The Characteristics of Visual Function and Intervention in Deprivation Amblyopia in Limbal Dermoid Children After Keratoplasty: A Pilot Study of Adopting Flank-Mask Perceptual Learning

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Research

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Abstract

Background

To compare visual acuity and CSF improvement with perceptual learning versus part-time patching in limbal dermoid children after keratoplasty.

Methods

All children in the limbal dermoid and normal group underwent visual acuity and CSF evaluation, and the normal group wore the optical defocus to simulate the corresponding visual acuity of the limbal dermoid group. Among the limbal dermoid children, 9 underwent perceptual learning (PL), and 8 underwent part-time patching for 6 months and were followed for 6 months to evaluate visual acuity and CSF.

Results

Regarding CSF, the area under log CSF (AULCSF) and the cutoff spatial frequency (cutoff SF) were obviously reduced in the limbal dermoid group compared with the optical defocus group and normal viewing group (1.29±0.27 vs 0.40±0.05 vs 0.70±0.05, and 5.38±0.75 vs 8.81±0.74 vs 14.81±0.89, all p value <0.05). Following PL, visual acuity increased from 0.63±0.11 to 0.32±0.09 (P=0.04) . Contrast sensitivity increased mainly in the low special frequencies as AULCSF improved from 0.49±0.15 to 0.73±0.18 (P=0.32), 0.78±0.21 (P=0.28), 0.80±0.19 (P=0.22) and 1.06±0.20 (P=0.04) from baseline to the 6th month in the PL group, while it remained unchanged in the part-time patching group.

Conclusions

Children suffering from limbal dermoid with amblyopia exhibited CSF deficits and perceptual learning was found to improve VA and CSF in the amblyopic eye better than patching.

Trial registration

The study was registered at clinicaltrials.gov (PRS, ID NCT03447041).

Background

Limbal dermoid (LD) is a congenital benign tumor that consists of overgrowths of epidermal appendages that influence vision and cause visual abnormalities due to induced corneal astigmatism [1]. A large proportion of patients, all of whom had epibulbar dermoids, had amblyopia [2]. In a previous study, keratoplasty, such as LKP (lamellar keratoplasty) or PKP (penetrating keratoplasty), was shown to facilitate the reconstruction of appearance and improve visual acuity significantly postoperatively [3]. However, the reestablishment of visual acuity and visual function are always ignored by parents after visual appearance recovery. Several studies have evaluated the visual acuity and objective and subjective visual function of patients after keratoplasty. These outcomes include contrast sensitivity (CS) [4, 5],
refractive error, graft clarity, anterior and posterior corneal higher order aberration, and vision-related quality of life [6]. Although a subjective visual function assessment has been deemed critical, postkeratoplasty patients with vision complaints are not uncommon despite clear grafts and relatively good visual acuity [7], and the visual function evaluation for LD was relatively less common.

Amblyopia is a common complication in LD patients postoperatively, and the loss of vision is thought to be secondary to abnormal relationships within the neuronal network in the primary visual cortex [8]. Amblyopia is characterized by several functional abnormalities in spatial vision, including reductions in visual acuity, contrast sensitivity function and spatial distortion [9]. Traditional treatment for amblyopia is based on penalization of the good eye while optimizing the visual function of the amblyopic eye in childhood [10]; however, it is accompanied by problems of a social or emotional nature, skin irritation and other problems that might affect compliance [11].

Perceptual learning describes a process whereby practicing certain visual tasks leads to improvement in visual performance, including visual acuity and contrast sensitivity [12]. Perceptual learning can indeed modify visual functions in amblyopia, which has been applied in adult hypermetropic anisometropic amblyopia [12], children with amblyopia [11] and presbyopia [13]. This study evaluated visual function, such as contrast sensitivity function (CSF), and the efficacy of perceptual vision therapy in enhancing best-corrected visual acuity (BCVA) and CSF in children with LD postoperatively.

Methods

Subjects and inclusion criteria

This study was conducted in LD children after keratoplasty from the Corneal Disease Department of Zhongshan Ophthalmic Center, Guangzhou, China. The research was performed according to the tenets of the Declaration of Helsinki. The protocol was approved by the Zhongshan Ophthalmic Ethical Committee (ID ZOC20171217) and was registered at clinicaltrials.gov (PRS, ID NCT03447041).

The study included 25 children with LD who underwent keratoplasty (the LD group) and 25 normal subjects (the normal group) (Table 1). The inclusion criteria for the LD group were as follows: 1) diagnosed with LD, underwent keratoplasty and underwent corneal stitch removal at 1 year postoperatively; 2) age > 7 years; and 3) diagnosed with amblyopia with a logMAR BCVA of 1.00 or better. The inclusion criteria for the control group were as follows: 1) age > 7 years, 2) logMAR BCVA of 0.00 or better, and 3) no history of any ocular pathology and normal physical and mental health.
|                              | Limbal Dermoid Group (N = 25) | Normal Group (N = 27) |
|------------------------------|-------------------------------|-----------------------|
|                              | N    | %  | N    | %  |
| Sex Female                   | 12   | 48%| 12   | 48%|
| Age (Years)                  |      |    |      |    |
| 7 to < 10                    | 12   | 48%| 12   | 48%|
| 10 to < 13                   | 13   | 52%| 13   | 52%|
| Mean (SD)                    | 10.2 ± 1.9 (7–13)             | 10.2 ± 2.0 (7–13)     |
| Amblyopic-Eye Spherical Equivalent (Diopters) | -3.8 ± 3.7 (-0.25 - -8.00) | -4.3 ± 2.0 (0 - -6.00) |
| Amblyopic-Eye Cylinder Equivalent (Diopters) | 4.9 ± 2.9 (1.00–9.00) | 0.3 ± 0.2 (0- 0.50) |
| Perceptual learning Group (N = 9) |      |    | Patching Group (N = 8) |      |
| Sex Female                   | 5    | 55%| 4    | 50%|
| Age (Years)                  |      |    |      |    |
| 7 to < 10                    | 4    | 45%| 3    | 37.5%|
| 10 to < 13                   | 5    | 55%| 5    | 63.5%|
| Mean (SD)                    | 9.4 ± 1.7 (7–11)              | 10.4 ± 2.0 (7–12)     |

All subjects were screened using a detailed baseline eye examination, which included manifest refraction, BCVA using the Early Treatment Diabetic Retinopathy Study (EDTRS) logMAR chart, CSF at 1.5, 3, 6, 12, and 18 cycles per degree of spatial frequency, intraocular pressure measurement, slit-lamp biomicroscopy, and fundus examination.

**Study design**

The studies were divided into two parts. In part 1, all patients underwent the visual function evaluation test, and part 2 consisted of perceptual learning or part-time patching therapy.

In part 1, there were two groups, including the LD group and normal group. In the LD group, 25 patients were diagnosed with amblyopia and had occlusion for more than 6 months, while no obvious VA improvement was observed. They underwent monocular and binocular VA assessments and a qCSF assessment under full optical correction after a routine ophthalmic examination. In the normal group, 25 normal children wore an optical defocus (+1.00 D to +6.00 D positive spherical lens) on the right eye to blur the distance BCVA, with the vision of the left eye unaltered [14,15]. They then underwent the qCSF
assessment for the right eye and left eye separately. Optical defocusing was used to simulate the monocular blurred BCVA in the LD group. For example, five patients had a logMAR VA of 0.40; accordingly, the vision of five normal subjects was blurred to a logMAR VA of 0.40 using optical defocus to match the vision of the LD patients while undergoing the qCSF assessment.

In part 2, all the LD children after keratoplasty with amblyopia were divided randomly into two groups, namely, the perceptual learning group (N = 9) and the part-time patching group (N = 8). After randomization (± 1 week), follow-up visits were planned at the 1st week and the 1st, 2nd, 3rd, 4th, 5th and 6th months. The 9 children in the LD group underwent perceptual learning for successive 30-minute sessions daily and were prescribed 2 hours of daily patching with an adhesive style patch (i.e., Coverlet, 3M Opticlude, Ortopad), and the 8 children in the control group were prescribed 2 hours of daily patching with an adhesive style patch (i.e., Coverlet, 3M Opticlude, Ortopad). At each visit, VA was measured in each eye with optimal refractive correction by a mask study-certified examiner using the ETDRS, and CSF was measured using the quick CSF methods, which would be explained below.

After completing the 6-month training sessions, all the children were evaluated at the 1st, 3rd and 6th months after completing the training. Flowchart showing study completion in each treatment group (Supplementary Fig. 1).

**CSF measurements based on the qCSF paradigm**

The qCSF method included ten alternative forced-choice digit identification tasks to assess the CSF. Stimuli were displayed on a gamma-corrected 46-inch LCD monitor (Model: NEC LCD P463, Samsung, Suwon City, Korea) with 1920 × 1080-pixel resolution, a 50-cd/m² mean luminance and a 60-Hz vertical refresh rate. Thirty trials were conducted, with a total testing time of approximately 5 minutes. The qCSF data were scored to generate 1) the AULCSF, a summary descriptor of contrast thresholds in spatial vision, at spatial frequencies of 1, 1.5, 3, 6, 12, and 18 cpd; and 2) the cutoff SF, which was defined as the spatial frequency acuity corresponding to a perceptual CS at 50%. The AULCSF and cutoff SF values were used for further analysis.

**Perceptual learning therapy**

All patients’ refractive status was best corrected one month prior to starting therapy. At each session, an algorithm analyzed the subject’s responses and accordingly adjusted the level of visual difficulty to the range most effective for further improvement. The treatment was applied in successive 30-minute sessions daily and was prescribed 2 hours of daily patching with an adhesive style patch (i.e., Coverlet, 3M Opticlude, Ortopad). The sessions in the first week were performed at the clinic under supervision, with additional sessions performed at home. Each treatment station (home PC) was connected to the central database server via the Internet. After each training session, the results were automatically sent to the server via the Internet. The algorithm, which was located in the central server, calculated specific patient results and sent them back to the specific station as a tailored training task.

**Statistical analysis**
The data are presented as the means ± standard deviations. A t-test was used for statistical comparisons of the CSF results, including the cutoff SF and AULCSF. Welch's correction was performed for comparisons of the CSF results for each spatial frequency, and Bonferroni correction was added for multiple comparisons. Statistical analyses were performed using SPSS version 24.0 (SPSS, Inc., Chicago, IL, USA), and p-values < 0.05 were considered statistically significant.

Results

Clinical demographics

The study group included 25 children with limbal dermoid (LD group) and 25 healthy children (N group) with the specific demographics shown in Table 1. There were 12 females (48%) with an average age of 10.2 ± 1.9 (7–13) years in the LD group and 12 females (48%) with an average age of 10.2 ± 2.0 (7–13) years in the N group. The mean sphere and cylinder measurements were 3.8 ± 3.7D (-0.25 - -8.00), 4.9 ± 2.9D (1.00–9.00) and −4.3 ± 2.0 (0 - -6.00), 0.3 ± 0.2 (0- 0.50) in the LD and N group, respectively. In the LD group, there were 9 children in the perceptual learning group with an average age of 9.4 ± 1.7 (7–11) years. The average age of children in the control group was 10.4 ± 2.0 (7–12) years.

CSF metrics in the LD group

The qCSF test showed that CSF was low in LD patients, as demonstrated by the mean AULCSF in Fig. 1a. Compared with the normal group, the LD group and optical defocus group showed significant reductions in AULCSF values (1.29 ± 0.27 vs. 0.40 ± 0.05 (p = 0.0006) and 0.70 ± 0.05 (p = 0.00009)). Moreover, the LD group had a lower cutoff SF (mean ± SD, 5.38 ± 0.75 cpd) compared with the optical defocus group (mean ± SD, 8.81 ± 0.74 cpd) and normal viewing group (mean ± SD, 14.81 ± 0.89 cpd) (p = 0.004, 0.005, respectively) (Fig. 1b).

The cumulative probability distributions of the AULCSF for the LD and N groups are shown in Fig. 1c. The log CS of the LD group was significantly lower than that of the optical defocus group (p = 0.0004, 0.008, 0.006, 0.028, 0.045 and 0.026 at spatial frequencies of 1, 1.5, 3, 6, 12 and 18 cpd, respectively) and the normal viewing group (p = 0.037, 0.042, 0.031, 0.033, 0.032 and 0.031 cpd, respectively) after Bonferroni correction (Fig. 1d). For example, at a spatial frequency of 1 cpd, the log CS for the LD group was 0.97 ± 0.07 vs. 1.35 ± 0.04 (p = 0.0004) and 1.55 ± 0.07 (p = 0.037) for the optical defocus and normal viewing groups, respectively. Similarly, at 1.5 cpd, the CS was 0.89 ± 0.08 vs. 1.23 ± 0.05 (p = 0.008) and 1.42 ± 0.08 (p = 0.042), respectively.

Figure 2a-i illustrates the reduction in the AULCSF at each spatial frequency (from 0.5 to 18 cpd) for the LD group compared with that for the optical defocus group, with a simulated reduction in matched BCVA (from logMAR BCVA 1.0 to 0.04). The results of the normal viewing group served as a reference AULCSF for the normal population.
Improvement in visual acuity in the LD group with perceptual learning

At the 1st week, after adjusting for baseline VA, the mean BCVA improved from baseline 0.63 ± 0.11 to 0.53 ± 0.12, with a difference between means of 0.10 ± 0.16 (P = 0.542) in the perceptual learning group, while that in the control group improved from 0.67 ± 0.09 to 0.65 ± 0.08 (P = 0.899). In the perceptual learning group, the mean BCVA increased to 0.49 ± 0.11 (P = 0.377), 0.48 ± 0.11 (P = 0.332) and 0.32 ± 0.09 (P = 0.04) at the 1st, 3rd and 6th months, respectively. At the 6th month, the mean BCVA difference was 0.31 ± 0.14 and 0.03 ± 0.12 in the perceptual learning group and patching group, respectively. The visual acuity in the follow-eye was the same as that in the better eye, which was from 0.00 ± 0.00 to 0.00 ± 0.00 in both the perceptual learning group and patching group (Fig. 3a, Table 2). None of the follow-eyes showed a decrease in the BCVA, and the refractive degree was almost stable. During the follow-up at the 1st, 3rd and 6th months after completing training, no obvious improvement or reduction in the BCVA of the amblyopic eye was observed.

| Group                  | Perceptual Learning Group (N = 9) | Patching Group (N = 8) |
|------------------------|------------------------------------|------------------------|
|                        | Time point                         |                        |
|                        | Baseline                           | 6-month visit          | Difference value |
|                        | Visual Acuity in Amblyopic Eye     | 0.63 ± 0.11            | 0.32 ± 0.09       | 0.31 ± 0.14  |
|                        | Visual Acuity in Fellow Eye        | 0.00 ± 0.00            | 0.00 ± 0.00       | 0.00 ± 0.00  |
|                        | AULCSF in Amblyopic Eye            | 0.49 ± 0.15            | 1.06 ± 0.20       | 0.56 ± 0.25  |
|                        | AULCSF in Fellow Eye               | 1.34 ± 0.12            | 1.37 ± 0.11       | 0.23 ± 0.02  |

Improvement in the contrast sensitivity function in the LD group

The mean improvements in AULCSF were from 0.49 ± 0.15 to 0.73 ± 0.18 (P = 0.32), 0.78 ± 0.21 (P = 0.28), 0.80 ± 0.19 (P = 0.22) and 1.06 ± 0.20 (P = 0.04) at five time points, namely, baseline, 1st week, 1st month, 3rd month and 6th month, in the perceptual learning group. The results showed that the efficacy of therapy was significantly correlated with treatment duration. Comparatively, the AULCSF was from 0.50 ± 0.14 to 0.54 ± 0.13 (P = 0.83), 0.55 ± 0.14 (P = 0.79), 0.51 ± 0.13 (P = 0.97) and 0.49 ± 0.14 (P = 0.96) at five time points, namely, baseline, 1st week, 1st month, 3rd month and 6th month, in the patching group, which did not show an obvious increase in the AULCSF (Fig. 3b, Table 2).
The cumulative probability distributions of the AULCSF for the perceptual learning group and patching group from baseline to 6 months are shown in Fig. 3b. The intersection at 50% probability represents an indicative AULCSF value for the respective conditions, i.e., 0.345 and 0.812 for the perceptual learning group at baseline and 6 months and 0.348 and 0.335 for the patching group at baseline and 6 months. Each patient’s performance in the perceptual learning group is shown in Fig. 3c-k. None of the follow-eyes showed a decrease in the CSF. During the follow-up at the 1st, 3rd and 6th months after completing training, no obvious improvement or reduction in the CSF was observed.

**Discussion**

Our previous study established a grading system for limbal dermoids for clinical diagnosis and revealed that a lower grade dermoid was associated with better vision postoperatively [16]; however, little research has been conducted on visual function evaluation and vision reconstruction postoperatively. In this study, the LD patients exhibited obvious visual impairment in visual acuity and contrast sensitivity compared with the normal children, as many factors can influence the ability to discern contrast, such as the media opacities caused by the remaining focus, the stray light and glare sources induced by astigmatism and background illumination [4, 5]. Most epibulbar dermoids were excised with lamellar excision, and the remainder were excised with lamellar keratoplasty or eccentric sclerocorneoplasty. Hussein et al. [17] identified astigmatism greater than 1.5 D preoperatively and postoperatively as a risk factor for amblyopia. The mean spherical and astigmatic refractive errors in our participants were -3.78±3.71 D and -4.92±2.91 D, respectively, which were deemed to be associated with a high risk of amblyopia, while no conclusions were drawn regarding whether surgical resection facilitated amblyopia treatment or improved visual outcome. Our study indicated that obvious CSF impairment was observed in these LD children. In Nielsen and Hjortdal’s [4] study, the patients underwent posterior lamellar keratoplasty and had similar VAs and refractive statuses. The mean log CS was 1.06±0.25, compared with 0.49±0.15 in our study, in which Nielsen’s patients showed better CSF performance. We deduced that this is because the lamellar keratoplasty procedure could help to rebuild visual function, including CSF [4, 18]. These patients showed worse visual function than the children who had the same visual condition under the optical defocus. Optical defocus was used in this study to simulate the visual conditions of LD patients, which did not degrade binocular function and was the most permissive for binocular function [15]. The LD children exhibited obvious contrast sensitivity function impairment, especially at high spatial frequencies, compared with the corresponding optical defocus group, at almost each spatial frequency ranging from 1 to 0.04 LogMAR BCVA. Although refractive errors have been corrected prior to visual function evaluation, visual recovery may be dependent on further changes in the subepithelial and host stroma, ultimately leading to light scatter and amblyopia [19]. Management of amblyopia must continue after surgical excision to yield optimal results when or if the surgery is done at a younger age.

The term “perceptual learning” describes a process whereby practicing certain visual tasks leads to an improvement in visual performance [20]. Visual performance can be improved with repetitive practice of specific controlled visual tasks. These repetitive tasks initiate neural modifications that can lead to
improvement in neuronal efficiency [21]. It should be emphasized that the patients had not shown any improvement with patching for 6 months. Nevertheless, they improved remarkably by training using the perceptual learning technique. The mean BCVA increased from 0.67±0.09 to 0.32±0.09, with an improvement of 0.35, under perceptual learning, and the AULCSF in the contrast sensitivity increased from 0.49±0.15 to 1.06±0.20, which is encouraging and reveals a positive trend. Polat et al. [11] studied 54 adult amblyopic patients who were randomized to a perceptual vision treatment program or a placebo vision training program for amblyopia. Pretreatment visual acuity in both study groups was 0.42 logMAR, and this improved by 2.5 lines in the perceptual vision treatment group, with no improvement in the control group [22]. It is likely that the advantage of perceptual learning is due to an active task that the subject is required to perform, whereas patching is passive [23]. More importantly, perceptual learning involves specifically training spatial frequencies within a range that can be improved. It is worth noting that the improvement of CS only appeared at the low and middle spatial frequencies, not at the high spatial frequencies. However, the middle and high spatial frequencies have been documented to be particularly useful for target detection and identification tasks, even in patients in whom visual acuity is not excellent [24]. We deduced that the high spatial frequencies require better visual acuity to recover [25].

Some experiences have been acquired in our study on perceptual learning for LD children. First, the logMAR BCVA should be at least 1.00 or better to ensure that the children could recognize the visual target clearly, as persistence of the improved visual function showed that learning is not just a temporary adaptation effect but a long-lasting change in the visual cortex [26], and attention plays an important role in selecting what we do (and do not) learn effectively [4]. Then, strict supervision and follow-up visits were significant to ensure learning efficiency and compliance because the learning process was constant and gradual and the interruptions worsened the impression of the visual cortex [27], so statistical significance on visual improvement was not observed until 6 months in our study.

To the best of our knowledge, this is the first perceptual learning study to focus primarily on LD children, and perceptual learning therapy was helpful for improving the CSF as well as VA, which holds promise for treating LD children with amblyopia when conventional treatment fails.

**Abbreviations**

Perceptual learning(PL); the area under log CSF (AULCSF); cutoff spatial frequency (cutoff SF); Limbal dermoid (LD); LKP (lamellar keratoplasty); PKP (penetrating keratoplasty); contrast sensitivity (CS); contrast sensitivity function (CSF); best-corrected visual acuity (BCVA); Limbal Dermoid (LD); Normal (N); Early Treatment Diabetic Retinopathy Study (EDTRS)

**Declarations**

*Ethics approval and consent to participate*

This study adhered to the tenets of the Declaration of Helsinki and was approved by the
Ethics Committee of Zhongshan Ophthalmic Center of Sun Yat-sen University. All patients provided written consent to participate in this study.

*Consent for publication*

Not applicable.

*Availability of data and materials*

We would like to share all the original data reported in the manuscript to researchers related to this field for noncommercial use. Email could be sent to the corresponding authors to obtain the shared data.

*Competing interests*

The authors declare that they have no competing interests.

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*Authors’ contributions*

Conception and design: Jin Yuan and Jinrong Li; Administrative support: Jin Yuan and Jinrong Lin; Provision of study materials or patients: Jin Yuan and Jinrong Lin; Collection and assembly of data: Jing Zhong, Yiyao Wang, Xiaoqing Hu; Data analysis and interpretation: Jing Zhong, Yiyao Wang, Xiaoqing Hu, Lei Feng, Qingqing Ye, Yiming Luo and Yair Morad; Manuscript writing: All authors. Final approval of manuscript: All authors.

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Figures

![Figure 1](image1.png)

Figure 1
CSF metrics in the LD group. A qCSF Statistics Summary for LD and Normal Groups. (1a) A comparison of the area under log CSF (AULCSF), where a value < 1.0 indicates a reduction from the normal viewing range. (1b) Comparison of the cutoff spatial frequencies among the groups. A significant reduction is noted from the cutoff SF value of normal viewing conditions. (1c) A cumulative probability distribution of the AULCSF is projected for the LD and normal groups. The intersection at 50% probability represents an indicative AULCSF value for the respective conditions, i.e., 0.41 (LD group), 0.68 (plus lens-induced blur viewing group) and 1.27 (normal viewing group). (1d) A between-group comparison of log contrast sensitivities at 1, 1.5, 3, 6, 12, and 18 cpd. A reduction in CSF can be observed across all spatial frequencies tested. *, p<0.05; **, p<0.01; ***, p<0.001.

Figure 2

Comparison of the CSF metrics between the LD and control groups. The contrast sensitivities from BCVA logMAR 1.00 to 0.04 in the LD group and optical defocus under simulated reduced BCVA conditions. Normal viewing with normal BCVA was plotted as a reference range. A reduction in the area under the contrast sensitivity curve of the LD group was noted compared with that of control subgroups 1 and 2 (Fig. 2a@logMAR=1.00: 0.465 vs. 1.399 and 3.311, Fig. 2b @logMAR=0.70: 0.643 vs. 1.632 and 6.311, Fig. 2c@logMAR=0.52: 1.067 vs. 2.015 and 6.311, Fig. 2d@logMAR=0.40: 1.995 vs. 3.477 and 6.311, Fig. 2e@logMAR=0.30: 2.182 vs. 3.806 and 6.311), Fig. 2f@logMAR=0.22: 2.401 vs. 4.518 and 6.311, Fig.
Figure 3

BCVA and CSF improvement in LD patients under perceptual learning. LogMAR best corrected visual acuity at baseline, 1 week and 1, 3 and 6 months in the perceptual learning group and patching group (3a). A cumulative probability distribution of the AULCSF is projected for the LD and normal groups (3b). Each patient's CSF performance in the perceptual learning group is shown from 3c to 3k.

Supplementary Files
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- Protocol.doc
- Sfigure1.jpg