

Urinary iodine excretion after using povidone iodine or chlorhexidine gluconate for topical disinfectant in patients undergoing thyroidectomy due to thyroid carcinoma: When to do radio active iodine therapy?

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Background: Povidone Iodine (PI) is the most frequent antiseptic used as a topical disinfectant in surgery. It has been reported high transcutaneous iodine absorption due to topical PI usage, but there is a lack of data in periods of excess iodine depletion. **Materials and Methods:** This is a cross-sectional study designed to assess serial urinary iodine concentration (UIC) after topical administration of PI to evaluate the transcutaneous iodine absorption and the proper iodine depletion time for safe administration of Radio Active Iodine (RAI) therapy as ablative or adjuvant therapy. **Results:** Thirty-seven patients with papillary thyroid carcinoma undergoing total thyroidectomy were assigned to the PI group ($n = 20$) or chlorhexidine gluconate (CHG) group ($n = 17$). In the PI group, the UIC levels rose to a maximum of 2 times in the 4th week after administration and returned to pre-operative levels in the 8th week after. In the CHG group, there was a decrease in UIC levels due to a low iodine diet (LID) with a significant P-value of 0.001, <0.001, and 0.001 in the 2nd, 4th, and 8th weeks follow up respectively compared to the PI group. The urinary excretion of excess iodine lasts about 8 weeks after total thyroidectomy until iodine levels turn back to pre-operative values. **Conclusion:** If the thyroidectomy was prepared with PI, RAI is better to be performed 6-8 weeks after surgery rather than the standard prescription of 4 weeks.

Key words: Chlorhexidine, povidone-iodine, radioactive iodine therapy, thyroid cancer, thyroidectomy

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INTRODUCTION

Povidone-iodine (PI) is the most frequent antiseptic used as a safe and effective topical disinfectant in various fields of surgery.^[1,2] It has been reported transcutaneous iodine absorption in some instances. In infants and burned skin patients, iodine absorption was reported due to thin and permeable skin.^[3-6] Lately, in 2005, Tomoda *et al.* reported transcutaneous iodine absorption in adults undergoing surgery who were disinfected with PI.^[7]

Furthermore, a substantial elevation of urinary iodine is found after pleural lavage, vaginal mucosal, and oral mucosal preparation with PI.^[8-10] Mentioned evidence has been published to support iodine absorption after PI usage, although a safe antiseptic in clinical practice. However, there is a lack of data supporting long-term urinary iodine excretion in the patients with thyroid cancers undergoing thyroidectomy. Since urinary iodine excretion (UIC) must be 150 µg/L before radioactive iodine (RAI) administration, further RAI therapy may be

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delayed in time in these patients.^[11-13] Finally, this study was designed to assess UIC weeks after topical administration of PI to evaluate the proper iodine depletion time to start radioactive iodine therapy (RAIT).

MATERIALS AND METHODS

Study design & setting

This is a cross-sectional study of 42 patients with thyroid cancers undergoing total thyroidectomy that were candidates for further RAI from March to December 2017. This study was carried out in an academic hospital of Isfahan University of Medical Sciences with 37 patients enrolled in the final analysis. The research protocol has followed the tenets of the Declaration of Helsinki and was approved by the regional ethics committee of Isfahan University of medical sciences (IR.MUI.REC.1396.3.202).

Participants

Patients were eligible for our study according to the followings: Age more than 18 years old; definite thyroid cancer but not metastatic; neither pregnant nor breastfeeding; have no renal, pulmonary, or cardiac insufficiency; no history of iodine-containing medications e.g. amiodarone, levothyroxine, etc.; capable of adhering to a low iodine diet. All patients signed written informed consent before they were recruited.

They were assigned into two groups by block randomization. We used Povidone Iodine 10%, Kaveh Co., Saveh, Iran in the PI group, and Chlorhexidine Gluconate (CHG) 20% solution, Fengchen Group, China in the CHG group. On the admission date, demographic characteristics, venous blood, and spot morning urine samples were achieved. All patients were kept on an iodine-restricted diet (i.e. iodized salt, radiologic dye, egg, seafood, soy, etc.^[14]

Technical

After the patients were intubated by general anesthesia in the operating room, preparation was done by PI or chlorhexidine gluconate. Sterilization was done in the usual fashion (apply from chin to nipples with a single topical application). There was no other contact with PI before or

after the operation during the study. All thyroid surgeries in this study were performed by the same surgeon. Then, 2, 4, and 8 weeks after thyroidectomy, morning urinary samples were collected since UIC in morning single specimens reflects dairy UIC.^[15]

Statistical

Statistical analysis was performed using the SPSS statistical software (version 18.0; SPSS, Chicago, IL, USA). Descriptive data were presented as mean, standard deviation (SD), confidence interval, and numbers (%). To compare the studied variables, *t*-test, paired sample test, and repeated measures analysis were used. The Kolmogorov–Smirnov normality test was used to examine if variables are normally distributed. Missing data (five patients) due to unavoidable causes were managed by intention-to-treat analysis (ITT). ITT analysis includes every patient who is randomized according to randomized treatment assignment. In this study, ITT included all patients who received at least one time of the study intervention (regardless of what happened to the patient after the initial visit). *P* < 0.05 was considered statistically significant.

RESULTS

Total thyroidectomy was performed in 42 patients with thyroid cancer between March 2017 and December 2017 in our center. Through all, 37 were eligible for recruiting study. Demographic characteristics were taken. Twenty and seventeen patients were assigned to groups PI and CHG, respectively. Thirty patients (81.1%) were females. The age of patients ranged from 22 to 54 years. There was no significant difference between these features between the two groups, as illustrated in Table 1.

Sterilization was done with a volume of 13 ± 1.5 cc (mean \pm SD) of each antiseptic. The mean time of surgery was 57.6 ± 9.7 (mean \pm SD) minutes.

Serial changes of individual UIC ($\mu\text{g}/\text{mg}$ of creatinine) from the admission date through the 8th week after thyroidectomy in Groups PI and CHG are shown in Figure 1. In the PI group, the mean \pm SD of UIC on the preoperative day

Table 1: The clinical and biochemical characteristics of the patients

Variables	Povidone Iodine Group (n=20)	Chlorhexidine Gluconate group (n=17)	P
Number (F:M)	20 (16: 4)	17 (14:3)	0.855
Age (year)	36.5 \pm 9.6	36.6 \pm 9.1	0.990
Cr (mg/dl)	0.83 \pm 0.13	0.78 \pm 0.14	0.363
Duration of surgery (minutes)	57.7 \pm 9.7	57.6 \pm 9.6	0.997
Pre-operative UI ($\mu\text{g}/\text{L}$)	149.3 \pm 74.7	176.9 \pm 116.6	0.390
2 weeks after thyroidectomy UI ($\mu\text{g}/\text{L}$)	271.4 \pm 106.7	146.9 \pm 88.1	0.001
4 weeks after thyroidectomy UI ($\mu\text{g}/\text{L}$)	347.7 \pm 105.9	127.6 \pm 79.4	<0.001
8 weeks after thyroidectomy UI ($\mu\text{g}/\text{L}$)	181.0 \pm 66.7	77.9 \pm 56.1	0.001

Data are expressed as numbers or mean \pm standard deviation. F: Females; M: Males; UI: Urine iodine

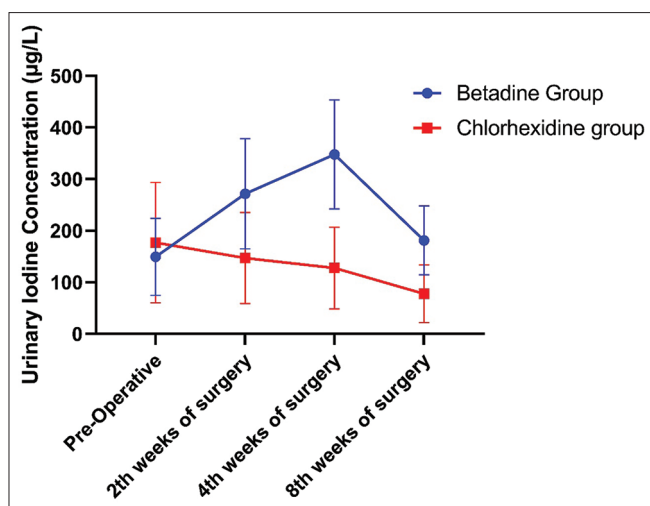


Figure 1: Comparisons between PI and CHG groups in four-time points. The differences between the four-time points were significant within the betadine group, however, the differences between time points within the CHG group were not significant

is 149.3 ± 74.7 with no significant differences compared with another group (P -value = 0.390). As it is shown in Figure 1, the urinary iodine levels rose nearly two times in the 4th week after the operation. The average level of urine iodine excretion in Group CHG at the admission date is 176.9 ± 116.6 (mean \pm SD), and there is no increase in UIC levels in the CHG group. The decreasing average of UIC in group CHG indicates the use of a low-iodine diet.

Table 1 shows the exact values of UIC (mean \pm SD) between the two groups. The PI group UICs are significantly higher than the CHG group except in preoperation time. These findings show iodine transcutaneous absorption due to PI application which continues for about 8 weeks to deplete and return to preoperative values. Repeated measurement analysis revealed that the difference between the UIC of the two groups was statistically significant adjusted by pre-operative UIC values ($F = 29.329$, P -value < 0.001) and by pre-operative UIC, age, Cr level, duration of surgery ($F = 31.641$, P -value < 0.001).

DISCUSSION

The most important findings in this study are: (1) notable transcutaneous absorption of iodine after PI application comparing chlorhexidine (an iodine-free antiseptic) preparation and (2) the urinary excretion of excess iodine lasts about 8 weeks after total thyroidectomy until iodine depletion.

In our study, patients have undergone total thyroidectomy and the metabolism of absorbed iodine may be altered. All patients were candidates for further RAI and low-iodine diets. We expected a decrease in UIC as is shown in group CHG. In the PI group, the serial changes of UIC

projects marked transcutaneous absorption of Iodine. Previous studies have shown iodine absorption in damaged (e.g., burned), permeable skin (i.e., infants), or through other sites (e.g., in mediastinal douching, vaginal douching, gargling, ophthalmic preparation, and oral mucosal preparation) after PI application.^[3-10,16]

The second major finding is the period that took for UIC to return to pre-operational levels. Noteworthy is the fact that UIC must be confirmed to be >150 $\mu\text{g/L}$ before RAI. In our study, we evaluated the spot urinary iodine excretion as an indicator of 24 h-urinary iodine excretion which has been confirmed by Zöller *et al.*^[17] As it has been shown in the figures above, the mean progression of iodine level in Group CHG is decreasing. This downturn in iodine levels reveals low iodine diet was kept for patients. In PI patients, we observed a 2-time rise in UIC levels in the 4th week after PI exposure and then a downtrend to reach normal values. In a similar study reported by Tomoda *et al.*, transcutaneous iodine absorption was shown after PI application.^[7] They showed UIC levels at the most on the 1st day after the operation and normalized after 5 days. This discrepancy is maybe due to high-iodine diets in Japan, whereas iodine deficiency is more frequent in Iran which coerces further studies.

The absorbed iodine in PI group reduces the efficacy of RAI in these patients. Nimmons *et al.* showed a median of 43 days for urinary iodine level to normalize after intravenous contrast computed tomography scan with 75% of patients returning to baseline within 60 days and 90% of their patients within 75 days.^[18] This interference with adjuvant RAIT in patients with thyroid cancer shows the importance of minimum interval days between iodine-containing exposure and RAI therapy.

CONCLUSION

Although further studies are crucial, it seems that the main recommendation to receive RAI about 4 weeks after surgery in patients who have been performed thyroidectomy, while preparation was done with PI, should be postponed to 6–8 weeks after, to prevent inactivation of RAI uptake.

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Conflicts of interest

There are no conflicts of interest.

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