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Antipsychotic Effects of Celecoxib Add-On Haloperidol in Schizophrenia: A Randomized Double-Blind Placebo-Controlled Clinical Trial

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Abstract

Background: Previous studies have indicated abnormalities in the immune system, such as central nervous system inflammation and high levels of activating cytokines in the cerebrospinal fluid of schizophrenic patients. Celecoxib, a modulator of proinflammatory cytokines, as an adjunctive therapy add-on risperidone (a well-established atypical antipsychotic) and amisulpiride (a benzamide antipsychotic), had improved these patients significantly.
Objectives: A trial was conducted to evaluate the therapeutic effects of celecoxib add-on haloperidol, a classic antipsychotic that has been reported to have an immunomodulatory effect and mainly affects positive psychotic symptoms in schizophrenia.
Methods: In a prospective, double-blind study, after a washout period, 49 patients with schizophrenia were randomly assigned to either 15 - 30 mg/day haloperidol plus 400 mg/day of celecoxib or the same dose of haloperidol plus placebo for 5 weeks. Psychopathology was evaluated via the Positive and Negative Symptoms Scale (PANSS). The data were reported as mean ± standard deviation and frequency. An Independent *t*-test was carried out when comparing the data of these two groups for each week. The proportion comparison was carried out using the chi-square test. In terms of age, gender, marital and educational state, and duration or severity of disease or psychopathology and subtypes of schizophrenia, there were no significant differences.
Results: Over 5 weeks, there was significantly greater improvement in the celecoxib group in scores on the total PANSS and on positive symptoms and general psychopathology subscales ([t = 2.89, P = 0.006], [t = 2.37, P = 0.022], and [t = 3.34, P = 0.002] respectively).
Conclusions: Celecoxib is an efficient adjuvant agent in the treatment of patients with schizophrenia. Significant superiority of management with a modulator of proinflammatory cytokine, which balances immune responses over haloperidol alone, reconfirms the immune dysfunction and inflammation hypothesis of schizophrenia.

Keywords: Celecoxib, COX-2 Inhibitor, Haloperidol, Immune System, Schizophrenia

1. Background

Major psychiatric disorders (e.g., schizophrenia) and mood disorders (e.g., bipolar and major depressive disorders) have been hypothesized to be affected by inflammatory conditions (1-3). In many cases, these disorders have poor outcomes (4). In particular, schizophrenia is associated with a deteriorative process in most of the affected patients (5).

One study demonstrated decreased gene expression for the cytokines interferon-gamma (IFN-γ) and tumor necrosis factor-alpha (TNF-α) in schizophrenia, which is associated with disturbed type 1 cellular immunity (6). The assumption that both inflammation and neuropsychiatry disorders, such as this one, have the same molecular pathways is supported by the fact that sickness-like behavior can be induced by inflammatory cytokines (7). Schizophrenia has been considered to be an idiopathic autoimmune/inflammatory disease related to a deviant amount of circulating pro- and anti-inflammatory immune biomarkers and peripheral cytokines (6-13).

Several other immunological abnormalities, such as high levels of interleukin-1 (IL-1) and interleukin-2

(IL-2), have also been reported in schizophrenic patients (8, 14, 15). A high amount of lL-2 in the cerebrospinal fluid (CSF) is a known predictor of a greater likelihood of relapse in these patients (16). Therefore, activating cytokines' down-regulation in the central nervous system (CNS) resulting from anti-inflammatory therapy might have beneficial consequences for some schizophrenic patients (10). The immunomodulatory properties of some antipsychotic agents, especially atypical neuroleptics (17-19), and some classical antipsychotic drugs, such as haloperidol, support this hypothesis (16, 20, 21).

This interesting etiological hypothesis has been challenged by studies that have attempted to assess whether immunomodulatory drugs show beneficial effects on schizophrenia symptoms. For instance, subchronic prescription of a cyclooxygenase-2 (COX-2) inhibitor improved schizophrenia-like behavioral deficits and accordingly regulated dopamine turnover in animal studies (22). Some studies have demonstrated the effectiveness of aspirin, a nonsteroidal anti-inflammatory drug (NSAID), on the reduction of schizophrenia symptoms (23-25). Several clinical trials have studied the effect of risperidone plus celecoxib (a selective COX-2 inhibitor [pdCOX-2 inhibitor]) compared to the group with risperidone plus placebo in the treatment of schizophrenia (10, 26, 27).

Another clinical trial has examined the advantageous antipsychotic consequences of celecoxib plus amisulpride therapy compared to amisulpride alone in schizophrenia (28). Risperidone is a second-generation neuroleptic with a high impact on both positive and negative symptoms of schizophrenia (26, 29, 30). Amisulpiride, a benzamide antipsychotic, affects the negative symptoms (31). The effect of amisulpiride on the negative symptoms of schizophrenia has been improved by celecoxib (28). However, celecoxib add-on risperidone has resulted in different effects on positive symptoms and no effect on negative symptoms (10, 26, 27). On the other hand, different antipsychotic drugs have been reported to affect (i.e., increase or decrease) different interleukins (3, 17, 20, 21, 32-35).

With these controversial findings, it seems useful to study the effects of anti-inflammatory therapy (i.e., celecoxib) plus a different neuroleptic (i.e., haloperidol). Haloperidol was selected because it is one of the most widely used antipsychotics, which is more effective in the reduction of positive symptoms of schizophrenia than in the treatment of negative symptoms. It is generally believed that paranoid symptoms are treated more effectively than non-paranoid symptoms by this drug and that women are more responsive than men (36). On the other hand, haloperidol has been reported to have immunomodulatory properties (16, 20, 21).

2. Objectives

This trial evaluates the therapeutic effects of celecoxib add-on haloperidol in comparison to haloperidol plus placebo on the reduction of positive and negative symptoms of schizophrenia.

3. Methods

3.1. Patients

Forty-nine eligible inpatients with schizophrenia in the Zare Hospital (Sari, Mazandaran, Iran) were included in the study (IRCT registration number: IRCT138809201457N6). The inclusion criteria were the diagnostic and statistical manual of mental disorders, fourth edition, text revision (DSM-IV-TR) criteria for schizophrenia and the informed consent of patients and their guardians to participate in the study. The exclusion criteria were infectious diseases, inflammatory diseases, and anti-inflammatory drug consumption. By using a table of random numbers and block randomization, 25 patients (4 women, 21 men) were randomly assigned to treatment with haloperidol plus celecoxib, and 25 (4 women, 21 men) were assigned to haloperidol plus placebo. All participants were in the active phase of the disorder and had been hospitalized at the same facility, and none of them was affected by infectious or inflammatory diseases. Two independent psychiatrists made the diagnosis of schizophrenia according to the criteria of the DSM. No patient fulfilled the criteria for treatment resistance.

3.2. Procedure

This study was a prospective, double-blind clinical trial of parallel comparison groups of patients with schizophrenia who were stratified according to gender and subtype of schizophrenia (paranoid and non-paranoid) and randomly allocated to treatment with either "haloperidol plus celecoxib" or "haloperidol plus placebo". The division of patients into paranoid and non-paranoid was due to the fact that the ego resources of the paranoid subtype tend to be more outstanding, and they display less regression of their mental capacities, emotional responses, and conduct than other subtypes of schizophrenia (37). The study was accomplished in accordance with the Declaration of Helsinki and subsequent revisions and approved by the Research Committee and the Human Subject Review Ethics Committee of Mazandaran University of Medical

Sciences (ethics committee reference number: 108-82). The patients were included after they and/or their guardian had given their informed consent to participate in the trial.

After diagnosing and screening, the patients who were consuming oral neuroleptic medication underwent a washout period of 3 - 5 days. No patients were taking long-acting injectable neuroleptic before admission to the hospital.

The patients were medicated with lorazepam, if necessary, during the washout period. During the trial, patients with agitation, anxiety, or sleep problems also received lorazepam.

A psychiatry resident assessed psychopathology via the Positive and Negative Symptoms Scale (PANSS) (38), recorded drug side effects with a checklist for each patient at the beginning of the study and repeated these measures weekly until 35 days (5 weeks). The psychiatry resident and patients were blind to the treatment groups.

In this study, 15 - 30 mg haloperidol was prescribed for each patient. Celecoxib was started with a dosage of 200 mg BID (400 mg/day) for the first group. The control group was also prescribed with placebo capsules, which had the same shape, color, taste, and size as celecoxib, in the same way as the first group. This regimen was followed through for the next 5 weeks.

For the treatment of extrapyramidal side effects of haloperidol, biperiden was available. Lorazepam was used for the treatment of insomnia, agitation, or anxiety. No other anti-inflammatory or sedative-hypnotic drug was used. Both of these medications were used for the patients in an ad libitum dose schedule.

3.3. Statistical Analysis

All of the statistical analyses were carried out with the statistical package for social sciences (SPSS) version 20.0 (SPSS Inc., Chicago, IL). The data were reported as mean ± standard deviation (SD) and frequency (%). An independent *t*-test was used to compare the data from each group on a weekly basis. For the comparison of proportions, the chi-square test was used. This process was performed for the PANSS total scale and the positive, negative, and general psychopathology subscales. A significance level of 0.05 was considered in all analyses.

4. Results

It was supposed to study 50 patients. However, the trial was stopped due to the Ministry of Health and Medical Education's Celecoxib Related Sudden Death warning at the time of the study and because there was a case of sudden death in the studied patients.

The mean doses of haloperidol in the celecoxib group and placebo group, in addition to the age of the patients and duration of the disorder, can be observed in Table 1. These variables were not significantly different in the two groups.

Table 1. Comparison of Celecoxib and Placebo Groups in Terms of Age (y), Amount of Haloperidol (mg) and Course of the Disorder (y)

	Mean ± SD	*t*-Value	Sig.
Age			
Celecoxib group	37.71 ± 11.61	0.39	0.53
Placebo group	36.57 ± 10.41		
Amount of haloperidol			
Celecoxib group	20.60 ± 2.63	1.52	0.22
Placebo group	21.43 ± 2.80		
Course of the disorder			
Celecoxib group	12.78 ± 8.97	0.33	0.56
Placebo group	16.29 ± 9.08		

The mean age was 37.71 years (± 11.61) and 36.57 (± 10.41) years in the celecoxib and placebo groups, respectively. Two groups were matched according to gender and subtype of schizophrenia. Moreover, 20 men and 3 women in the celecoxib group and 19 men and 4 women in the control group completed the study (χ^2 = 0.02, df = 1, P = 0.87). The celecoxib group consisted of 11 paranoid and 12 non-paranoid schizophrenic patients; however, the control group consisted of 10 paranoid and 13 non-paranoid patients (χ^2 = 0.08, df = 2, P = 0.58). Additionally, there was no significant difference in the marital (χ^2 = 1.74, df = 3, P = 0.62) and educational (χ^2 = 6.06, df = 4, P = 0.19) states of the two groups.

At the beginning of the study, the mean score of the PANSS and its subscales scores did not show any significant difference in the two groups (Table 2).

Before the end of this trial, 2 patients discontinued treatment with celecoxib, and 1 patient dropped out of treatment with a placebo. The dropout from the placebo group was aged 37 years (one man) due to unexplained sudden death. The dropouts from the celecoxib group were aged 38 and 43 years (one woman, one man). The reason for dropping out of these two patients was noncompliance with oral medication. In general, the dropout rate of the trial was low in both groups; for celecoxib, it was 8%, and for placebo, it was 4.2%.

A significant amelioration in psychopathology was observed over the 5 weeks of trial in both groups. The effects of haloperidol treatment, however, were not the focal point of our trial.

More effect on the mean improvement in the total

Table 2. Comparison of Positive and Negative Symptoms Scale Scores and Its Subscales' Scores at the Beginning of the Study in Celecoxib and Placebo Groups [a]

Subscales and Group	n	Mean ± SD	*t*-Value	Sig.
P			0.96	0.34
Celecoxib group	21	18.08 ± 5.50		
Placebo group	25	16.52 ± 5.43		
N			0.52	0.6
Celecoxib group	21	27.52 ± 8.37		
Placebo group	25	26.29 ± 7.53		
G			1.57	0.12
Celecoxib group	21	36.28 ± 8.16		
Placebo group	25	32.52 ± 7.89		
S			0.19	0.85
Celecoxib group	21	4.95 ± 2.32		
Placebo group	25	5.08 ± 2.17		
Total			1.37	1.76
Celecoxib group	21	86.96 ± 17.97		
Placebo group	25	80.29 ± 14.26		

[a] P, positive symptoms; N, negative symptoms; G, general psychopathology; S, supplementary items of aggression.

PANSS score was observed in the celecoxib group than in the placebo group over the 5 weeks of the trial (t = 2.89, P = 0.006). In particular, reductions in the scores on the positive symptoms subscale (t = 2.37, P = 0.022) and on the general psychopathology subscale (t = 3.34, P = 0.002) contributed to this effect; nevertheless, negative symptoms (t = 1.78, P = 0.81) and supplementary items of aggression (t = 0.87, P = 0.385) were different significantly between two groups (Table 3).

The side effects of haloperidol were not significantly different in the two groups. No side effects were observed, which were attributed to celecoxib administration, in particular gastrointestinal problems. Celecoxib was well tolerated, and there was no significant difference in drug side effects between the two groups.

5. Discussion

Neuroimmune-endocrine dysregulation is a fundamental mechanism underlying psychiatric disorders, including schizophrenia (8). Several immune system abnormalities, including dysregulation of cytokines production, immunoglobulins, and T-cell subsets, have been reported in this disorder (39). Possibly, another mechanism of schizophrenia pathogenesis is an imperfect connection between the central and peripheral immune systems (40-42).

In the current study, a significant improvement in the total PANSS score and in all subscales during the 5 weeks of the trial with haloperidol was observed in both haloperidol plus celecoxib and haloperidol plus placebo groups. It was an expected event because both groups had received a well-established antipsychotic drug, which also has immunomodulatory properties. This improvement was higher in the experimental group, which had received celecoxib. The improvement in the total PANSS score, total positive subscale, and general psychopathology subscale were significantly higher in the celecoxib group than in the placebo group. However, the improvement in the total negative subscale and supplementary items of the aggression profile was not significantly different.

As there were no significant differences regarding the demographic and clinical features of the patients, such as age, gender, marital and educational state, duration or severity and subtype of the disorder, and haloperidol dosage, the differences in therapeutic outcome cannot be attributed to these variables.

Celecoxib in 400 mg/day dosage was well tolerated, and no significant clinical adverse effects were reported.

There are a few contentions with respect to the immunomodulatory properties of haloperidol (39). Haloperidol normalized (i.e., decreased the increased) serum IL-2, CD3 (+), CD4 (+), CD8a (+), CD3 (+) CD8a (+), and CD3 (+) CD4 (+) T-cell subsets, and immunoglobulin A (IgA), immunoglobulin M (IgM), and immunoglobulin G (IgG) levels in experimental animal models of

Table 3. Comparison of Differences in Positive and Negative Symptoms Scale Scores and Its Subscales' Scores in Celecoxib and Placebo Groups After the Intervention [a]

Subscales and Group	n	Mean ± SD	*t*-Value	Sig.
P			2.37	0.022
Celecoxib group	21	7.56 ± 4.22		
Placebo group	25	4.43 ± 4.72		
N			1.78	0.081
Celecoxib group	21	9.12 ± 6.72		
Placebo group	25	6.00 ± 5.00		
G			3.34	0.002
Celecoxib group	21	12.20 ± 5.37		
Placebo group	25	6.00 ± 7.18		
S			0.87	0.385
Celecoxib group	21	1.80 ± 2.29		
Total			2.89	0.006
Celecoxib group	21	30.68 ± 12.97		
Placebo group	25	18.14 ± 16.43		

[a] P, positive symptoms; N, negative symptoms; G, general psychopathology; S, supplementary items of aggression.

schizophrenia and schizophrenic patients (3, 19, 43, 44). However, although there is some evidence indicating the normalizing effect of haloperidol on CD4 (+)/CD8a (+) T cells, IL-6, IL-1β, and TNF-α, this outcome is partial or controversial (39, 44-47).

Overall, despite the above-mentioned controversies regarding the effects of haloperidol on cytokines production, immunoglobulins, and T-cell subsets switch, and despite the synthesis of new drugs for the treatment of schizophrenia, haloperidol is still widely used, and its therapeutic effects on schizophrenia are a benchmark against which newer antipsychotic drugs can be measured. Additionally, immunomodulatory therapy might be a beneficial approach to the management of schizophrenia (39).

The beneficial response of the experimental group in the current study has to be related to the celecoxib effects. Celecoxib is a nonsteroidal anti-inflammatory, inexpensive, cost-effective drug with few side effects and is easily available in many countries. Celecoxib is an inhibitor of COX-2, a major selective mediator of inflammation in the periphery and brain, and a key regulatory enzyme associated with the synthesis of prostaglandins (48, 49). The removal of COX-2 expression of neurons in the forebrain has been shown to produce neuroprotective effects (50).

Some authors have reported a reduction of plasma IL-2 (20, 21, 51, 52), which activates the COX-2 and mediates the inflammation of the CNS (26). Others have not mentioned reductions in IL-6 (32, 46, 52).

A recent meta-analysis has concluded that celecoxib is safe in the treatment of psychotic symptoms (53), which is in line with the results of the current study. Several mechanisms have been suggested for the effects of celecoxib as follows:

(A) The observation of psychotic symptoms in chronic abusers of the glutamate/N-methyl-d-aspartate (NMDA) receptor antagonist phencyclidine (PCP) has led to the glutamatergic hypothesis of schizophrenia (54); that is, NMDA receptors and glutamatergic neurons hyperactivity are involved in the pathogenesis of schizophrenia (17, 55, 56). On the other hand, glutamate/NMDA receptor-mediated neurotoxicity involves COX-2 (57), and COX-2 inhibitors make this state adverse (28, 58). However, there are some controversies regarding the effects of COX-2 inhibitors on NMDA. Some researchers have reported inhibited effects mediated by the NMDA receptor (28). Nevertheless, others have not mentioned the kainite receptors' mediated effects of COX-2 (32). This finding might be the mechanism of the celecoxib effects.

(B) Type-1 immune response is blunt in schizophrenia. This phenomenon is associated with an imbalance in the tryptophan–kynurenine acid and in the activation of the enzyme indoleamine 2,3-dioxygenase (IDO) and, in turn, with an imbalance in the glutamatergic neurotransmission and then NMDA antagonism. The resulting inflammation has been attributed to immunological deficit, more COX-2 expression, and

prostaglandin E2 (PGE2) production (59). Celecoxib might rebalance this immunity imbalance, a property that overcomes the production of kynurenic acid (60).

Some studies refer to changes in T helper cells with a relative shift to anti-inflammatory T helper-2 activity over proinflammatory T helper-1 activity in schizophrenia (61, 62). The inhibition of PGE2 synthesis and regulating anti-inflammatory cytokine production, which leads to T helper-1/T helper-2 cytokine ratio by NSAIDs (such as celecoxib), restore this imbalance (25, 62, 63), and celecoxib's COX activity is the result of PG synthesis inhibition by the selective inhibition of the PG G/H synthase-2 (54-67).

Peripheral cytokines have an important role in the regulation of the hypothalamic-pituitary-adrenal axis (7), which is involved in the pathogenesis of schizophrenia. Decreased levels of IL-4 have been observed during the acute phase of schizophrenia (68). However, on the other hand, increased anti-inflammatory cytokines, particularly soluble IL-1RA (sIL-1RA), IL-2R, TNF-α, IL-10, TGF-β, IL-2, sL-2R, and soluble IL-6 receptors observed in the serum and the CNS of patients with schizophrenia might be accompanied by increased COX-2 expression (69, 70). Interleukin-2, IL-6, and IL-I0 activate the COX-2 and mediate the inflammation of the CNS (15, 16, 71, 72). It has been hypothesized that the mechanism of celecoxib effects is probably through the inhibition of COX-2 (26).

Structurally, epidermal growth factor (EGF)-like peptides (ErbB1 ligands) inhibit death and improve neurite outgrowth of CNS dopaminergic neurons and are involved in dopamine-associated brain diseases, such as schizophrenia (73). The administration of celecoxib has improved the abnormalities in prepulse inhibition (PPI) and suppressed learning and normalized dopamine metabolism in animal models (22). This EGF-triggered neuroinflammatory course of action, which is mediated in part by COX-2 activity and disturbs dopamine metabolism, might be involved in schizophrenic patients.

The anti-inflammatory COX-2 inhibitor celecoxib might improve this irregular connection and transmigration of immune cells (18, 74). This relationship between psychoneuroimmunology and psychopathology has been hypothesized to mediate negative symptomatology (75, 76).

Several clinical trials have examined the effect of the combination of celecoxib and different antipsychotic medications on positive and negative symptoms of schizophrenia. The current study has shown no effect of celecoxib add-on haloperidol on negative symptoms. On the other hand, celecoxib plus amisulpiride has been effective on the negative symptoms (28), and celecoxib combined with risperidone has resulted in different effects on positive symptoms and no effect on negative symptoms (10, 26, 77-79).

Considering that haloperidol is mainly effective in positive symptoms and has immunomodulatory properties (80, 81), amisulpiride is another neuroleptic drug that affects the negative symptoms (31) and risperidone is an antipsychotic medication with high effect on both positive and negative symptoms of schizophrenia (29, 30). The effect of celecoxib on negative symptoms should be more attributed to the antipsychotic component of the drug combinations rather than the celecoxib component.

On the other hand, a report of the acute onset of auditory hallucinations, which is an important positive symptom, has been reported after the initiation of celecoxib therapy (29). Lantz and Giambanco, who had reported the acute onset of this positive psychotic symptom by celecoxib, have concluded that celecoxib is effective in a special subgroup of patients (82). Rapaport et al. have reported that celecoxib added to the neuroleptic regimen of continuously ill patients with schizophrenia did not make a difference in any of the clinical psychopathology, functional disability, and extrapyramidal side effects (79). Additionally, Zheng et al., in their meta-analysis, indicated that celecoxib usually affects the first-episode schizophrenia (53). This finding is despite the fact that none of our patients was in the first episode of schizophrenia. The duration of the disorder in the patients of the current study ranged from 3.81 to 25.37 years.

The unexplained sudden death in the present study occurred in a deteriorated cachectic patient who had received a placebo. A review article that has studied the population data and clinical studies linking COX inhibition to cardiovascular side effects concluded that there is a great body of evidence to support the safety of celecoxib at recommended doses in the treatment of arthritis (83). This finding has been confirmed later in a cross-trial safety analysis of six randomized placebo-controlled clinical trials (83). However, some authors believe that although many considerable clinical trials have studied its efficacy/safety and mechanism of action, there is insufficient knowledge about the resources in the incident of side effects (67, 84).

5.1. Limitations

This study did not monitor the plasma levels of haloperidol/celecoxib and/or their metabolites. The differences in treatment response between the groups might be due to non-adherence during haloperidol/celecoxib prescription or to differences in haloperidol/celecoxib metabolism. However, an inpatient

treatment method lowers the chance of noncompliance. The limited follow-up period was another limitation of this trial.

5.2. Suggestions for Further Studies

The investigation of the effects of add-on celecoxib to different antipsychotic medications in first-episode psychosis, extension of the duration of the study, different doses of celecoxib, and add-on of different COX-2 inhibitors are recommended for further clinical trials.

5.3. Conclusions

Celecoxib is an effective adjuvant medication in the treatment of patients with schizophrenia. The significant superiority of treatment with a modulator of the proinflammatory cytokine, which balances immune responses over haloperidol alone, reconfirms the immune dysfunction and inflammation hypothesis of schizophrenia.

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Footnotes

Authors' Contribution: Mehran Zarghami, Nasrin Dodangi, Paria Azari, and Alireza Khalilian conceived and designed the evaluation. Nasrin Dodangi collected the clinical data. Alireza Khalilian performed the statistical analysis. Mehran Zarghami, Nasrin Dodangi, and Paria Azari interpreted the clinical data. Mehran Zarghami drafted the manuscript. Nasrin Dodangi, Paria Azari, and Alireza Khalilian revised it critically for important intellectual content. All the authors read and approved the final manuscript.

Clinical Trial Registration Code: IRCT138809201457N6.

Conflict of Interests: The correspond author is the EIC of the journal.

Data Availability: The dataset presented in the study is available on request from the corresponding author during submission or after publication. The data are not publicly available due to privacy.

Ethical Approval: The study was performed in accordance with the Declaration of Helsinki and subsequent revisions and approved by the Research Committee and the Human Subject Review Ethics Committee of Mazandaran University of Medical Sciences (ethics committee reference number: 108-82).

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Informed Consent: The patients were included after they and/or their tutor had given their informed consent to participate in the study.

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