences in 5-HTR2A function and expression levels in the brain, whereas differences in 5-HT2A function and expression levels are determined by 5-HTR2A gene polymorphisms.

There are many studies on PTSD and its pathogenesis, but the influence of genetic factors is still unclear. The genetic research of PTSD is still in its infancy, and the number of studies is small, and it is mostly in the polymorphic analysis of single genes and single sites. Because PTSD itself is highly heterogeneous in clinical practice, it should be combined with epigenetics and traditional genetics to explore its pathogenesis from the interaction between genetic susceptibility and environment of PTSD. The mechanism of 5-HT system in PTSD pathology is unclear, but 5-HT is thought to be associated with PTSD's mood swings, irritability, and sleep abnormalities [14]. The 5-HT transporter gene (5-HTT gene) is one of the most widely studied genes involved in increased 5-HT activity following stress events. Abnormal 5-HT activity may mediate emotional abnormalities. Susceptibility to PTSD [15]. Therefore, regulation of the 5-HT system gene may play a role in the depression response of various stressors in the susceptibility or life process of PTSD. Allelic variation in human 5-HTT expression is due to a 5-HTTLPR polymorphism in the promoter region containing two major alleles, which are long alleles (L) and short Gene (S). In vitro experiments showed that long fragment L had higher transcriptional activity than short fragment S. Brain tissue and cultured cells with LL genotype produced 5-HTT mRNA and protein expression were higher than SS genotype, Therefore, 5-HTTLPR may affect the serotonin system function by affecting the transcriptional activity of the gene and the function of the 5-HTT protein, thereby affecting the individual's emotional, mental, and personality disorders [16] [17]. Annette M *et al.* [18] analyzed the 5-HTTLPR gene in patients with PTSD and healthy subjects and found that the SS genotype of patients with PTSD was significantly higher than that of healthy controls. Fernando *et al.* [19] found that the S allele in the 5-HTTLPR polymorphism significantly increased the risk of PTSD in hurricane-affected populations. The highest risk was SS genotype, low social support, and severe hurricane trauma. A large number of previous studies have shown that 5-HTTLPR is associated with many mental illnesses, such as SS genotypes in

patients with severe depression and anxiety [20] [21] [22]. A large sample of twin studies showed that 5-HTTLPR individuals with SS or SL were prone to PTSD depressive responses after stress events, and further analysis revealed 5-HTT gene polymorphism and post-stress affective disorder. The occurrence is related [23]. Other studies have shown that SS or SL allele carriers have higher amygdala activity than LL alleles when they encounter fear stimulation, while SL carriers have lower anxiety than LL, suggesting that fear and anxiety may be related to 5-HTT gene mutation [24]. Some studies have shown that individuals with a 5-HTT polymorphism with two short alleles (SS or SL) are more sensitive to stress than individuals with only one or two long alleles (LL) [25]. In conclusion, 5-HTT may play a role in the degree of stress response, and its gene mutation can regulate the depression sensitivity of individuals to stress. Although there are few studies on the susceptibility of 5-HTT and PTSD, however, the increase in amygdala activity caused by fear stimulation is more likely to occur in individuals carrying the homozygous SS gene or the heterozygous SL gene than the homozygous LL gene.

We analyzed the 5-HTTLPR gene polymorphism in 50 children with PTSD and 50 healthy children in Hainan, and found that there were significant differences in genotype and gene frequency. This indicates that the 5-HTTLPR gene polymorphism is associated with pathological and behavioral changes under stress. Therefore, it can be shown that the 5-HTTLPR gene polymorphism is associated with PTSD. The sequencing results of this study showed that the proportion of S allele was significantly higher than that of L allele (S = 78.0%; L = 22.0%), and genotype SS and LS alleles were dominant, this is basically consistent with the results of Asian populations such as China (S = 77.0%; L = 23.0%) and Japan (S = 82.3%; L = 17.7%), However, there are differences between European and North American populations. Among these populations, allele L (S = 45.3%; L = 54.7%) and genotype LL account for a high proportion [26]. This series of differences considers racial heterogeneity, so ethnic background effects need to be considered in the 5-HTTLPR polymorphism study [27]. For the relationship between PTSD and 5-HTTLPR polymorphism, there are related studies abroad, but there is no clear report on the Chinese population. This study can clarify that PSTD and 5-HTTLPR are also related in the Han population of Hainan Province.

5. Conclusion

Post-traumatic stress disorder is an important manifestation of mental and behavioral disorders after unconventional emergencies. It has the characteristics of high incidence, high prevalence, long course of disease and poor curative effect, which seriously affects clinical treatment. At present, domestic and international research on the internal relationship between 5-HT system and children's PTSD is of great concern. It is helpful to clarify the etiology and pathogenesis, and may have positive significance for diagnosis, treatment and prevention.

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Conflicts of Interest

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

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