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Effect of Cold Application and Heparinoid on Periorbital Edema and Ecchymosis after Craniotomy: A Randomized Controlled Clinical Trial

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Abstract

Research Article

This study was performed to determine the effect of cold application and heparinoid cream on periorbital edema and ecchymosis after craniotomy. The sample of this prospective parallel-arm, randomized controlled trial included 90 neurosurgical patients who underwent anterior craniotomy in two medical faculty hospitals of a university in Turkey. The patients were randomly assigned (1:1:1) to the cold application, heparinoid or control groups. Those patients in the cold application group received cold application with gel pack on their periorbital areas for 20 minutes per hour for three days beginning from the 3rd hour following craniotomy. On the other hand, the patients in the heparinoid group received heparinoid cream on their periorbital areas once at the 3rd and 9th hours after craniotomy and then four times/day at 6-hour intervals for three postoperative days. Periorbital edema and ecchymosis were evaluated for three days after craniotomy using Kara & Gökalan's scale by blinded observers. In all the measurements after craniotomy, except for those at the 3rd hour, the periorbital edema score of the cold application group was significantly lower than those of both the heparinoid and control groups ($p<0.001$). The upper and lower eyelid ecchymosis scores of the cold application group were significantly lower than those of both the heparinoid and control groups on the 1st, 2nd and 3rd days after craniotomy ($p<0.001$). In the cold application group, periorbital edema score decreased significantly as the skin temperature decreased only on the 3rd day after craniotomy ($p=0.01$). The study revealed that cold application and heparinoid cream administered for three days beginning from the 3rd hour after craniotomy did not prevent postoperative periorbital edema and ecchymosis, but cold application significantly reduced periorbital edema and ecchymosis.

INTRODUCTION

Anterior craniotomy is an approach that provides access to the skull base in the surgery of anterior circulatory aneurysms and lesions such as tumors located in the anterior cranial fossae[1]. As with other cranial interventions, complications leading to increased intracranial pressure (ICP), such as cerebral edema and intracranial hematoma, may occur in the early period after anterior craniotomy[1-3]. Pupillary examination by nurses is critical in early diagnosis of these complications and ICP increase[3]. However, subgaleal fluid collection caused by significant soft tissue manipulation and cutting of drainage veins in the frontal region during craniotomy lead to temporary edema and ecchymosis in one or two eyelids of patients in the early postoperative period[1-4].

Periorbital edema with or without hematoma, which occurs within the first 36 hours after anterior craniotomy[3] and lasts 3-7 days[1,4], hampers or makes pupillary examination difficult[3]. In addition, periorbital edema and ecchymosis, a natural result of surgical trauma are not considered as a complication[3,5]. However, they decrease visual acuity and make it difficult for the patient to see, especially on the first postoperative day and causing fear and discomfort[3,5,6]. In some studies, the rate of periorbital edema after anterior craniotomy was 36.8-100%[1-4], the ecchymosis rate was 62.5%[5] and pupillary examination could not be performed for the first 36 hours after craniotomy in 30% of patients with edema[3]. Despite advances in neurosurgical techniques, subgaleal fluid collection and periorbital edema formation cannot be prevented[2,3], and there is no standard care or protocol for control of periorbital edema and ecchymosis[5].

Preventing or at least reducing the severity of periorbital edema and ecchymosis associated with surgical intervention is essential in maintaining patient safety and increasing patient satisfaction[6-9]. There are various studies in the literature examining the effect of different methods such as steroids[9-12], cold application[5,7,13] and local heparinoid (mucopolysaccharide polysulphate)[6,8] on periorbital edema and ecchymosis. All of these studies, except the Shin et al.'s study[5], were conducted with patients treated with rhinoplasty, and there is currently only one study that was conducted with patients with craniotomy. On the other hand, the study by Shin et al.[5] investigated only the effect of cold application on periorbital edema and facial ecchymosis, and it provided no findings related to periorbital ecchymosis. In addition, the

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authors neither specified the temperature of the material used in cold application nor investigated the relationship between decrease in skin temperature and periorbital edema and ecchymosis.

During our clinical observations, we determined that pupillary examination was not performed on patients with severe periorbital edema in the neurosurgical intensive care units (NICUs) and clinics, where we conducted the current study, and different procedures were applied to reduce edema and ecchymosis. These applications, which were performed after periorbital edema and ecchymosis occurred, included covering the periorbital area with saline-soaked gauze, applying heparinoid cream once a day, or applying cold with ice pack 2-3 times a day for about 5-10 minutes. The interventions varied depending on the preference of the nurse in charge.

In the light of the current literature and clinical observations, the purpose of this study was to determine the effect of heparinoid cream and cold application in the prevention of periorbital edema and ecchymosis after anterior craniotomy and to evaluate the relationship between decrease in the skin temperature and periorbital edema and ecchymosis. The null hypothesis is that there is not a significant difference between the average periorbital edema and ecchymosis scores of the control, cold application, and heparinoid groups.

MATERIAL and METHODS

Study Design

This study was performed as a prospective, parallel, three arm [1:1:1], randomized controlled clinical trial at the NICUs and neurosurgery clinics in two medical faculty hospitals of a university in Istanbul, Turkey.

This trial was approved by the Local Ethics Committee of Istanbul Faculty of Medicine (Number=5) and Istanbul Research Ethics Committee-No: 1 (Number=C-032). All patients and their close relatives provided written informed consent before starting the study.

The trial is registered at ClinicalTrials.gov (NCT04119297).

Sample size

The effect size of the difference between the means of periorbital edema and ecchymosis scores to be obtained from the five repeated measures according to the three groups (i.e., control, heparinoid and cold application) would be at least 0.30 (i.e., medium impact for variance test) with a two-sided type I (alpha) error rate of 0.05, 80% power and 16% dropout rate, and the calculations performed in G*Power program showed that each of the groups should have at least 35 patients and there should be a total of 105 people. The study was completed with 90 patients.

In the power analysis that was performed to evaluate the adequacy of the sample size at the end of the study, the effect size according to time and difference between the groups ($\eta 2$) was 94% and 39% for edema, respectively, 81% and 15% for upper eyelid ecchymosis, respectively, and 75% and 22% for lower eyelid ecchymosis, respectively. Post hoc power according to time and difference between the groups was found to be 100% for edema and lower eyelid ecchymosis and 100% and 87% for upper eyelid ecchymosis, respectively, and the sample size was large enough.

Participants

The study population consisted of 120 patients who underwent anterior craniotomy at the NICUs and neurosurgery clinics between October 2009 and July 2011.

The inclusion criteria were as follows: 1) age 18 years and older, 2) Glasgow Coma Scale (GCS) score equal to 15, 3) lack of any mental and physical problems that interfere with communication, 4) having normal vital signs, 5) absence of ptosis, 6) voluntary participation in the study, and 6) signing informed consent.

The exclusion criteria were as follows: 1) refuse to participate in the study, 2) pass away during surgery, 3) GCS score less than 15, and 4) presence of postoperative ptosis. As a result of these criteria, 15 patients were excluded from the study during enrollment (Figure 1). Also, 15 patients were excluded from the study during the follow-up: two patients who did not want to receive cold application, four patients who did not want to receive heparinoid cream, five patients who were discharged on postoperative 2nd day, two patients transferred to another hospital and two patients who passed away during the follow-up (Figure 1).

Randomization and masking

The eligible patients were randomly allocated to the groups using the block randomization method, with a block size of three in a 1:1:1 ratio. The random allocation cards were

developed using a computer-generated randomized sequence by a biostatistician who was not associated with the study. Group allocation was concealed using individual sealed opaque envelopes. As the patients were enrolled in the study, the next envelope was extracted and the patients were allocated to the groups accordingly. When one of the patients was transferred from the operating theatre to the NICUs or clinics, the nurse in the study (NA) assigned the patient to one of the groups according to the list in the envelope. The other investigator nurse (SY), two observer nurses (DG, YT), and all the patients were blinded from group allocation. Also, all the patients were blinded to all the measurements, and the investigator (SY) and two observers (DG, YT) were blinded to each other's measurements.

Interventions

The eligible patients transferred to the NICUs or clinics from the operating theatre following craniotomy were randomly assigned to the cold application, heparinoid or control groups by the investigator nurse (NA). All the patients were placed in the supine position with a head elevation of 30° following craniotomy. Firstly, data concerning the patients' socio-demographic and medical characteristics (Table 1) were collected using a data collection form developed based on the relevant literature by the investigator nurse (SY).

Cold application

In order to prevent periorbital edema and facial ecchymosis after craniotomy, it is recommended to start cold application at postoperative 3rd hour for three days, for 20 minutes each hour, except from 10 pm to 7 am[5]. In line with this recommendation, patients in the cold application group received cold application on the periorbital area for 20 minutes per hour beginning from 3rd hour following craniotomy, except from 10 pm to 7 am (in order to allow the patients to sleep and rest), and for three days using gel packs cooled to -14 ºC and wrapped in sterile gauze of the same size and weight by the investigator nurse (SY). The cold gel packs were attached to the periorbital area with Velcro strip. Separate gel packs were used for each patient and, after the application, the gel packs were cleaned by washing with soapy water.

No patient required termination from the study due to adverse events associated with cold application.

Heparinoid cream application

As recommended by similar studies with different patient groups[6,14], the investigator nurse (SY) applied the same dose of heparinoid cream on the heparinoid group patients' eyelids and lid perimeters in the form of a thin layer once at 3rd and 9th hours following craniotomy and four times a day on the 1st, 2nd and 3rd days. Before each application, the investigator nurse (SY) cleaned of the heparinoid cream residues using sterile gauze pad moistened with water.

No patient required termination from the study due to adverse events associated with heparinoid cream.

Routine clinical applications

The patients in the control group received only routine clinical applications for the control of periorbital edema and ecchymosis (i.e. covering the periorbital area with saline-soaked gauze, application of heparinoid cream once a day, or irregular cold application 2-3 times a day for 5-10 minutes with ice pack). These applications were performed by nurses in the NICUs and clinics. Investigators did not perform any application to this group.

Outcomes

Primary outcomes

The primary outcome measures of this study were periorbital edema and periorbital ecchymosis. Periorbital edema and ecchymosis of patients in all the groups were evaluated at the 3rd and 9th hours, and on the 1st, 2nd and 3rd days following craniotomy using Kara and Gökalan's Scale. Periorbital edema and ecchymosis are scored between 0 and 4 in this scale, which was developed for patients with rhinoplasty by Kara and Gökalan[10]. Edema scoring in the scale: 0: none, 1: minimal, 2: extending onto the iris, 3: covering the iris, 4: massive edema with the eyelid swollen shut. Ecchymosis scoring in the scale: 0: none, 1: medial, 2: extending to the pupil, 3: past the pupil, 4: extending to the lateral cantus[10].

Periorbital edema and ecchymosis were evaluated by the investigator nurse (SY) and two independent clinical nurse observers (DG, YT) who did not know the purpose of the study and the interventions delivered to the patients. On the other hand, these nurse observers were trained by the investigator nurse (SY) about Kara & Gökalan's Scale and scoring of periorbital edema and ecchymosis. The investigator (SY) and

two observers (DG, YT) were blinded to the measurements performed by each other. The reliability between the five repetitive measurements by the investigator (SY) and the two observers (DG, YT) was assessed with Intraclass Correlation Coefficients (ICC) (i.e. two-way random effects model: consistency). ICC analysis showed that there was a perfect agreement (ICC value: > 95%) between their periorbital edema (ICC values ≥ 97%), upper eyelid ecchymosis (ICC values ≥ 98%), and lower eyelid ecchymosis (values ≥ 98%) scores ($p<0.001$). Since there was a perfect agreement between the observers' and the investigator's results, the data were analyzed using the investigator's measurements.

Secondary outcomes

The secondary outcome measures of this study were change in periorbital skin temperature after cold application using gel pack cooled to -14 ºC and the relationship between this change and periorbital edema and ecchymosis scores. The temperature of the gel packs was measured by the investigator nurse (SY) prior to each application using a digital thermometer capable of measuring -50-300 ºC with an accuracy of ±0.1 ºC (Barbecue Thermometer TBT-08H, Guangdong, China). Periorbital skin temperature was also measured before and after each application using a digital thermometer (ThermoFlash LX-26, Visiomed, France) with a range of measurement of 0-60 ºC, an accuracy of ±0.2 ºC, and a time of measurement of five seconds.

Data analysis

Data were analyzed using the Statistical Package for Social Sciences (SPSS) (IBM Corp. Released 2011, Version 20.0. Armonk, NY: IBM Corp.). Continuous data were described using mean, standard deviation, standard error, and 95% confidence interval (CI) values, and categorical variables were analyzed using frequency and percentage. Pearson's Chi-square test and one-way ANOVA were used to compare the similarity of the groups in terms of their socio-demographic and medical characteristics.

Parametric tests were used in the analysis because of continuous variables met the assumptions of normality and homogeneity. Whether there was a difference in periorbital edema and ecchymosis scores between the groups was evaluated using one-way ANOVA and post hoc test (Tukey HSD test or Dunnett T3). The repeated measures ANOVA and post hoc test (Bonferroni analysis) were used to determine the time-dependent change of periorbital edema and ecchymosis scores measured at different times within the group. The relationship between change in periorbital skin temperature after cold application and periorbital edema and ecchymosis were evaluated using Pearson correlation analysis. The reliability between the observers was verified using ICC. The level of statistical significance was set at 95% confidence interval (CI) ($p<0.05$).

RESULTS

Participant characteristics

One hundred and five patients were enrolled in the study. Approximately, 15% of the sample was lost to follow-up. The study was completed with 90 patients randomized into the cold application, the heparinoid and the control groups (in a 1:1:1.1 ratio) (Figure 1).

The mean age of the patients was 47.68 years (SD=13.71), most of them were female (67.8%), 80% underwent pterional craniotomy. As can be seen in Table 1, the patients in the three groups were similar to each other in terms of characteristics ($p>0.05$).

Primary outcomes

Periorbital edema score increased in all the three groups beginning from the 3rd hour following craniotomy until the 1st day. There was an insignificant increase on the 2nd postoperative day only in the control group. Periorbital edema decreased significantly in the cold application group on the 2nd postoperative day and in the heparinoid and control groups on the 3rd postoperative day ($p<0.05$, Table 2). According to the results of the comparison between the groups, in all the measurements except for those at the 3rd hour following craniotomy, edema score was significantly lower in the cold application group than in the control and heparinoid groups ($p<0.05$). There was a significant difference between the heparinoid and control groups only on the 3rd postoperative day in favor of the heparinoid group ($p<0.05$, Table 2).

Upper and lower eyelid ecchymosis scores increased in all the groups beginning from the 3rd hour after craniotomy. These scores reached the highest level on the 1st postoperative day in the heparinoid and cold application groups and on the 2nd day in the control group. Both upper and lower eyelid ecchymosis scores were significantly decreased in the cold

application group on the 3rd postoperative day (p<0.05, Table 2), but there was not any significant decrease in the heparinoid and control groups (p>0.05, Table 2). According to the results of the comparison between the groups, the upper and lower eyelid ecchymosis scores of the cold application group were significantly lower than the scores of those in the heparinoid group at the 9th hour after craniotomy and then both the heparinoid and control groups on the 1st, 2nd and 3rd postoperative days (p<0.05, Table 2). There was no significant difference between the heparinoid and control groups in any of the measurements (p>0.05, Table 2).

Secondary outcomes

The mean temperature of the periorbital skin, which was 33.81 °C (SD=0.85 °C) prior to cold application, decreased to 24.61 °C (SD=1.15 °C) after cold application. The mean decrease in the periorbital skin temperature was 9.20 °C (SD=0.94 °C). It was determined that there was a significant relationship between decrease in periorbital skin temperature and periorbital edema score only on the 3rd day after craniotomy, and that edema score decreased as the temperature decreased (p<0.05, Table 3). No significant correlation was found between the decrease in skin temperature and upper and lower eyelid ecchymosis scores (respectively p>0.05; p=0.05, Table 3).

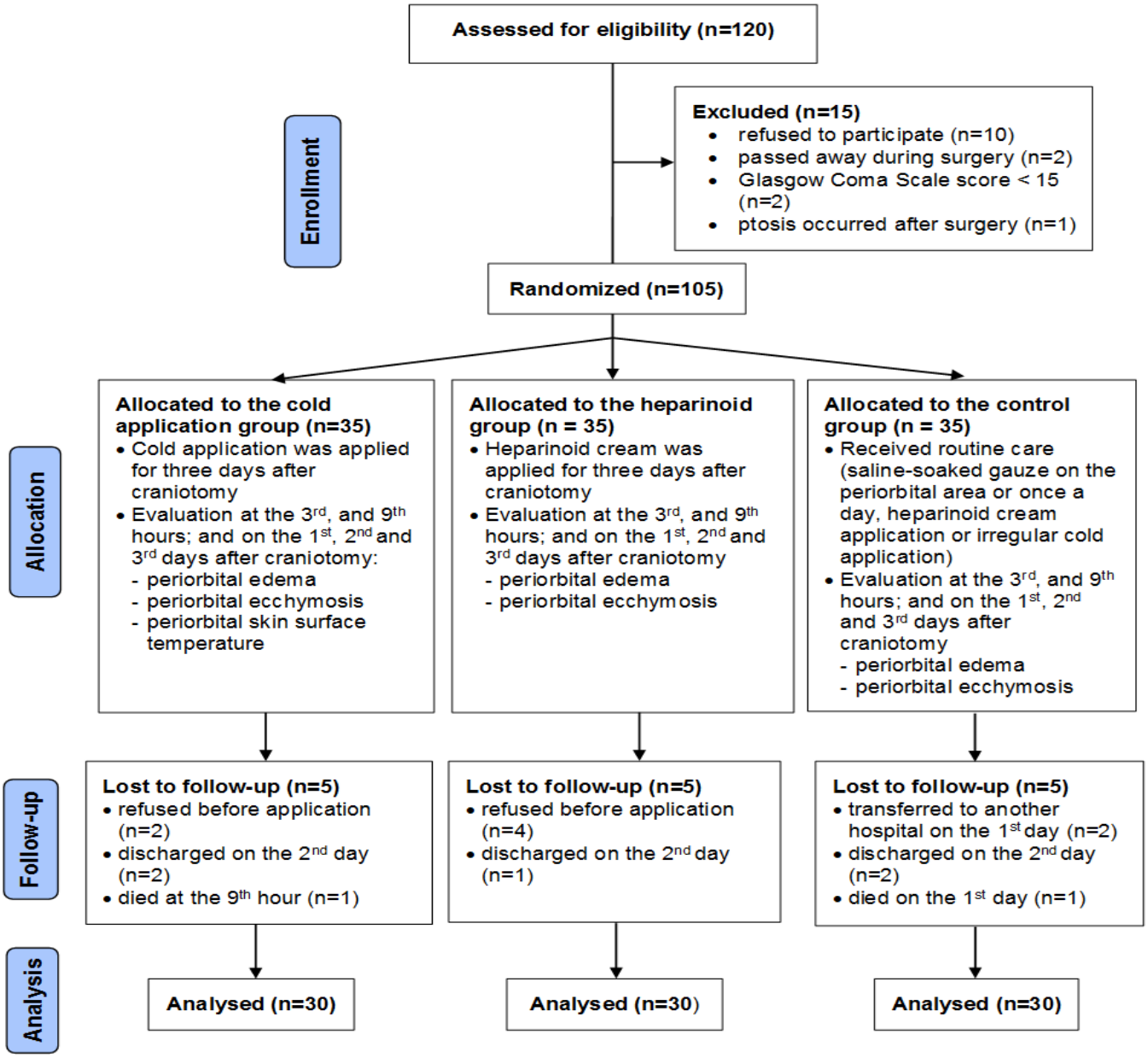

Figure 1. The consolidated standards of reporting trials diagram

Table 1. Demographic and medical characteristics of patients.

Characteristics	**Total**	**Control (n=30)**	**Heparinoid (n=30)**	**Cold application (n=30)**	**Test / p value**
Age (year), Mean ± SD	47.68 ± 13.71	51.37 ± 11.32	48.70 ± 14.15	42.97 ± 14.49	3.078 / 0.05*
Gender n (%)					1.323 / 0.52ψ
Female	61 (67.8)	22 (73.3)	21 (70.0)	18 (60.0)	
Male	29 (32.2)	8 (26.7)	9 (30.0)	12 (40.0)	
Diagnosis n (%)					
Brain tumor	43 (47.8)	15 (50.0)	14 (46.7)	14 (46.7)	4.388 / 0.36ψ
Cerebral aneurysm	30 (33.3)	11 (36.7)	12 (40.0)	7 (23.3)	
Aneurysmal SAH	17 (18.9)	4 (13.3)	4 (13.3)	9 (30.0)	
Type of surgery n (%)					
Aneurysm clipping	47 (52.2)	15 (50.0)	16 (53.3)	16 (53.3)	0.089 / 0.96ψ
Tumor resection	43 (47.8)	15 (50.0)	14 (46.7)	14 (46.7)	
Type of craniotomy n (%)					
Pterional	72 (80.0)	24 (80.0)	23 (76.7)	25 (83.3)	0.417 / 0.81ψ
Temporal	18 (20.0)	6 (20.0)	7 (23.3)	5 (16.7)	
Duration of the surgery, hour, Mean ± SD	3.97 ± 2.28	4.40 ± 2.69	3.80 ± 2.25	3.70 ± 1.80	0.827 / 0.44*
Preoperative steroid dose (mg), Mean ± SD	98.81 ± 75.64	93.63 ± 63.67	129.6 ± 98.68	65.50 ± 34.74	1.716 / 0.20*
Postoperative steroid dose (mg), Mean ± SD	95.69 ± 75.64	71.19 ± 15.92	49.77 ± 10.61	99.56 ± 21.23	0.340 / 0.71*
Steroid using duration (day), Mean ± SD	9.8 ± 6.97	10.57 ± 7.39	10.82 ± 7.98	8.05 ± 5.24	1.062 / 0.35*
Osmotic diuretic dose (g), Mean ± SD	28.63 ± 14.0	34.12 ± 15.44	27.78 ± 13.96	23.75 ± 10.88	2.444 / 0.09*
NSAID dose (mg), Mean ± SD	138.0 ± 147.03	168.67 ± 178.05	107.12 ± 104.84	170 ± 194.72	1.108 / 0.34*

SD=Standard deviation; NSAID=Non-steroid anti-inflammatory drug; SAH=Subarachnoid hemorrhage
* One-way ANOVA
ψ Pearson's Chi-square test

Table 2. Comparison of the periorbital edema and ecchymosis scores of the patients

Evaluation time	Control[1] (n=30)		Heparinoid[2] (n=30)		Cold application[3] (n=30)		F* / p value	Difference
	Mean ± SD	95% CI	Mean ± SD	95% CI	Mean ± SD	95% CI		
Periorbital edema score								
3rd hour[a]	0.40 ± 0.93	0.05-0.75	0.40 ± 0.72	0.13-0.67	0.37 ± 0.67	0.12-0.62	0.018 / 0.98	
9th hour[b]	1.90 ± 1.27	1.43-2.37	2.37 ± 0.96	2.01-2.73	1.13 ± 0.82	0.83-1.44	10.867 / < 0.001	1, 2 > 3
1st day[c]	3.72 ± 0.49	3.53-3.90	3.90 ± 0.24	3.80-3.99	2.08 ± 0.49	1.90-2.27	167.553 /< 0.001	1, 2 > 3
2nd day[d]	3.87 ± 0.22	3.78-3.95	3.63 ± 0.39	3.49-3.78	1.68 ± 0.58	1.47-1.90	239.323 / < 0.001	1, 2 > 3
3rd day[e]	3.37 ± 0.45	3.20-3.54	2.83 ± 0.74	2.56-3.11	1.00 ± 0.63	0.76-1.24	121.397 / < 0.001	1 > 2 > 3
F† / p value	142.665 / < 0.001		160.687 / < 0.001		58.527 / <0.001			
Difference	a < b < c, d, e d > e		a < b, c, d, e b, e < c, d		a < b, c, d, e b < c, d c > d > e			
Upper eyelid ecchymosis score								
3rd hour[a]	0.47 ± 1.14	0.04-0.89	0.97 ± 1.63	0.39-1.57	0.60 ± 1.13	0.18-1.02	1.154 / 0.32	
9th hour[b]	2.73 ± 1.48	2.18-3.29	3.33 ± 1.09	2.93-3.74	1.80 ± 1.63	1.19-2.41	8.887 / < 0.001	2 > 3
1st day[c]	3.40 ± 0.89	3.07-3.73	3.80 ± 0.66	3.55-4.05	2.60 ± 1.43	2.07-3.13	10.235 / < 0.001	1, 2 > 3
2nd day[d]	3.53 ± 0.82	3.23-3.84	3.63 ± 0.89	3.30-3.97	2.50 ± 1.47	1.96-3.04	9.887 / < 0.001	1, 2 > 3
3rd day[e]	3.43 ± 1.01	3.06-3.81	3.53 ± 0.94	3.18-3.88	1.93 ± 1.57	1.35-2.52	16.549 / < 0.001	1, 2 > 3
F†/p value	71.636 / < 0.001		50.102 / < 0.001		23.630 / <0.001			
Difference	a < b, c, d, e b < d		a < b, c, d, e		a < b, c, d, e b < c c, d > e			
Lower eyelid ecchymosis score								
3rd hour[a]	0.40 ± 0.97	0.04-0.76	0.70 ± 1.39	0.18-1.22	0.33 ± 0.88	0.00-0.66	0.938 / 0.40	
9th hour[b]	2.33 ± 1.42	1.80-2.86	2.83 ± 1.37	2.32-3.34	1.50 ± 1.41	0.97-2.03	6.952 / 0.002	2 > 3
1st day[c]	3.10 ± 0.96	2.74-3.46	3.30 ± 1.15	2.87-3.73	2.23 ± 1.28	1.76-2.71	7.467 / 0.001	1, 2 > 3
2nd day[d]	3.13 ± 1.07	2.73-3.53	3.20 ± 1.27	2.73-3.67	1.97 ± 1.19	1.52-2.41	10.358 / <0.001	1, 2 > 3
3rd day[e]	3.07 ± 1.14	2.64-3.49	3.07 ± 1.39	2.55-3.58	1.33 ± 1.30	0.85-1.82	18.356 / <0.001	1, 2 > 3
F†/p value	67.961/ < 0.001		39.841/ < 0.001		22.666/ <0.001			
Difference	a < b < c, d, e		a < b, c, d, e		a < b, c, d, e b < c c, d > e			

SD = Standard deviation; CI = Confidence interval, *One-way ANOVA, †Repeated Measures ANOVA

Table 3. Relationship between decrease in skin temperature and periorbital edema and ecchymosis scores

Periorbital skin temperature (°C)				**Correlation**		
Evaluation time	Before cold application	After cold application	Average difference	Periorbital edema	Upper eyelid ecchymosis	Lower eyelid ecchymosis
	Mean ± SD	Mean ± SD	Mean ± SD	r_p / p value	r_p / p value	r_p / p value
3rd hour	34.00 ± 1.26	25.06 ± 2.67	8.94 ± 2.46	0.27 / 0.14	0.30 / 0.11	0.36 / 0.05
9th hour	33.71 ± 1.26	24.32 ± 2.00	9.40 ± 1.62	0.11 / 0.56	0.16 / 0.41	0.19 / 0.32
1st day	33.68 ± 0.96	24.11 ± 1.96	9.58 ± 2.17	-0.11 / 0.58	-0.17 / 0.38	0.14 / 0.45
2nd day	33.88 ± 0.90	24.73 ± 1.59	9.16 ± 1.30	-0.27 / 0.14	-0.20 / 0.29	-0.14 / 0.47
3rd day	33.77 ± 0.90	24.82 ± 1.18	8.94 ± 0.92	-0.45 / 0.01	-0.25 / 0.18	-0.36 / 0.05
Total	33.81 ± 0.85	24.61 ± 1.15	9.20 ± 0.94			

SD = Standard deviation, r_p = Pearson correlation

DISCUSSION

In this randomized clinical trial, we determined that regular cold application for 3 days beginning from the 3rd hour after anterior craniotomy did not prevent periorbital edema and ecchymosis, but it was still effective in alleviating the severity of edema and ecchymosis. None of the patients in the cold application group had edema severe enough to prevent pupillary examination (≥ 3 points) or ecchymosis severe enough to pass through the pupil and extend to the lateral cantus (≥ 3 points). In addition, we found that local heparinoid was not effective in reducing and preventing craniotomy-induced periorbital edema and ecchymosis. These findings can be presented as evidence-based information in the limited literature in this field.

Effect of cold application

Cold application reduces blood leakage by causing vasoconstriction, slows down the metabolism of the damaged area and surrounding tissues, and reduces the inflammatory response in the damaged tissue[15,16]. These physiological effects of cold application are utilized to prevent and reduce swelling, edema and ecchymosis associated with soft tissue trauma[7,16].

Similar to the study by Shin et al.[5], which reported that cold application was effective on craniotomy-induced periorbital edema, the periorbital edema score of our patients in the cold application group was significantly lower than the scores of those in the control group in all the measurements except for the 3rd postoperative hour. Again similar to that study, none of our patients in the cold application group developed massive edema that would cover the iris or completely make the eyelid swollen shut. Shin et al.[5] found that edema increased until the 2nd postoperative day in the cold application group and until the 3rd postoperative day in the control group. In our study, however, edema increased until the 1st postoperative day in the cold application group and until the 2nd postoperative day in the control group. The reason for the difference is probably the fact that the patients in Shin at al.'s study[5] had longer surgical intervention and some patients required reoperation within three days after craniotomy.

The periorbital edema score (≥ 1 point) of our patients in the cold application group was significantly higher than the score (0.59 points) determined by Shin et al.[5] in all the measurements except for the 3rd hour after craniotomy. This could be due to the fact that cold application was performed to the craniotomy incision area as well as the periorbital area in Shin at al.'s study[5]. Cold application to the incision area may reduce edema formation by suppressing the inflammatory response secondary to tissue trauma and slowing tissue metabolism. Future studies to prove the effect of cold a pplication on the craniotomy incision area on periorbital edema are important as they could guide the care protocols to be implemented by nurses.

There are currently no studies in the literature examining the effect of cold application on upper and lower eyelid ecchymosis due to craniotomy. Shin et al.[5] evaluated both periorbital and facial ecchymosis and found that the rate of ecchymosis was lower in the cold application group and facial ecchymosis gradually deteriorated in all the patients, including those who underwent cold application, but they presented no information about upper and lower eyelid ecchymosis. Therefore, our findings showing that both upper and lower eyelid ecchymosis scores of the patients in the cold application group were significantly lower than the scores of the patients in the control group in all the measurements except for the 3rd postoperative hour after craniotomy provide valuable evidence of the effect of cold application on craniotomy-induced upper and lower eyelid ecchymosis.

Also, similar to our study, in few studies with different

patient groups, it was found that cold application significantly reduced periorbital edema and ecchymosis scores[7,13]. Furthermore, the meta-analysis results of these studies showed that periorbital edema and ecchymosis scores of rhinoplasty patients who received cold application beginning from the first postoperative hour were significantly lower on the first day[17]. Current literature knowledge and our research findings suggest that cold application administered beginning from the 1st and 3rd postoperative hours is effective in reducing the severity of periorbital edema and ecchymosis after surgical trauma.

Effect of local heparinoid

Heparinoid (mucopolysaccharide polysulphate), a semisynthetic glycosaminoglycan, is effective on blood coagulation and fibrinolysis, which increases the tissue metabolism and provides absorption of superficial inflammatory exudate[14], and reduces inflammation signs and symptoms, especially in subcutaneous hematoma and sports injuries[6,8]. In the literature, there are currently two studies evaluating the effect of heparinoid on periorbital edema and ecchymosis after rhinoplasty[6,8]. However, there are currently no studies performed with craniotomy patients. This is the first study to provide evidence-based information on the effect of heparinoid on periorbital edema and ecchymosis following anterior craniotomy.

Similar to our patients in the control group, edema severe enough to cover the iris (≥ 3 points) and ecchymosis severe enough to cover past the pupil (≥ 3 points) occurred in the heparinoid group. These findings are similar to those of a study indicating that local heparinoid has no effect on periorbital edema and ecchymosis[6]. In contrast, Şimsek et al.[8] found that periorbital edema and ecchymosis scores of the patients in the heparinoid group were significantly lower on the 1st day after rhinoplasty. In the same study[8], similar to our study, no significant difference was found between the periorbital edema and ecchymosis scores of the patients in the heparinoid and control groups on the 2nd postoperative day. In addition, unlike the results from Kelleş et al.'s study[6], the edema scores of our patients in the heparinoid group on the 3rd postoperative day were significantly lower than those in the control group. The difference may be due to the different patient groups in the studies mentioned. In fact, research suggests that periorbital edema after rhinoplasty is critical in the first hours[10], and progressively increases for three days after craniotomy[5] which confirms our thinking about the difference.

An important finding of the study was that, when compared with the scores of the patients who received cold application, the periorbital edema and ecchymosis scores of the heparinoid group were significantly higher in all the measurements except for the one at the 3rd hour after craniotomy. This finding suggests that cold application is more effective than heparinoid cream in controlling periorbital edema and ecchymosis after anterior craniotomy.

Change of skin temperature after cold application

Among those studies evaluating the effect of cold application on periorbital edema and ecchymosis[5,7,13], only one study[5] provided information about the decrease in periorbital skin temperature after cold application, but none reported the temperature of the tool used in cold application. Therefore, this study provides evidence that cold application with gel packs can be applied to the periorbital area with an average temperature of -14 ºC for 20 minutes each hour without causing any complications.

Shin et al.[5] found that periorbital skin temperature decreased by 9.82 ºC on average after cold application for 20 minutes. Similarly, in our study, periorbital skin temperature decreased by 9.20 ºC after cold application. Also, another study showed that the average limb temperature of patients with soft tissue injury decreased by 9.77 °C after ice pack therapy for 20 minutes[16].

Unlike our study, in a study by Kennet et al.[15], healthy individuals' ankle skin temperature was found to decrease 13.19 ºC on average after cold application for 20 minutes with gel packs cooled to -14 ºC. The reason for this difference may be the application of cold gel pack to different areas outside the periorbital area and to healthy tissue without trauma-induced inflammatory response.

There are currently no studies examining the relationship between periorbital edema and ecchymosis scores and the decrease in the skin temperature of the periorbital area. In our study, we found that the decrease in the skin temperature did not affect the periorbital ecchymosis score and that the periorbital edema score reduced in parallel with the decrease in the skin temperature only on the 3rd postoperative day. Further studies investigating the relationship between the decrease in the skin temperature and periorbital edema and ecchymosis are necessary as they would provide evidence of optimal

temperature reduction required for the maximal effect of cold application.

Limitations, future directions, and implications

Our study had several limitations. The most significant of these limitations was that periorbital edema and ecchymosis were evaluated only in the first three postoperative days because some of the patients in the clinics where this study was conducted were discharged after the 3rd postoperative day. This prevented the determination of whether the effect of cold application would continue in the following days. Future studies with longer follow-up periods are vital because they would contribute to the limited literature[5] suggesting that the effect of cold application on periorbital edema after craniotomy is continuous between the 9th hour and 7th day. Another limitation of the study was that cold application and heparinoid cream were administered at the 3rd hour after craniotomy and not at the first hour. Our findings showing that edema and ecchymosis occurred at the 3rd hour after craniotomy in all of our groups, albeit at a low degree, suggest that prevention interventions should be performed at an early stage. Future studies could investigate the preventive effect of cold application or heparinoid on periorbital edema and ecchymosis at the first hour after craniotomy. The fact that skin temperature should be kept in the range of 10-15 ºC in order to decrease the cellular metabolism and improve the therapeutic effect of cold application[15] draws attention to another important limitation of our study. In our study, the periorbital skin temperature decreased to an average of 24.61 ºC after cold application. In the literature, there is currently no evidence of a change in tissue due to decreasing the periorbital skin temperature to 10-15 ºC. Therefore, future laboratory studies are needed to investigate the change in periorbital tissue caused by these low temperatures and its effect on periorbital edema and ecchymosis.

Our study revealed that cold application, an independent nursing practice, was effective in reducing the severity of periorbital edema and ecchymosis following anterior craniotomy, and that heparinoid and routine clinic applications were not as effective. These findings contribute to the literature suggesting that cold application is an effective, inexpensive, safe and easily applicable method for reducing craniotomy-induced periorbital edema and ecchymosis. It is important that future studies investigate this effect of cold application since their results could guide the establishment of protocols for control of periorbital edema and ecchymosis after craniotomy and guide the spread of cold application.

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Conflicts of Interest

The authors declare that they have no conflict of interests.

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