PROGNOSTIC SIGNIFICANCE OF ORAL FLUID FLUORIDE MEASUREMENT IN ACUTE PERICORONITIS

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Oral fluid is a valuable substrate for assessing dental health and other aspects of physical status. New methods for early diagnosis and prognosis of dental diseases on the basis of oral fluid composition are in constant demand. Excessive fluoride concentrations, often oversighted by dental therapists, negatively affect organs and tissues of the oral cavity. This study aimed at development and approbation of a method for reliable measurement of fluoride ions in oral fluid by capillary electrophoresis to be used in patients with dental diseases. The fluoride ion concentrations were measured in health (2.16 ± 0.48 mg/L), in isolated acute pericoronitis (15.2 ± 2.7 mg/L) and in acute pericoronitis combined to multiple caries (18.9 ± 4.2 mg/L). By post-operative day 3, fluoride levels in the group with isolated acute pericoronitis dropped to normal values (2.28 ± 0.52 mg/L), whereas in the group with acute pericoronitis combined to multiple caries fluoride levels remained high (8.7 ± 1.9 mg/L; $p < 0.0001$). The developed protocol is efficient for studying fluoride ion concentrations in isolated and combined dental diseases.

Keywords: pericoronitis, multiple caries, fluorides, oral fluid, capillary electrophoresis

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Compliance with ethical standards: the study was approved by ethical review board of the Omsk State Medical University (Protocol № 113 of 26 November 2019); all participants or their representatives provided informed consent for participation in the study.

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ПРОГНОСТИЧЕСКАЯ ЗНАЧИМОСТЬ ОПРЕДЕЛЕНИЯ ФТОРИД-ИОНОВ В РОТОВОЙ ЖИДКОСТИ ПРИ ОСТРОМ ПЕРИКОРОНИТЕ

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Разработка новых методов ранней диагностики и исхода стоматологических заболеваний по концентрации различных ионов в ротовой жидкости является перспективным направлением. По составу ротовой жидкости можно оценивать состояние не только стоматологического здоровья, но и всего организма в целом. Превышение концентрации фторид-ионов оказывает негативное влияние на органы и ткани полости рта, а контроль за его поступлением в организм врачами не проводится. Целью исследования было разработать и апробировать методику определения фторид-ионов в ротовой жидкости методом капиллярного электрофореза при стоматологических заболеваниях. Получены данные о концентрации фторид-ионов в норме (2,16 ± 0,48 мг/л), при множественном кариесе и остром перикоронарите (18,9 ± 4,2 мг/л), остром перикоронарите (15,2 ± 2,7 мг/л). На третьи сутки после оперативного вмешательства значения в группе с острым перикоронитом пришли в норму (2,28 ± 0,52 мг/л), при множественном кариесе и остром перикоронарите, даже после хирурического вмешательства, остались высокими (8,7 ± 1,9 мг/л; $p < 0,0001$). Разработанная методика эффективна для изучения концентрации фторид-ионов при изолированных и сочетанных стоматологических заболеваниях.

Ключевые слова: перикоронит, множественный кариес, фториды, ротовая жидкость, капиллярный электрофорез

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The influence of fluorides on human health is a long-studied issue. The negative influence of fluorinated compounds on human body has been confirmed by advanced research in the fields of medicine, chemistry, occupational safety and nutritional health [1]. The known effects of fluorides on dental health include endemic diseases (fluorosis, caries) associated with excessive intake/exposure or deficiency [2]. Fluoride ions can act on phosphoenolpyruvate kinase, thereby inhibiting glycolysis, which leads to reduced production of lactic acid and favors cariesogenic microflora in the oral cavity. The action of fluorine on other organs and tissues remains understudied [3]. Fluorides inhibit enzymatic activities through depletion of

cofactor ions of Mn, Ca, Fe and Mg. Humans receive fluorides with drinking water, foods, inhaled dust and gaseous fluorinated compounds. The average daily requirement of fluorides in adults is 2–3 mg [4]. Up to 70% of this amount enters the body with drinking water and about 30% is retrieved from foods. Fluorides play an important role in caries prophylaxis. Fluoride levels in the body have been linked to the morbidity of fluorosis, including endemic forms of the disease. Caries and fluorosis of both decidual and definitive teeth, especially in children, have been associated with drinking water fluorination levels [5].

The influence of fluorine on the outcomes of dental conditions hallmarked by decay of hard tissues (caries, fluorosis) was elucidated in seminal publications both domestically and abroad. We have found no published evidence on a possible shift in fluoride ranges during complicated wisdom tooth eruption. Meanwhile, such shifts might prove clinically relevant given the hypomineralized condition of such teeth during eruption [6, 7]. The presence of inflammatory process during wisdom tooth eruption negatively affects oral homeostasis, and critically increased fluoride concentrations may exacerbate the consequences especially in the presence of other infectious foci in the oral cavity.

Fluoride-based medications are widely used in therapeutic dentistry as an affordable and accessible method of the focal enamel demineralization management. Fluoride ions prevent caries and inhibit metabolic processes in dental plaque bacteria through enzymatic interference, thus suppressing acidification and alleviating demineralization of carious lesions at early stages [8]. Still, such 'simple' low-molecular fluorides cannot effectively prevent caries due to the brevity of their stay at the tooth surface and low concentrations of the released fluorine. Administration of the low-efficient fluorides as tooth pastes, gels, rinses and coatings for local fluorination is one of additional factors of carious and non-carious tooth decay. The toothpastes and rinses containing antimicrobial components exert certain suppressive action on the microbial biofilm, but have no remineralizing effect [9]. This situation necessitates the use of deep fluorination. However, prescription of fluorine medications is conventionally based solely on dental status and unsupported by laboratory tests of fluoride content in the body. Importantly, fluorine belongs to chemical elements showing a sharp transition from physiologically beneficial concentrations to those promoting toxicosis [10], which accentuates the need for its reliable measurement in biological substrates [11]. The fluoride content can be assessed by their presence in blood, saliva, urine, bones and hair [12].

Oral fluid is a valuable substrate mirroring the overall physiological condition of the body [13–15]. Unlike capillary or venous blood sampling, the oral fluid sampling is non-invasive, which is definitely advantageous [16]. Biochemical composition of oral fluid is highly indicative of various shifts in homeostasis [17].

The utility of oral fluid for fluoride measurements is limited by the lack of unified protocol. Capillary electrophoresis is one of the most versatile methods for ion composition analysis [18, 19] increasingly applied in various fields of analytical chemistry [20]. The simplicity, accessibility and accuracy of this approach favor its use in clinical laboratories and make it applicable in various fields of medicine, notably dentistry, for diagnostics and monitoring.

Based on literature analysis, we have found it reasonable to study associations of dental diseases with fluoride concentrations in oral fluid. Elevated concentrations of these ions can interfere with maturation and mineralization of hard dental tissues and/or aggravate dental diseases.

This study aimed at development and approbation of a method for reliable measurement of fluoride ions in oral fluid by capillary electrophoresis to be used in patients with dental diseases exemplified by multiple caries and/or acute pericoronitis.

METHODS

Clinical study

The control group enrolled 200 individuals with satisfactory dental status (care index (CI) score of 0–4.4, mean 3.3 ± 0.4). Approbation of oral fluoride measurements on clinical samples involved two groups of patients: group 1 enrolled patients with acute pericoronitis and satisfactory dental status (CI score 0–4.4, mean 3.6 ± 0.5) aged 20–25 (n = 20); group 2 enrolled patients with acute pericoronitis against the background of multiple caries and CI scores over 6.6, mean 11.9 ± 0.6, aged 20–25 (n = 20). Inclusion criteria were established in accordance with survey data: control group — satisfactory dental status, CI score 0–4.4, age 20–25 years, female; group 1 — acute pericoronitis, satisfactory dental status, CI score 0–4.4, age 20–25 years, female; group 2 — acute pericoronitis combined to multiple caries (CI score over 6.6), age 20–25 years, female. Exclusion criteria were as follows: age below 20 years or over 25 years, unsatisfactory oral hygiene, male, chronic diseases (somatic, inflammatory and/or infectious) with a negative impact on hard tissues of teeth and periodontium, drug and alcohol addiction, ulcerogenic medications. All patients were examined at the premises of the Department of General Dentistry of the Omsk Region State Healthcare Institution "City Clinical Dental Clinic № 1" in 2021–2022. The recruitment was accomplished during the appointed reception by a dental therapist upon confirmation of the diagnosis.

Oral fluid samples of the control group, collected fasting in sterile test tubes, were used to determine the normal reference range of oral fluoride levels. In patients of groups 1 and 2, the samples were collected similarly before surgical intervention for acute pericoronitis (extraction of teeth 38 and 48 at the stage of semi-retention beneath the mucosa and the hood as shown by X-ray scan) and subsequently on post-operative days 1 and 3. The samples were centrifuged at 7,000 rpm. Concentrations of fluoride ions were measured using two methods: capillary electrophoresis and photometry.

Capillary electrophoresis

The oral fluid capillary electrophoresis protocol was developed using a KAPEL-105M capillary electrophoresis system (Lumex; Russia) [21, 22] with instrumentation and preparation of capillaries for operation described previously [22]. The oral fluid aliquots (100 μL) were diluted 20-fold with distilled water. By contrast with the previously published protocol [22], there was no need for protein precipitation prior to sample loading. The anions (chlorides, nitrites, nitrates, phosphates, fluorides and sulfates) were measured using a leading electrolyte containing CrO_3 (10 mM), diethanolamine (30 mM) and cetyltrimethylammonium hydroxide (2 mM).

Photometry

The method involves determination of the color change of the zircon-alizarin complex solution reflecting formation of a colorless, more stable complex compound of fluoride ions with zirconyl chloride (IV) [23]. Upon reaction with fluoride,

Table 1. Electropherogram parameters for fluoride measurement

Calibration solution №	Elution time, min	Peak height, mAU	Peak area	Concentration, mg/L
Solution 1	6.317	0.368	12.68	0.25
Solution 2	6.323	2.398	64.32	1.0
Solution 3	6.128	7.117	268.7	5.0
Solution 4	6.048	9.299	504.2	10.0

the zircon-alizarin complex releases alizarin, which turns the solution yellow. For each measurement, a 5 μL aliquot of oral fluid was added to a 100 mL volumetric flask filled with distilled water, 5 mL of alizarin red C solution and 5 mL of acidic solution of zirconyl chloride prepared according to state standard (GOST) 23268.18-78. The solution was thoroughly mixed and incubated for 1 hour at room temperature. The optical density was measured in a spectrophotometer at 540 nm wavelength in cuvettes with 10 mm path length against a blank sample.

Statistics

Statistical processing of experimental data involved distribution tests, which confirmed normality of the distributions; so the confidence intervals were calculated using Student's t-test. The differences were assessed for a significance level of $p < 0.05$.

RESULTS

Development of the capillary electrophoresis protocol for fluoride ion measurement

The first step was calibration; the peak area calibration plot for fluoride is shown in Fig. 1. Since the protocol was intended for oral fluid as a substrate for fluoride measurements, the calibration used a solution of all inorganic anions possibly found in saliva (Fig. 2A). The insert illustrates the change in the peak area of fluoride ion depending on its concentration in the sample. Major parameters of the fluoride peaks, determined in electropherograms for a series of standard ion mixtures, are given in Table 1.

The analysis of oral fluid samples revealed no peaks for nitrite and nitrate ions (peaks 2 and 4, respectively). A typical electropherogram of salivary anions is given in Fig. 2B. The data were collected in three–four technical replicates for each sample to account for measurement error. To verify the correct identification of the fluoride ion peak, a series of experiments was carried out using the "added-detected" principle: a reference amount of a relevant additive with known concentration was introduced in the system (we used the registered standard sample of 1 mg/mL). The step-wise addition substantially increased the height and area of the peak identified with fluoride (Fig. 2B) and the measurement error did not exceed 10%.

To validate the developed method through comparison with a different protocol, the fluoride ion content of the samples was additionally determined by photometry. The concentrations were calculated using a pre-built calibration plot (Fig. 3). It should be noted that photometry assay covers just a narrow range of low fluoride concentrations, because at higher concentrations the absorbance-concentration curve is non-linear. Thus, the use of photometry requires serial dilutions of sample aliquots (Table 2) which negatively affects the accuracy.

The concentrations of fluoride ions determined by capillary electrophoresis matched those measured by spectrophotometry (Table 2). This result allows consideration of both methods for clinical purposes. However, clinical utility of spectrophotometry assay is limited by the narrow range of suitable concentrations and the uncertainty of fold dilution required in each individual case. Photometry requires a dilution falling within the concentration range (Table 2), while capillary electrophoresis is suitable for non-diluted samples. Mean oral fluid fluoride content for the control group was 2.27 ± 1.07 mg/L, albeit the total range for this group was 0.16–8.7 mg/L. It would be more expedient and advisable to use a method that does not require adjusting the concentration of fluoride ions in a sample by pre-dilution. The developed method of capillary electrophoresis satisfies these requirements.

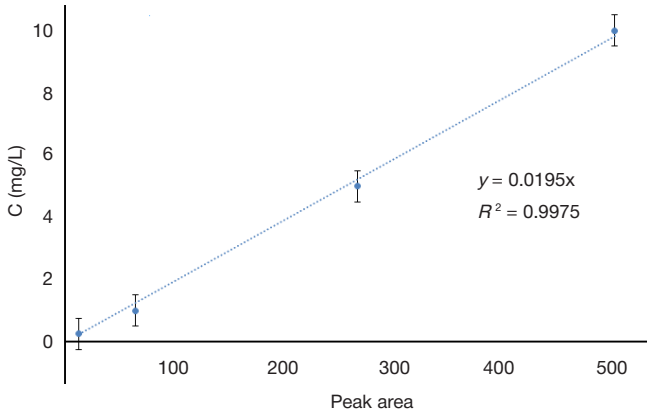

Fig. 1. Calibration curve for fluoride measurement by capillary electrophoresis, built in a standard range of 0.1–10 mg/L

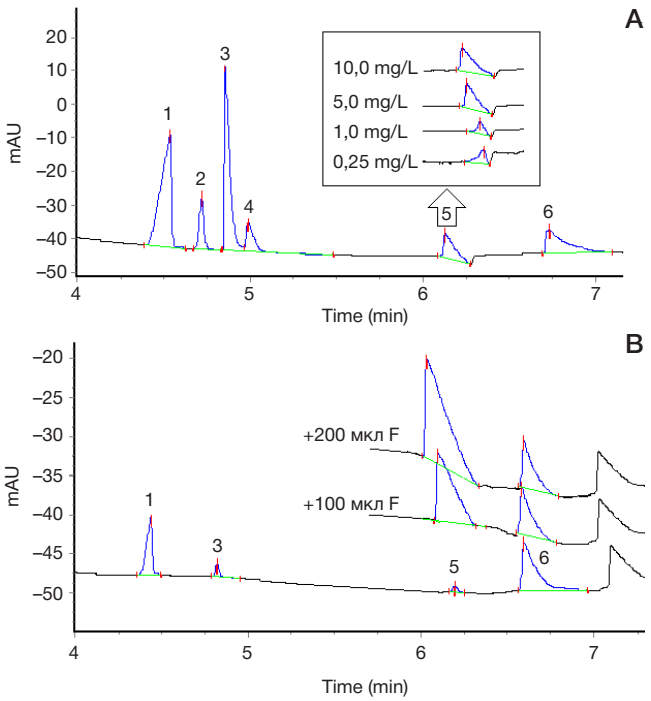

Fig. 2. A. Electropherogram for calibration solution containing a mixture of anions (1 — chlorides, 2 — nitrites, 3 — sulfates, 4 — nitrates, 5 — fluorides, 6 — phosphates). The insert shows fluoride ion peaks within the range of 0.25–10.0 mg/L. **B**. Electropherogram of saliva (100 μL), pure or mixed with 100 μL and 200 μL aliquots of fluoride standard solution (diluted 20-fold)

Approbation of the oral fluid fluoride measurements on clinical samples of multiple caries and acute pericoronitis

For the control group, mean fluoride content constituted 2.16 ± 0.48 mg/L. The obtained ranges of oral fluid fluoride concentrations measured by capillary electrophoresis method encouraged using it in groups of patients with clinically unfavorable oral status (carious lesions, acute pericoronitis).

The highest oral fluoride levels were measured in patients before surgery for acute pericoronitis (isolated or combined to multiple caries: respectively, 15.2 ± 2.7 mg/L in group 1 and 18.9 ± 4.2 mg/L in group 2).

On post-operative day 1, fluoride concentrations decreased significantly to 9.4 ± 2.1 mg/L in group 1 and 11.4 ± 2.8 mg/L in group 2.

On post-operative day 3, fluoride concentrations in group 1 (isolated acute pericoronitis) reached the control group values (2.16 ± 0.48 mg/L), whereas fluoride concentrations in group 2 stayed high (8.7 ± 1.9 mg/L) indicating the persisting influence of multiple carious lesions combined to acute pericoronitis on oral fluoride levels. The identified differences were significant ($p < 0.0001$) (Fig. 4).

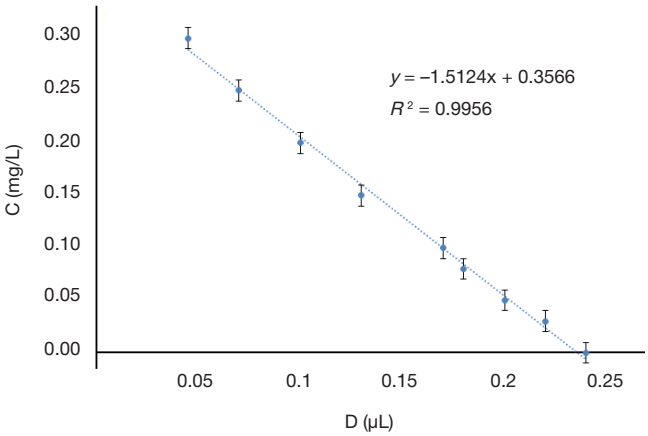

Fig. 3. Calibration curve for fluoride measurement by photometry

DISCUSSION

Analysis of literature on fluorine balance in the body identifies drinking water and foods as the main fluoride sources. Environmental factors, particularly professional intoxication in industrial facilities with high aerial content of fluorine and its chemical derivatives, should be considered as well. Fluorine content of various environmental objects has been elucidated in many studies [3, 4, 10]. Of note, environmental levels of fluorine depend on geography [11]; accordingly, the fluorine exposure varies geographically depending on the region of residence [24–26]. Many authors demonstrate correlations between fluoride levels and systemic diseases, though mostly indirectly, through environmental levels [27]. For example, a positive correlation has been demonstrated between fluoride content of drinking water and morbidity of diabetes, rheumatism, pyelonephritis and cervical erosion, whereas the fluorine/sulfate ratio correlates with morbidity of cerebrovascular, genitourinary, female reproductive, nervous and neurosensory disorders [27]. At the same time, data on possible disease-related shifts of fluoride content in biological fluids, including oral fluid, are sparse. As fluorine accumulates in dental tissues and is especially abundant at the enamel surface, salivary fluorine levels could be particularly informative. Fluoride concentrations in unstimulated saliva are a sum of their levels in ductal saliva, food and water [28]. Oral and dental diseases including fluorosis and caries are straightforwardly connected to oral levels of fluoride ions; accordingly, the timely determination and correction of fluoride intake is relevant to dental morbidity and prophylaxis. However, the lack of unified protocol of fluoride measurement and the diversity of available approaches hamper reliable comparison of data obtained by different authors (add in the inconvenience of using different units: mg/L, mmol/L, ppm, etc.) [11, 25, 29]. Environmental fluoride levels can be measured by capillary electrophoresis, potentiometry or photometry. These methods are suitable for oral fluid too, albeit most sources provide neither detailed description of the protocol, nor data confirming its validity [25]. Apart from the capillary electrophoresis and conventional photometry protocols used by us in this study, an alternative spectrophotometry assay is available, involving decolorization of trisodium 2-(4-sulfophenylazo)-1,8-dihydroxynaphthalene-3,6-disulfonate complex with fluorine ions detectable at 570 nm wavelength [29]. Potentiometric approaches are characterized by systematic errors and the necessity to get rid of impurities prior to measurements. Our methods, by contrast, allow measuring fluoride ions across the entire range of their salivary content both photometrically and by capillary electrophoresis. It should be noted that the latter approach allows simultaneous measurement of five other physiologically relevant inorganic ions (chlorides, nitrates, nitrites, sulfates and phosphates), which expands the scope of its application.

Table 2. Fluoride measurement for a selection of samples. CE, capillary electrophoresis

Sample	CE, mg/L	Photometry, mg/L				Δ, %
		Undiluted	Diluted 10-fold	Diluted 20-fold	Mean	
3	0.56	–	0.54	0.55	0.55	2.68
5	1.52	–	1.53	1.57	1.55	1.97
16	0.97	–	1.01	0.96	0.99	1.55
18	2.28	–	2.3	2.31	2.31	1.10
40	0.16	0.17	0.17	0.16	0.17	4.17
6	2.57	–	2.62	2.54	2.58	0.39
93	0.71	–	0.74	0.72	0.73	2.82
159	3.21	–	3.16	3.23	3.20	0.47
190	4.55	–	–	4.6	4.60	1.10
200	0.18	0.17	0.19	0.17	0.18	1.85

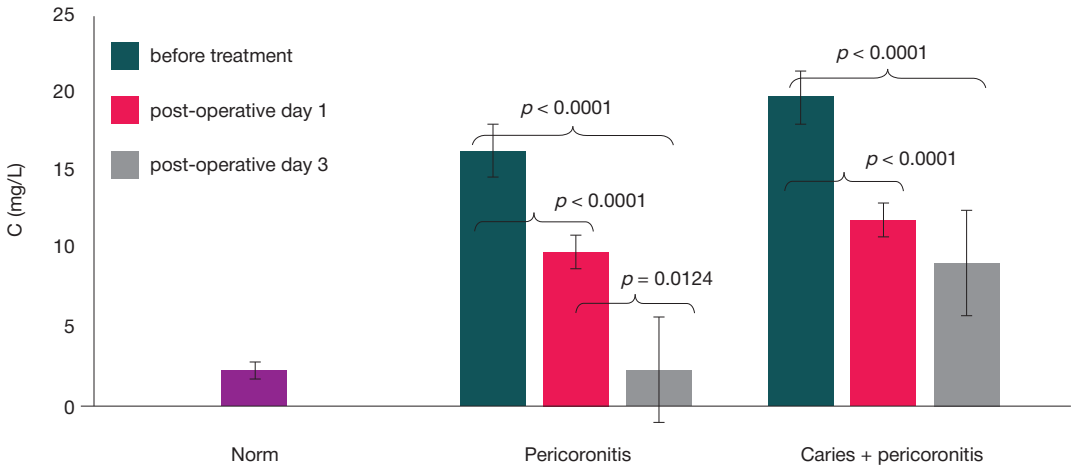

Fig. 4. Fluoride content for groups 1 and 2 before and after surgery (post-operative days 1 and 3) compared with the control group

Studies on oral fluid composition upon tooth fluorination procedure are fairly well elucidated in the literature [2, 8, 9], although the majority of studies focus on Ca/P ratio omitting the fluoride content.

Here we reveal substantially elevated oral fluoride levels in patients with inflammatory complications of the wisdom tooth eruption. Whether tooth eruption should be regarded as local or systemic process is an open issue [30]. The observed shift in physical and chemical salivary indicators suggests a profound systemic component. As long as in all cases of pericoronitis included in this study the eruption was almost complete, the observed increase in fluoride levels may reflect physiological response to this event, as wisdom teeth are known to be hypomineralized upon eruption and their enamel needs saturation with relevant ions to fortify the crystal lattice. Another factor causing the observed increase in oral fluoride levels is concomitant inflammation and bacterial flora expansion requiring appropriate treatment.

The limitations of the study include confinement to a single geographical area (Omsk region) as well as small size of both groups, necessitating further research on this problem.

CONCLUSIONS

Patients with pericoronitis combined to multiple caries reveal unfavorably high concentrations of fluoride ions in oral fluid, which stay elevated after surgical relief of acute pericoronitis. By contrast, in patients with isolated pericoronitis and CI score of 0–4.4, oral fluoride levels return to reference range by post-operative day 3. Despite the relevance of oral fluid as a source of fluoride, notably during teething, the retrieval should be regulatable and physiological, and proceed against the background of satisfactory oral hygiene and anti-inflammatory care. The capillary electrophoresis method is suitable for fluoride ion measurements in oral fluid.

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