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ORIGINAL ARTICLE

Effects of topical Povidone-iodine on thyroid function in surgical newborns

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ABSTRACT

Objective: Excessive iodine exposure during the neonatal period can lead to neonatal hypothyroidism due to their thinner and more permeable nature of skin. This study was conducted to evaluate the effects of Povidone-iodine on postoperative thyroid functions among surgical neonates.

Material and Methods: Surgical neonates with known pre-operative and post-operative thyroid function tests who had been operated by our department between January 2014 and 2016 were included this study. The post-operative thyroid function tests of these neonates were obtained between postnatal 7th and 21th days. Pre-operative and post-operative measurements of free Thyroxine 4 (fT_4) and thyroid-stimulating hormone (TSH) levels were analyzed retrospectively.

Results: Nineteen male and 14 female surgical neonates were included in this study. Their mean gestational age and age at operation were 37 weeks + 1 day and 10 days. Mean duration of hospitalization was 12.6 days and mean number of dressings per day during hospitalization was one. Mean pre-operative and post-operative values of fT_4 and TSH were 1.12 mIU/L, 1.14 mIU/L, 6.1 mIU/L, and 2.77 mIU/L, respectively. During the post-operative period, fT_4 values mildly increased and TSH levels decreased, however, all values remained within reference values. The change in TSH levels between preoperative and postoperative periods was statistically significant. Patients did not require thyroid hormone replacement therapy.

Conclusion: Although not necessitating hormone replacement therapy, the use of topical Povidone-iodine significantly and transiently affects the thyroid functions of surgical neonates due to transdermal iodine absorption..

Keywords: Congenital hypothyroidism; free thyroxine 4; neonatal hyperthyrotropinemia; neonate; thyroid dysfunction; thyroid-stimulating hormone; topical Povidone-iodine.

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INTRODUCTION

Povidone-iodine is an effective disinfectant used in many surgical operations.[1] Excessive iodine exposure during fetal and neonatal periods can lead to neonatal thyroid dysfunction due to their thinner and more permeable nature of skin, and thyroid function tests can be guiding during this process.[2] The dosage and amount of exposure to topical Povidone-iodine that may cause thyroid dysfunction are not commonly researched among surgical neonates. This study was conducted to evaluate the effects of Povidone-iodine on post-operative thyroid functions among the surgical newborns.

MATERIAL AND METHODS

After approval by the ethical body (2017/157), this retrospective study was conducted among the surgical neonates with known preoperative and postoperative levels of free Thyroxin4 (fT_4) and thyroid-stimulating hormone (TSH) who had been operated on in our department between January 2014 and 2016. None of the neonates included in our study received thyroid replacement therapies. One female surgical patient who was preoperatively diagnosed with hypothyroidism and who received thyroid hormone replacement therapy was excluded. Pre-operative and post-operative measurements of free T4 and TSH levels were obtained from hospital records retrospectively. Pre-operative and post-operative fT_4 and TSH levels were compared with respect to gestational age, birth weight, age of surgery, surgical area, and hospitalization duration and outcomes.

Statistical Analysis

Our results were statistically evaluated using SPSS version 22.0.0.0. Statistical significance cut-off level was set at $p<0.05$. Paired-t-test was used for comparing preoperative and postoperative values.

RESULTS

Between January 2014 and 2016, 544 neonates were operated in our department. Thyroid function tests were not routinely obtained and of these 544, 33 surgical neonates with known pre-operative and post-operative thyroid function tests were included in this study. All 33 neonates had major operations due to various severe abnormalities. The pre-operative TSH and free T4 levels were obtained after the 1st neonatal week and the post-operative thyroid function tests were obtained within the 3th and/or 4th postnatal weeks before the discharge day.

19 of these neonates were male (58%) and 14 were female (42%). The mean gestational age of these patients was 37 weeks + 1 day (28–40 weeks). The gestational age of one patient was <28 weeks. Three patients were born between the 28th and 32nd weeks, eight patients were born between the 32nd and 35th weeks, 7 patients were born between the 36th and 38th weeks, and seven patients were born between the 38th and 40th weeks. The gestational ages of the other seven patients were unknown. Demographic characteristics of these patients are summarized in Table 1.

The mean±standard deviation levels of preoperative and postoperative free T4 and TSH levels for female patients were 1.17±0.33 ng/dL, 1.26±0.26 ng/dL (p=0.700); and 6.31±4.30 mIU/L, 3.54±2.40 mIU/L (p=0.06), respectively. The mean±standard deviation levels of pre-operative and post-operative free T4 and TSH levels for male patients were 1.08±0.38 ng/dL, 1.01±0.18 ng/dL (p=0.68); and 4.43±5.07 mIU/L, 2.08±1.58 mIU/L (p=0.060), respectively. The mean±standard deviation levels of pre-operative and post-operative free T4 and TSH levels for all patients were 1.11±0.37 ng/dL, 1.14±0.28 ng/dL (p=0.68); and 5.18±4.86 mIU/L, 3.00±2.04 mIU/L (p=0.040), respectively. The difference between pre-operative and post-operative mean TSH values for all patients was statistically significant while all of the other comparisons proved otherwise. Results of the pre-operative and post-operative thyroid function tests with respect to gender are summarized in Table 2.

Table 1: Demographic characteristics of patients included in the study

	Mean gestational age	Mean birth weight (grams)	Mean age at operations (days)
Females	37 weeks+5 day	2261 (1010–3800)	10.5 (0–30)
Males	36 weeks+6 day	2406	9.8
Total	37 weeks+1 day	2333	10

The pre-operative and post-operative mean free T4 levels for the patient with gestational age of <28 weeks were 0.92 ng/dL and 0.7 ng/dL (p:n/a), respectively. The same values for patients born between the 28th–32nd weeks, 32nd–35th weeks, 36th–38th weeks, and 38th–40th weeks were 1.02 ng/dL and 1.39 ng/dl (p=0.08); 1.27 ng/dL and 1.26 ng/dL (p=0.58); 1.1 ng/dL and 0.79 ng/d L (p=0.77); and 1.19 ng/dL ve 1.1 ng/dL (p=0.82), respectively.

The pre-operative and post-operative mean TSH values for the patient with gestational age <28weeks were 4.33 mIU/dL and 7.7 mIU/dL (p:n/a), respectively. The same values for patients born between the 28th–32nd weeks, 32nd–35th weeks, 36th–38th weeks, and 38th–40th weeks were 6.8 mIU/dL and 2.43 mIU/dL (p=0.01), 4.8 mIU/dL and 2.18 mIU/dL (p=0.07), 3.03 mIU/dL and 1.44 mIU/dL (p=0.16), and 3.8 mIU/dL and 4.22 mIU/dL (p=0.12), respectively. Among these values, a statistically significant difference in pre-operative and post-operative mean TSH values was detected for patients born between 28th and 32nd gestational weeks (p=0.01). The rest of the values did not prove to be statistically significant. Results of the preoperative and postoperative thyroid function tests with respect to gestational age are summarized in Table 3.

Out of 33 patients, the number of patients with birth weights between 1000–2000 g, 2000–3000 g, and 3000–4000 g was 6, 12, and 7, respectively. The birth weights of the rest of the eight patients were unknown. The mean pre-operative and post-operative free T4 levels for patients with birth weights between 1000 and 2000 g were 0.89 ng/dL and 0.9 ng/dL (p=0.55), respectively. The same values for patients with birth weights between 2000–3000 g and 3000–4000 g were 1.25 ng/dL, 1.20 ng/dL (p=0.37) and 1.16 ng/dL, 1.32 ng/dL (p=0.42), respectively. These changes were not statistically significant.

Table 2: The pre-operative and post-operative mean fT_4 and TSH levels with respect to gender

	Mean Preop±SD fT_4 (ng/dL)	Mean Postop±SD fT_4 (ng/dL)	p	Mean Preop±SD TSH (mIU/L)	Mean Postop±SD TSH (mIU/L)	p
Females	1.17±0.33	1.26±0.26	0.70	6.31±4.30	3.54±2.40	0.06
Males	1.08±0.38	1.01±0.18	0.68	4.43±5.07	2.08±1.52	0.06
Total	1.11±0.37	1.14±0.28	0.68	5.18±4.86	3.00±2.04	0.04

SD: Standard deviation; fT_4: Free thyroxine 4; TSH: Thyroid-stimulating hormone.

Table 3: The pre-operative and post-operative fT_4 and TSH levels with respect to gestational age

Gestational weeks: w (n)	Mean Preop fT_4 (ng/dl)	Mean Postop fT_4 (ng/dl)	p	Mean Preop TSH (mIU/L)	Mean Postop TSH (mIU/L)	p
<28 w (1 case)	0.92	0.7	n/a	4.33	7.7	n/a
28–32 w (3 cases)	1.02	1.39	0.08	6.8	2.43	0.01
32–34 w (2 cases)	1.27	1.26	0.58	4.8	2.13	0.07
36–38 w (7 cases)	1.1	0.79	0.77	3.03	1.44	0.16
38 w > (7 cases)	1.19	1.1	0.82	3.8	4.22	0.12

fT_4: Free thyroxine 4; TSH: Thyroid-stimulating hormone.

Table 4: The pre-operative and post-operative fT_4 and TSH levels with respect to birth weight

Birth weight: g (n)	Mean Preop fT_4 (ng/dL)	Mean Postop fT_4 (ng/dL)	p	Mean Preop TSH (mIU/L)	Mean Postop TSH (mIU/L)	p
<1000 g	–	–		–	–	
1000–2000 g (6 cases)	0.89	0.9	0.55	5.93	2.49	0.09
2000–3000 g (12 cases)	1.26	1.2	0.37	4.62	2.82	0.11
3000–4000 g (7 cases)	1.16	1.32	0.42	4.84	3.4	0.11

fT_4: Free thyroxine 4; TSH: Thyroid-stimulating hormone.

The pre-operative and post-operative mean TSH values for patients with birth weights between 1000 and 2000 g were 5.93 mIU/dL and 2.49 mIU/dL (p=0.09), respectively. The same values for patients with birth weights between 2000–3000 g and 3000–4000 g were 4.62 mIU/dL, 2.82 mIU/dL (p=0.11), and 4.84 mIU/dL, 3.4 mIU/dL (p=0.11), respectively. None of these changes were statistically significant. Results of the pre-operative and post-operative thyroid function tests with respect to birth weight are summarized in Table 4.

The mean age at operation of all patients was 10 days. 26 cases were operated on within the 1st postnatal week, 2 cases were operated on between postnatal 7th and 14th days. The operations of 2 cases were performed within the patients' 4th postnatal weeks. The pre-operative and post-operative mean free T4 levels of patients operated within their 1st postnatal weeks were 1.13 ng/dL and 1.08 ng/dL (p=0.41), respectively. The pre-operative and post-operative mean free T4 levels of patients operated within their 2nd and 4th postnatal weeks were 1.59 ng/dL, 1.33 ng/dL (p=0.40); and 1.35 ng/dL, 3.59ng/dL (p=0.53) respectively.

The pre-operative and post-operative mean TSH levels of patients operated within their 1st postnatal weeks were 5.6 mIU/dL and 2.78 mIU/dL, respectively (p=0.02). The pre-operative and post-operative mean free T4 levels of patients operated within their 2nd and 4th postnatal weeks were 4.32 mIU/dL, 2.2 mIU/dL (p=0.34); and 1.03 mIU/dL, 1.56 mIU/dL (p=0.39), respectively. The pre-operative and post-operative TSH changes were statistically significant in the group operated within their 1st postnatal week. The changes for the rest of the groups were not proven statistically significant. Results of the pre-operative and post-operative thyroid function tests with respect to age at operation are summarized in Table 5.

Table 5: The pre-operative and post-operative fT_4 and TSH levels with respect to age at operation

Age (n)	Mean Preop fT_4 (ng/dL)	Mean Postop fT_4 (ng/dL)	p	Mean Preop TSH (mIU/L)	Mean Postop TSH (mIU/L)	p
<7days (26 cases)	1.13	1.08	0.41	5.6	2.78	0.02
7–14 days (2 cases)	1.59	1.33	0.40	4.32	2.2	0.34
14–21 days	–	–		–	–	–
21–28 days (2 cases)	1.35	3.59	0.53	1.03	1.56	0.39

fT_4: Free thyroxine 4; TSH: Thyroid-stimulating hormone.

Table 6: The pre-operative and post-operative fT_4 and TSH levels with respect to anatomical location of operation

Age (n)	Mean Preop fT_4 (ng/dL)	Mean Postop fT_4 (ng/dL)	p	Mean Preop TSH (mIU/L)	Mean Postop TSH (mIU/L)	p
Thorax (8 cases)	1.13	1.06	0.20	4.67	3.61	0.32
Abdomen (18 cases)	1.17	2.2	0.52	5.1	2.99	0.02
Pelvic/genital (7 cases)	1.09	3.38	0.71	5.8	1.08	0.08

fT_4: Free thyroxine 4; TSH: Thyroid-stimulating hormone.

Table 7: The pre-operative and post-operative fT_4 and TSH levels with respect to duration of hospitalization

Duration (n)	Mean Preop fT_4 (ng/dL)	Mean Postop fT_4 (ng/dL)	p	Mean Preop TSH (mIU/L)	Mean Postop TSH (mIU/L)	p
<7 days (4 cases)	1.58	1.19	0.17	12.01	2.28	0.20
7–14 days (2 cases)	0.99	1.02	0.70	1.76	2.25	0.84
14–21 days (5 cases)	1.21	1.05	0.22	3.93	4.7	0.55
>21 days (22 cases)	1.07	1.11	0.83	6.21	2.77	0.01

fT_4: Free thyroxine 4; TSH: Thyroid-stimulating hormone.

The number of patients who underwent thoracic surgery, abdominal surgery and genital surgery was 8, 18, and 7, respectively. The pre-operative and post-operative free T4 levels of patients who underwent thoracic, abdominal and genital surgery were 1.13 ng/dL, 1.06 ng/dL (p=0.20); 1.17 ng/dL, 2.2 ng/dL (p=0.52), and 1.09 ng/dL, 3.37 ng/dL (p=0.71), respectively. The pre-operative and post-operative mean TSH levels of patients who underwent thoracic surgeries were 4.67 mIU/dL and 3.61mIU/dL (p=0.32). The same parameters for patients who underwent abdominal and genital operations were 5.1 mIU/dL, 2.99 mIU/dL (p=0.02); 5.8 mIU/L; and 1.08 mIU/dL (p=0.08), respectively. The difference between mean pre-operative and post-operative TSH levels was found to be statistically significant in the abdominal surgery group and statistically insignificant in the other groups. Results of the preoperative and postoperative thyroid function tests with respect to anatomical location of operations are summarized in Table 6.

The mean duration of hospitalization was 12.6 days and mean number of dressings changed per day during their hospitalization period was one. 4 patients were hospitalized for <7 days, two patients were hospitalized between 7 and 14 days, 5 patients were hospitalized between 14 and 21 days and 22 patients were hospitalized more than 21 days. The preoperative and post-operative mean free T4 levels of patients who were hospitalized for <7 days, between 7 and 14 days, between 14 and 21 days and for more than 21 days were 1.58 ng/dL and 1.19 ng/dL (p=0.17); 0.99 ng/dL and 1.02 ng/dL (p=0.70), 1.21 ng/dL and 1.05 ng/dL (p=0.22); and 1.07 ng/dL and 1.11 ng/dL (p=0.83), respectively. The pre-operative and post-operative free mean TSH levels of patients who were hospitalized for <7 days, between 7 and 14 days, between 14 and 21 days and for more than 21 days were 2.01 mIU /dL and 2.28 mIU/dL (p=0.20); 1.76 mIU/dL and 2.25 mIU/dL (p=0.84); 3.93 mIU/dL and 4.7 mIU/dL (p=0.55); and 6.21 mIU/dL and 2.77 mIU/

dL (p=0.01), respectively. The pre-operative and post-operative TSH changes were statistically significant in the longest-hospitalized group. Results of the pre-operative and post-operative fT_4 and TSH levels with respect to duration of hospitalization are summarized in Table 7.

DISCUSSION

The human body harbors various microorganisms which may be pathogenic given the convenient environment. For this reason, the medical equipment used for a patient should be thoroughly cleaned and appropriately sterilized before usage on another patient. Medical asepsis is the process of destroying pathogenic microorganisms after they leave the human body.[1,2] Surgical asepsis refers to all measures taken to prevent microorganisms from invading the body through open surgical incisions. One of the most commonly used agents for this purpose is Povidone-iodine.[1–3] Povidone iodine is used as a disinfectant and an antiseptic in contaminated wounds and for the antisepsis of skin and mucosal membranes during surgical operations. It is a water soluble complex containing 88–91% Polyvinylpyrrolidone and 9–12% iodine.[4] Its antibacterial activity was proven by *in vitro* tests conducted on rats and the toxicity of the developed complex was found to be significantly lower than that of iodine teinture.[4] The clinical studies conducted on humans have proven the superiority of the povidone-iodine complex over other iodine formulations.[5]

Patients with underlying thyroid dysfunction are more likely to be affected by iodine exposure due to various external sources, namely, Povidone-iodine solutions; however, thyroid dysfunction may be seen in patients with no history of thyroid-related diseases as well. The regulatory mechanisms of the body maintain the euthyroid state and do not solely depend on external ingestion of iodine for proper thyroid function.[6,7] Nevertheless, physiological regulation of various hormones are especially more difficult for surgical neonates due to their catabolic state and post-operative stress, which makes them more susceptible to iodine-induced thyroid dysfunction due to usage of povidone-iodine during and following their surgeries.

Several studies have been conducted on adults on the usage of Povidone-iodine solutions and thyroid functions, as well as prenatal and perinatal exposure to Povidone-iodine and iodine-induced transient neonatal thyroid dysfunction. A 6-weeks-old female infant with transient hypothyroidism after the application of topical iodine to the mother during pregnancy and lactation period was reported, emphasizing the importance of thyroid function monitoring while using these products and in fact, avoiding their usage altogether during pregnancy and lactation due to secretion of iodine into the breast milk.[8] In a study conducted by Yilmaz et al.[9] on 30 preterm and 40 full term newborns and 50 infants, effects of single dose povidone-iodine on thyroid functions and urinary iodine excretion were investigated, after which they reported no significant changes in thyroid functions in any of the groups but significantly elevated urinary iodine excretion in preterm and full-term neonates. While most of the related studies report transient hypothyroidism, iodine-induced hyperthyroidism, while rare, is reported by Nobukuni et al.,[10] who investigated the influence of long term treatment with povidone-iodine on thyroid functions in 40 adults, 27 of which had significantly increased serum levels of inorganic iodine, one of which was diagnosed with mild hyperthyroidism and seven of which were reported to have suspected subclinical hyperthyroidism. Five adult patients with iodine-induced hyperthyroidism due to exposure to commonly used drugs containing povidone-iodine were described in an another study,[11] and state that while iodine-induced hyperthyroidism is more commonly seen in those residing in iodine-deficient areas, it may also be seen in patients with or without underlying thyroid diseases.

In our study, there was no statistically significant difference in terms of thyroid function test results between female and male neonates before the surgery. In the post-operative period, free T4 values mildly increased and TSH levels decreased compared to the preoperative period, indicating iodine-induced hyperthyroidism; however, all values remained within reference values. Unlike the change in free T4, the change in TSH levels between the pre and postoperative periods was statistically significant, but it did not require any of the patients to start thyroid hormone replacement therapy.

The significant difference between the pre and post-operative mean TSH levels in patients with a gestational age of 28–32 weeks and in those who were younger than 7-days-old at the time of their operation may be due to prematurity and/or young age, which lead to increased uptake of Povidone-iodine through their thinner skin layer and poorer hormone regulation. The significant reduction in postoperative TSH levels in patients undergoing abdominal surgery may be due to larger operative areas as compared to other surgeries, demanding higher doses of povidone-iodine solution for asepsis. The significant decrease in mean TSH levels in patients with the longest hospitalization period may be due to prolonged dressing changes and increased use of Povidone-iodine, leading to increased absorption.

The exact amount of iodine exposure was unknown during the surgery or dressings because it was retrospectively study, which made comparisons slightly harder.[2] The few number of patients included in this study was another limitation. Furthermore, the change in laboratory settings due to the hospital's construction works within the time frame of this study may have caused imperfections in standardization of thyroid function tests. Further prospective studies should be conducted to get a clearer understanding of underlying mechanisms for this phenomenon and caution should be exerted when using iodine containing antiseptic solutions on neonates. In addition, further studies conducted in a more controlled environment and with more patients may make it possible to set a limit for the usage of such a common antiseptic solution as Povidone-iodine, as thyroid dysfunction may cause delayed wound healing, which may be more accentuated in neonates.

CONCLUSION

The use of topical Povidone-iodine causes changes in thyroid functions of surgical neonates in this study. Iodine absorption during preoperative and postoperative periods was seen to significantly affect thyroid functions by causing transient hyperthyroidism. However, these changes in thyroid functions did not require thyroid hormone replacement therapy in any of them.

Statement

Ethics Committee Approval: The Zeynep Kamil Maternity and Children's Diseases Training and Research Center, Clinical Research Ethics Committee granted approval for this study (date: 24.11.2017, number: 2017/157).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – AC, SMT; Design – AC, SMT, BA; Supervision – AC; Resource – SMT, BA, TE; Materials – SMT, BA, TE; Data Collection and/or Processing – SMT, BA, TE; Analysis and/or Interpretation – SMT, BA, TE, AC; Literature Search – SMT, BA, TE; Writing – SMT, BA, TE; Critical Reviews – AC.

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