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To Study Effect of Topical Betamethasone Dipropionate Cream (0.05% W/W) On Blood Pressure, Blood Sugar and Blood Calcium Level in Patients Requiring Topical Corticosteroids Therapy

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KEYWORDS

Topical, Betamethasone dpropionate cream, blood pressure, blood sugar, blood calcium

ABSTRACT:

In the skin diseases, corticosteroids are used for few days to few weeks and use of different corticosteroids according to potency, depends on site (location) of application and severity of disease. Adverse effects of corticosteroids depend on potency of corticosteroids, duration of treatment and area of involvement. In this study we investigated the effect of topical betamethasone on blood pressure, blood sugar and blood calcium after application of seven days. Also, correlated the absorbed concentration of corticosteroids with blood pressure, blood sugar, blood calcium and affected body surface area. Betamethasone cream application for seven days there was no effect on blood pressure, blood sugar and blood calcium level. Drug absorbing surface area is directly proportional to blood concentration of corticosteroids. Effect of corticosteroids on blood pressure, blood sugar and blood calcium level depend on absorbed concentration of corticosteroids in blood, Absorption depends on drug absorbing surface area.

INTRODUCTION

Corticosteroids are mainly used to reduce inflammation and suppress the immune system. Corticosteroids are used in a variety of conditions, ranging from brain tumours to skin diseases. Mainly cortiscosteroids are administered by oral, parenteral and topical route. Topical corticosteroids are often considered to have greater safety than oral corticosteroids. There are different topical corticosteroids used in skin diseases. e.g. clobetasol, mometasone, beclomethasone, betamethasone, desonide and fludrocortisone. Use of these steroids depends on strength of corticosteroids and anatomic location. In the skin diseases, corticosteroids are used for few days to few weeks and use of different corticosteroids according to potency, depends on site (location) of application and severity of disease. Adverse effects of corticosteroids depend on potency of corticosteroids, duration of treatment and area of involvement. High potency corticosteroids are used for longer duration in the treatment of diseases like psoriasis, discoid lupus erythematous and other. In topically used corticosteroids, the extent of percutaneous absorption is determined by many critical factors such as formulation, vehicle, anatomical site of application, integrity of the epidermal barrier, use of occlusive dressing and concentration and frequency of application [15]. Short-term corticosteroid use is associated with generally mild side effects, including cutaneous effects, electrolyte abnormalities, hyperglycemia, pancreatitis, hematologic, immunologic and neuropsychologic effects. Long-term corticosteroid use may be associated with more serious side effects including osteoporosis, hypertension, adrenal insufficiency, gastrointestinal, hepatic, and ophthalmologic effects, hyperlipidemia, growth suppression and possible congenital malformations [1].

Thus, the study was undertaken to estimate the effect of betamethasone dipropionate on the blood pressure, blood calcium and blood sugar level and to estimate the blood concentration of topically applied corticosteroids in patients and to correlate these effect with the concentration of corticosteroids in blood.

MATERIAL AND METHOD

This study was conducted in MGM Medical College and Hospital Kamothe, Navi Mumbai in patients from dermatology outpatient department (OPD). Total number of 10 healthy patients who were not using corticosteroid treatment for more than one month prior to inclusion in the

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study or they were freshly diagnosed and they required topical steroid therapy were included.

Study was carried out after the permission of Institutional Ethics Committee proper consents were taken from each healthy volunteer and patients before enrolling in the study.

Before enrolment, patients were explained each and every parameter of study including use of study, procedure of blood pressure measurement, blood sugar and blood calcium level estimation and blood samples collection.

All details of patients were taken while proceeding the study, name of patient, age, sex, disease history, drug history, general examination, affected body surface area was measured by palmar method [2], blood pressure was measured before and after seven days of treatment by sphygmomanometer, blood sugar level was measured before and after seven days of treatment by glucometer, blood calcium level was measured by biochemical method by collection of blood sample in plain tube before and seven days after treatment, blood collected in EDTA tube for estimation of corticosteroid in blood by HPLC method seven days after drug treatment.

Ten patients were enrolled those who required topical Betamethasone dipropionate cream 0.05% w/w. Blood pressure, blood sugar and blood calcium level were measured before and 7 days after drug application. Three ml of blood was collected in plain tube after patients enrolled in study for calcium estimation and on the 7th day after drug application, two ml of blood was collected in EDTA tube for betamethasone dipropionate concentration and three ml of blood was collected in plain tube blood calcium level estimation, four hours after drug application on the affected part.

INCLUSION CRITERIA

1. Human patients with skin diseases who required topical corticosteroid therapy & who were willing to participate in the study.
2. Vitiligo, eczema, psoriasis and lichenplanus disease patients.
3. Age 18 to 50 years.
4. Patients who did not use corticosteroid treatment before one month.
5. Freshly diagnosed patients.

EXCLUSION CRITERIA

1. Patients who took corticosteroids in previous one month.
2. Hypertensive and hypotensive patients.
3. Obese patients.
4. Diabetic patients

MEASUREMENT OF BODY SURFACE AREA

Affected body surface area were measured by palmar method [2] when patients for the first time attended skin OPD and after seven days of drug application also investigate severity of disease and affected site.

PALMAR METHOD

- Identified the affected site.
- Area of affected site was measured by study participant's hand including digits.

One patients hand is nearly equal to 1% body surface area.

BLOOD PRESSURE MEASUREMENT

Blood pressure was measured when study participant for the first time attended skin OPD and after seven days of drug application, on right hand in sitting position by using mercury sphygmomanometer.

METHOD OF BLOOD PRESSURE MEASUREMENT SUBJECT

- **POSITION:** Seated.
- The flexed elbow on the table at the level of the heart.

PROCEDURES

- The cuff was wrapped around the upper arm of right hand with the cuff's lower edge, one inch above the antecubital fossa.
- The stethoscope's bell was lightly pressed over the brachial artery just below the cuff's edge.
- The cuff was rapidly inflated to 180mmHg. Released air from the cuff at a moderate rate (3mm/sec).
- The stethoscope sounds were heard and simultaneously observed the sphygmomanometer. The first knocking sound (Korotkoff) was the subject's systolic pressure and when the knocking sound disappears, that was the diastolic pressure.

BLOOD COLLECTION

Blood samples were collected before and seven days after starting drug treatment.

- **METHOD:** 21 gauge needles and 10 ml syringes were used for blood collection, asked the study participant with the arm extended to form a straight-line form shoulder to wrist. Tourniquet was applied 3-4 inches above the collection site, the puncture site was cleaned with the 70% alcohol swab and venipuncture was performed. Blood samples were collected in EDTA

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tube (3 ml) and plain tube (2 ml) from group A volunteers and group B study participant for estimation of concentration of drug in blood and 3 ml of blood samples collected in EDTA tube from group C study participant for estimation of concentration of drug in blood.

SERUM SEPARATION AND STORAGE

- Once the blood samples were collected quickly transferred them into tubes with tops or caps. The samples were centrifuged at 2000 rpm for 15 minutes at room temperature. After centrifugation, serum was removed and placed into a polypropylene microcentrifuge tube. The serum samples were stored in Pharmacology laboratory of MGM medical college at-4 degrees centigrade.
- **DRUG STANDARD COLLECTION AND STORAGE:** Standard drug samples of Clobetasol propionate, Betamethasone dipropionate, Mometasonefuroate were purchased from Sigma Aldrich and stored in refrigerator as directed by company

BLOOD SUGAR MEASUREMENT

Blood sugar levels were measured when patients first time attended skin OPD and after seven days by glucometer.

PROCEDURE

- Middle finger was cleaned with the 70% alcohol swab
- The finger was pricked with lancet allowed the sample of blood to flow right onto the glucose strip.
- Glucose strip then inserted into the glucometer.
- The reading appeared on the glucometer was recorded.

BLOOD CALCIUM MEASUREMENT

Serum samples stored in plain tube were used for calcium investigation. Estimation of calcium done by OCPC method (O-cresol phthalein complex one).

PRINCIPLE

Calcium in alkaline medium combines with O-cresol phthaline complex one and forms a purple coloured complex. Intensity of the colour formed is directly proportional to the amount of calcium present in the sample.

Calcium + OCPC ⟶ Purple colour complex

REAGENT: Buffer reagent (L1), colour reagent (L2), Calcium standard (10 mg/ml) (S) Reagents were ready to use.

PROCEDURE OF O-CRESOL PHTHALEIN COMPLEX ONE METHOD

ADDITION SEQUENCE	BLANK (ML)	STANDARD (ML)	TEST (ML)
Buffer Reagent (L1)	0.5	0.5	0.5
Colour Reagent (L2)	0.5	0.5	0.5
Distilled Water	0.2	---	---
Calcium Standard (S)	---	0.2	---
Sample	---	---	0.2

Incubated at room temperature (25 0^c) for 5 min. measured the absorbance of standard (Abs S) and Test sample (Abs T) against the blank, within 60 min.

Wavelength/filter : 570 nm (Hg 578)/Yellow
Temperature : R.T
Light path : 1 cm
Calculation : Calcium in mg/dl = (Abs T ÷ Abs S) × 10

ESTIMATION OF BETAMETHASONE DIPROPIONATE CONCENTRATION IN THE BLOOD:

INSTRUMENTS: Weighing balance, refrigerated centrifuge, glassware's were used from pharmacology laboratory. High performance liquid chromatography instrument from OMICS research laboratory in MGM medical college, Navi Mumbai.

WEIGHING BALANCE: Weight balanced was standardized with standard weights before the use and mainly used to weight standard drugs.

COOLING CENTRIFUGE: Samples were centrifuged at-6^0 at 6000 rpm.

GLASSWARE: Glassware were washed with soap and rinsed with distilled water and dried in the oven at temperature 40 ^oC.

HPLC METHOD STANDARDIZATION

5 mg standard betamethasone dipropionate dissolved in 50

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ml acetonitrite to get concentration of 100 µg/ml and then serially dilutions were made in the concentration of 10 ng/ml, 20ng/ml, 30ng/ml, 50 ng/ml, 70ng/ml and 100ng/ml.

0.4 ml of betamethasone dipropionate from each dilution was added in 1 ml plasma in separate test tube and mixed properly.

EXTRACTION PROCEDURE:

LIQUID LIQUID EXTRACTION: 100 µl of plasma added in 1200ul of ethyl acetate (extracting solvent) in eppendorf tube and kept in vertex for proper mixing, then the eppendorf tube centrifuged at 6000 rpm at -6 ^{o}C for 10 minutes. The supernatant liquid was removed from eppendorf tube transferred into small test tube. Then small test tubes were kept on simple heater at 40 ^{o}C for evaporation of volatile solvent. Then remaining solid residue dissolved in 400 µl of acetonitrite to run in HPLC.

HPLC PARAMETER

MOBILE PHASE:

METHANOL: Water (80:20).

FLOW RATE: 1ml/min.

RETENTION TIME OF DRUG: 5.1 min.

COLUMN: C18.

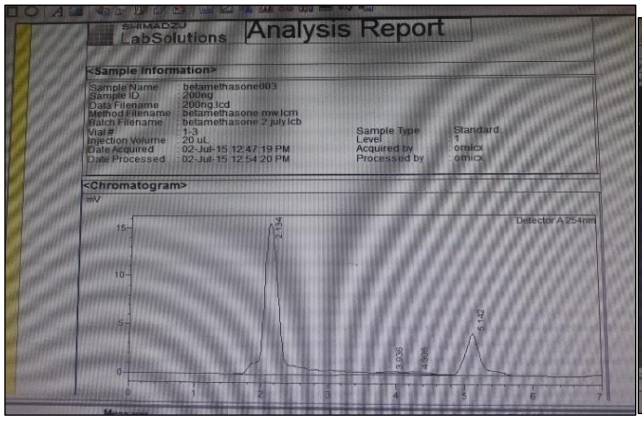
WAVELENGTH: 254nm.

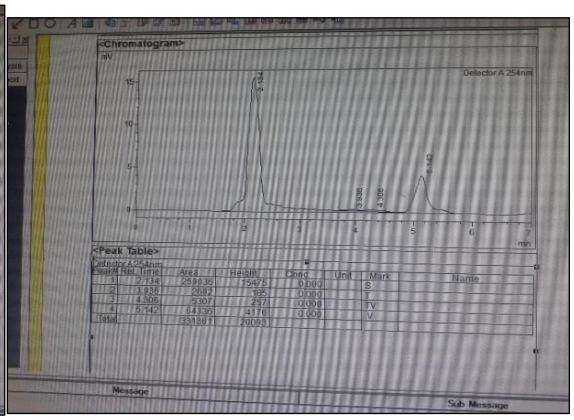
After running different dilutions of betamethasone dipropionate in HPLC at given HPLC parameter gives reading [area under curve (AUC)]. We plotted graph AUC Vs concentration, drown straight line.

HPLC GRAPHS AND TABLES

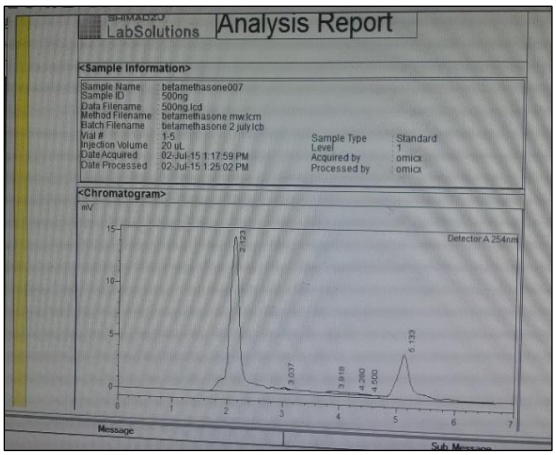
HPLC GRAPH OF BETAMETHASONE DIPROPIONATE

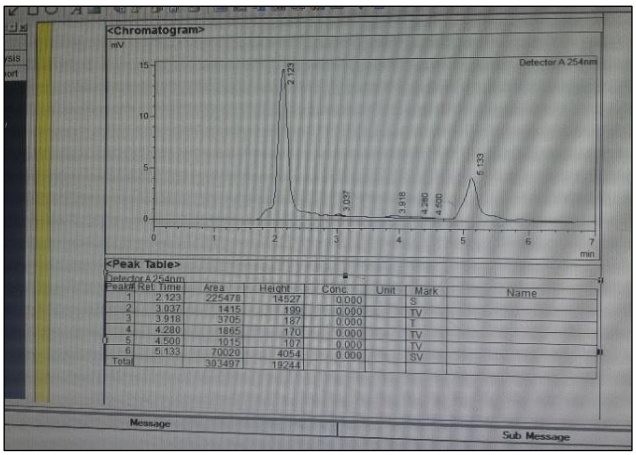
Betamethasone dipropionate 20 ng/ml.





Betamethasone dipropionate 50 ng/ml.





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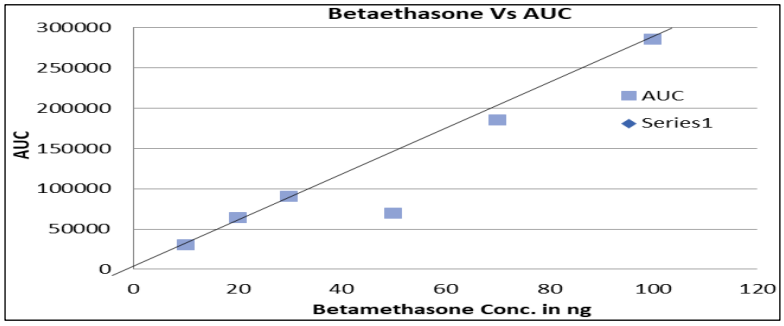
CONCENTRATION OF BETAMETHASONE DIPROPIONATE VS AUC

CONCENTRATION OF BETAMETHASONE DIPROPIONATE IN NG	AUC
10	30782
20	64336
30	90296
50	70020
70	185722
100	285485

CONCENTRATION OF BETAMETHASONE VS AUC



SERUM SAMPLES
EXTRACTION PROCEDURE

LIQUID LIQUID EXTRACTION: 100ul of serum sample added in 1200µl of ethyl acetate (extracting solvent) in eppendorf tube and kept in vertex for proper mixing, then the eppendorf tube centrifuged at 6000 rpm at -6 ºC for 10 minutes. The supernatant liquid was removed from eppendorf tube transferred into small test tube. Then small test tubes were kept on simple heater at 40 ºC for evaporation of volatile solvent. Then remaining solid residue dissolved in 400 µl of acetonitrite and run in HPLC.

HPLC gave reading (AUC), we compared AUC with plotted standard graph gave unknown concentration of Betamethasone dipropionate in serum sample.

RECOVERY EXPERIMENT

The recovery of betamethasone dipropionate determined by comparing the peak area of the extracted plasma samples of six dilutions with control samples. As control equivalent amount of betamethasone dipropionate was added directly into the mobile phase and injected.

Recovery was assed by comparing the chromatographic peak area of betamethasone dipropionate of the extracted the plasma standard to those obtained from equivalent amount of the betamethasone dipropionate directly into the mobile phase.

The extraction recovery of each concentration was calculated using the following equation.

Recovery = (Peak area of extracted analyte/Peak area of non-extracted analyte) × 100.

RECOVERY EXPERIMENT OF BETAMETHASONE DIPROPIONATE

CONCENTRATION (NG/ML)	AUC EXTRACTED ANALYTE	AUC NON-EXTRACTED ANALYTE	PERCENTAGE
10	30782	37214	82.7%
20	64336	74529	86.3%
30	90296	98257	91.9%
50	70020	14890	
70	185722	226529	81.9%
100	285485	361291	79.0%

MEAN RECOVERY: 84.6%

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RESULTS

This study was conducted in MGM Medical College and Hospital Kamothe, Navi Mumbai in patients from Dermatology OPD. Total number of 10 patients was enrolled. Who were not using corticosteroid treatment for more than one month or they were freshly diagnosed. Before enrolling, patients were explained each and every parameter of study including use of study, procedure of blood pressure measurement, blood sugar level estimation and blood samples collection.

Study was carried out after the permission of Institutional Ethics Committee, proper consents were taken from each healthy volunteers and patients before enrolling in the study.

Patients with age ranging between 24 years and 46 years were included. All patients were males. Those who required topical betamethasone dipropionate cream 0.05% w/w. Blood pressure, blood sugar was measured before and 7 days after drug application. Three ml of blood was collected in plain tube after patients are enrolled in the study for calcium estimation. On the 7th day four hours after drug application on the affected part two ml of blood was collected in EDTA tube for betamethasone dipropionate estimation and three ml of blood was collected for blood calcium level estimation.

Sr. No.	Age in year	ABSA %	Sex	Baseline BP (mm Hg)		7th day BP (mm Hg)		Concentration of betamethasone dipropionate in ng/ml
				S	D	S	D	
1	25	04	M	120	76	124	78	10
2	29	30	F	118	82	124	80	18
3	55	02	F	122	84	126	82	13
4	42	50	F	128	82	140	88	16
5	38	15	M	114	74	118	78	14
6	46	30	M	124	78	128	80	18
7	29	01	M	126	80	130	80	13
8	49	03	M	128	82	132	82	14
9	25	07	M	116	78	122	78	14
10	26	10	M	124	86	130	88	15
Mean (mm Hg)				122 ± 4.9	81.1 ± 4.18	127.4 ± 6.11	81.4 ± 3.78	14.5 ± 2.42

S = Systolic blood pressure; D = Diastolic blood pressure

Table 1: Blood pressure (mm Hg)

ABSA: AFFECTED BODY SURFACE AREA

The baseline systolic blood pressure ranged from 114 mm Hg to 128 mm Hg (mean 122 mm Hg, SD = 4.9). The diastolic blood pressure was between 74 mm Hg and 86 mm Hg (mean 81.1 mm Hg, SD = 4.18) on first day. Seven days after betamethasone dipropionate cream application, the systolic blood pressure was raised on an average by 5.4 mm Hg whereas rise in diastolic blood pressure was 0.3 mm Hg. Systolic blood pressure was increased statistically significantly over baseline value but this change is not significant clinically. The rise in diastolic blood pressure is not significant statistically.

Betamethasone dipropionate concentration in blood after seven days of drug application was in range between 10 ng/ml to 18 ng/ml and mean blood concentration was 14.5 ± 2.42.

Sr. No.	Age in year	ABSA%	Sex	Blood sugar(mg/dl)		Concentration of betamethasone dipropionate in ng/ml
				Before	After	
1	25	04	M	82	84	10
2	29	30	F	76	84	18
3	55	02	F	88	90	13
4	42	50	F	86	96	16
5	38	15	M	94	96	14
6	46	30	M	92	98	18
7	29	01	M	86	88	13
8	49	03	M	83	86	14
9	25	07	M	86	90	14

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10	26	10	M	74	78	15
Mean (mg/dl)				84.7 ± 6.29	89 ± 6.34	14.5 ± 2.42

Table 2: Blood sugar (mg/dl)

ABSA: AFFECTED BODY SURFACE AREA

The baseline blood sugar level ranged from 74 mg/dl to 94 mg/dl (mean 84.7 mg/dl, SD = 6.29) on first day. Seven days after betamethasone dipropionate cream application, the blood sugar level ranged from 78 mg/dl to 98 mg/dl. (mean 89 mg/dl, SD = 6.34) Blood sugar level was raised on an average by 4.3 mg/dl. Change in blood sugar level was not significant statistically.

Betamethasone dipropionate concentration in blood after seven days of drug application was in range between 10 ng/ml to 18 ng/ml and mean blood concentration was 14.5 ± 2.42.

Sr. No.	Age in year	ABSA %	Sex	Blood calcium (mg/dl)		Concentration of betamethasone dipropionate in ng/ml
				Before	After	
1	25	04	M	9.2	9.3	10
2	29	30	F	8.7	8.7	18
3	55	02	F	8.4	8.5	13
4	42	50	F	9.0	9.1	16
5	38	15	M	7.8	7.9	14
6	46	30	M	8.6	8.6	18
7	29	01	M	8.3	8.4	13
8	49	03	M	8.5	8.6	14
9	25	07	M	8.9	8.8	14
10	26	10	M	8.2	8.3	15
Mean (mg/dl)				8.6 ± 0.4	8.6 ± 0.4	14.5 ± 2.42

Table 3: Blood calcium (mg/dl)

ABSA: AFFECTED BODY SURFACE AREA

The baseline blood calcium level ranged from 7.8 mg/dl to 9.2 mg/dl (mean 8.6 mg/dl, SD = 0.4) on first day. Seven days after betamethasone dipropionate cream application, the blood calcium level ranged from 7.9 mg/dl to 9.3 mg/dl (mean 8.6 mg/dl, SD = 0.4). After the application of betamethasone dipropionate calcium level has not changed.

Betamethasone dipropionate concentration in blood after seven days of drug application was in range between 10 ng/ml to 18 ng/ml and mean blood concentration was 14.5 ± 2.42.

		Mean	SD
SBP (mm Hg)	Before	122	4.90
	After	127.4	6.11
DBP (mm Hg)	Before	81.10	4.18
	After	81.40	3.78
Blood Sugar (mg/dl)	Before	84.7	6.29
	After	89	6.34
Blood Calcium (mg/dl)	Before	8.6	0.4
	After	8.6	0.4

Significant at $p<0.05$; Name of test: t-test (paired)

Table 4: Comparison of blood pressure, blood sugar and blood calcium before and after betamethasone dipropionate administration in Patients

COMPARISON OF SYSTOLIC AND DIASTOLIC BLOOD PRESSURE BEFORE AND AFTER BETAMETHASONE DIPROPIONATE TOPICAL APPLICATION IN PATIENTS

Mean systolic and diastolic blood pressure before the betamethasone dipropionate application was 122 ± 4.90 mm Hg and 81.1 ± 4.18 mm Hg and after the betamethasone dipropionate application was 127.4 ±

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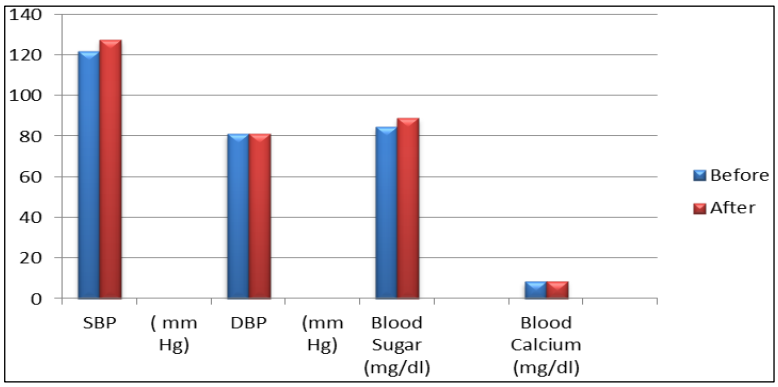
6.11 mm Hg and 81.4 ± 3.78 mm Hg respectively.
There was statistical significant difference in systolic blood pressure (P = 0.0428) but not diastolic blood pressure (P = 0.8681) after the betamethasone dipropionate application in patients. The change in systolic blood pressure although statistically significant it is not significant clinically.

COMPARISON OF BLOOD SUGAR LEVEL BEFORE AND AFTER BETAMETHASONE DIPROPIONATE TOPICAL APPLICATION IN PATIENTS

Mean blood sugar level before the betamethasone dipropionate application was 84.7 ± 6.29 mg/dl and after the betamethasone dipropionate application was 89 ± 6.34 mg/dl.
There was no statistically significant difference in blood sugar level (P = 0.1453) after the betamethasone dipropionate application in patients.

COMPARISON OF BLOOD CALCIUM LEVEL BEFORE AND AFTER BETAMETHASONE DIPROPIONATE TOPICAL APPLICATION IN PATIENTS

Mean blood calcium level before the betamethasone dipropionate application was 8.6 ± 0.4 mg/dl and after the betamethasone dipropionate application was 8.6 ± 0.4 mg/dl. There was no significant difference in blood calcium level (P = 0.7766) after the betamethasone dipropionate application in patients.



Significant at $p<0.05$; Name of test: t-test (paired)

Fig 1: Comparison of blood pressure, blood sugar and blood calcium before and after betamethasone dipropionate administration in Patients

DISCUSSION

This study was conducted in MGM medical college and hospital Kamothe, Navi Mumbai. In this study, we have investigated effect of topical betamethasone dipropionate on systolic blood pressure, diastolic blood pressure, blood sugar level and blood calcium level after seven days in patients who were not using corticosteroid treatment for more than one month and they were freshly diagnosed.

BLOOD PRESSURE

In our study there was no change in systolic and diastolic blood pressure after seven days of betamethasone cream application. Betamethasone dipropionate concentration in blood after seven days was 14.5ng/ml respectively.
In 1983 animal experiment conducted by Häusler A and coworkers on spontaneously hypertesive rat and normotensive wister rat, concluded that both rats responded with a significant elevation in average blood pressure after seven weeks of oral betamethasone treatment [3].
Koenen SV and co-workers conducted animal experiment in 2002 on pregnant baboon investigated that fetal blood pressure increased significantly after intramuscular betamethasone treatment [4].
A comparative animal study conducted by Derks J B *et al.* in 1997 concluded that prenatal betamethasone and dexamethasone treatment of late-gestation fetal sheep, in doses similar to those employed clinically, is associated with fetal cardiovascular, endocrine and behavioural effects. Both betamethasone and dexamethasone induce similar increases in fetal blood pressure [5].
Bartorelli A and co-workers in 1984 explained that 9-year-old boy suffering from exzematous dermatitis who was treated for 6 years with a daily dose of 100 mg of a dermatological ointment containing 9 alpha-fluoroprednisolone-21-acetate. At examination the patient's blood pressure was persistently 230/160 mm Hg [6].

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In april 1986, Judith A. Whitworth and coworkers told that systolic blood pressure (SBP) was increased by both ACTH and hydrocortisone treatment, but more by ACTH [7].

In another study by Krishnankutty Sudhir and coworkers in 1989 showed that Oral hydrocortisone increases blood pressure, diastolic blood pressure remained unchanged, systolic blood pressure increased from 119 to 135 mm Hg [8].

A study conducted by Marinis Pirpiris and coworkers in 1992also showed increase mean arterial pressure from 82±3 to 91 ±3 mm Hg by dexamethasone [9].

Another study conducted by Atsuhisa Sato and coworkers in 1995 showed glucocorticoid-induced hypertensionin elderly patients and/or in those with positive family history of essential hypertension [10].

In 1999 Dodic M and coworkers concluded that foetal exposure to maternal dexamethasone during defined developmental stage or 'window' programmes elevated blood pressure, which persists later in life [11].

Case-control study conducted by Marie-Josée Martel and coworkers in 2005 explained that, there was no significance dose-response relation was observed between inhaled corticosteroids and pregnancy induced hypertension or pre-eclampsia. Oral corticosteroids were significantly associated with the risk of pregnancy induced hypertension [12].

From our results and from literature, it showed that corticosteroids increases blood pressure and change in blood pressure was more after oral administration than topical application. Ultra-high potent and high potent corticosteroids increase only systolic blood pressure and there is no effect of moderately potent corticosteroids on blood pressure this may be due to the molecular weight of corticosteroids.

BLOOD SUGAR

In our study after seven days application of betamethasone dipropiponate has not changed blood sugar level.

In 2009 study conducted by Peter Gonzalez MD and coworkers in patients with Diabetes mellitus they showed that Lumbosacral transforaminal and caudal epidural betamethasone injections are associated with statistically significant elevations in blood glucose levels in diabetic subjects [13].

Ramírez-Torres MA and co-workers in 2011 reported that betamethasone induced hyperglycemia was greater in insulin treated women with gestational or type 2 diabetes [14].

Study conducted by Jolley JA and coworkers in 2016 on pregnant women of diabetic and without diabetic, administration of betamethasone for threatened preterm delivery they find out that both subjects with and without diabetes demonstrate significant hyperglycemia after receipt of antenatal betamethasone [15].

Iwamoto T and co-workers in 2004 investigated that Steroid-induced diabetes mellitus was diagnosed if the patient had either a fasting glucose concentration of 126 mg/dl or greater, or a random glucose concentration of 200 mg/dl or greater [16].

In 2006 study conducted by Angela A and co-workers on diabetic patients, reported that blood glucose level increased in diabetic patients who received methylprednisolone injection [17].

Van Raalte DH and co-workers in 2013 investigated that prednisolone-induced impairment of insulin-stimulated capillary recruitment was paralleled by insulin resistance, increased postprandial glucose levels, hypertension and increased circulating resistin concentrations in healthy men [18].

From our results and from literature, it showed that betamethasone dipropionate increases blood pressure and change in blood pressure was more after oral and parental administration than topical application.

BLOOD CALCIUM

In our study blood calcium levels have not changed after seven days application of betamethasone. Betamethasone absorbed in blood after topical application, but it does not produced any change in blood calcium.

Study conducted by C. Gennari, in 1993 revealed that low and high doses of betamethasone and high doses of prednisone induced a significant decrease in intestinal calcium absorption [19].

In 1981 Theodore J. Hahn *et al*. investigated that intestinal calcium absorption reduced by 31% after prednisone administration [20].

Yasuo Suzuki and coworkers in 1983 studied Parathyroid function and calcium metabolism in 44 patients under glucocorticoid therapy conclude that urinary calcium excretion increased in patients under glucocorticoid therapy [104].

Most of the literature explained that corticosteroids decreases calcium absorption and increases excretion of calcium but not a single study correlated blood concentration of corticosteroids with calcium level in the blood.

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CONCLUSION

1. Betamethasone dipropionate application to skin lesions does not get adsorbed into blood stream in substantial measurable levels.
2. Blood sugar level and calcium level was not changed by betamethasone dipropionate.
3. After seven-day application of betamethasone dipropionate there was no change in systolic as well as diastolic systolic blood pressure.
4. As area of application of topical steroids increase there were increases in blood concentration of corticosteroids.

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ETHICS APPROVAL

Before starting study ethical approval was taken from Institutional Ethics Committee MGM Medical College Navi Mumbai Maharashtra India.

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