THE EFFECT OF INSURE METHOD IN THE TREATMENT OF RESPIRATORY DISTRESS SYNDROME IN PRETERM INFANTS

Nguyen Tien Dung[1], Hoang Thi Nhung[1], Nguyen Thi Quynh Nga[2]

1. Pediatric Department, Bach Mai Hospital,

2. Pediatric course, Hanoi Medical University

ABSTRACT

Background: *The INtubation-SURfactant-Extubation (INSURE) is a method that is often used to treat the respiratory distress syndrome in preterm infants.* ***Objectives:*** *To evaluate the effect of INSURE method in the treatment of respiratory distress syndrome in preterm infants.* ***Patients and Methods:*** *The INSURE method is indicated for newborns with gestational age of 28-36 weeks with respiratory distress syndrome immediately or a few hours after birth on clinical manifestations, X ray, and need nCPAP with $FiO_2 \geq 30\%$ to maintain SpO_2 from 88-90%.* ***Results:*** *During the period from Jan 2014 to October 2016, we studied 30 preterm infants with respiratory distress syndrome that received INSURE method in pediatric department of Bach Mai Hospital, Hanoi, Vietnam. Of those, there were 7/30 (23.3%) newborns with gestational age of 28-30 weeks and 16/30 (53.6%) newborns with gestational age of 30-32 weeks. The average birth weight is: 1103.3 ± 196 g (900g-1700g). There were 23.3% pregnancies with diabetes mellitus and there were 46.6% pregnancies injected with antenatal corticosteroids. Chest Xray imaging showed that there were 46.7% hyaline membrane disease of stage II, 33.3% of stage III, and 20% of stage IV. Thirty (100%) preterm infants were used surfactant with dose of 100mg/kg in the first time and no one were used surfactant the second time or more. There were 46.7% preterm infants using INSURE method within the first 6 hours of age and there were only 10.3% preterm infants using this method after 12 hours of age. Seventeen (56.7%) infants were successfully treated with the INSURE method. Clinical signs, chest X ray and blood gas analysis were markedly improved after 6 to 48 hours of using INSURE method. There were 3 (10%) infants with hemorrhagic pulmonary complications, 1 (3.3%) with pneumothorax and no one with bronchopulmonary dysplasia. Predicting factors of INSURE failure is very low birth weight and gestation, severe respiratory distress and hyaline membrane disease of stage II, IV.* ***Conclusions:*** *The INSURE method is well applied to the preterm infants with a particularly high percentage of success in the group of infants aged 30 weeks, weighing 1000g or more, the Silverman score below 5 points and hyaline membrane disease of stage II.*

Received: October 20th, 2020
Accepted: November 25th, 2020
Corresponding author: Nguyen Tien Dung
Address: Pediatric Department, Bach Mai Hospital

1. INTRODUCTION

The respiratory distress syndrome (RDS), also known as Hyaline membrane disease (HMD), is one of the most common causes of premature infants due to lack of surfactant, a substance which plays a role in reducing alveolar surface tension to prevent atelectasis [3].

Treatment with surfactant followed by intrusive ventilation offered positive results, but there were also complications of lung damage associated with mechanical ventilation and an increased incidence of bronchopulmonary dysplasia. [3].

Recently, there are many studies in the world on the use of the INSURE (INtubation-SURfactant-Extubation) method with or without nCPAP (nasalContinuous Positive Airway Pressure) which significantly reduces the rate of children requiring invasive ventilation, reducing the risk of lung damage and bronchopulmonary dysplasia [3]; 10]. However, in Vietnam, there are very few studies on this method, especially finding out what risk factors make this method unsuccessful [1]; [2]. Therefore, this study was carried out with the goal: To evaluate the treatment effects and failure risks of the INSURE method in the treatment of respiratory distress syndrome (RDS) in preterm infants.

2. SUBJECTS AND METHODS

The study was conducted from January 2014 to October 2016 at the Pediatric Department of Bach Mai Hospital.

2.1. Criteria for selecting patients

Including the newborns with gestational age of 28-30 weeks based on last menstrual period or New Ballard Score for gestational age assessment. Diagnosis of endothelial disease was based on following criteria:

- Acute respiratory failure occurred immediately or a few hours after giving birth with a score of Sivermam> 3 points and need to breathe oxygen with a concentration of FiO_2>30% to maintain SpO_2> 89%.

- Acute respiratory distress syndrome occurred immediately or a few hours after birth with a score of Sivermam> 3 and need nCPAP with FiO_2≥30% to maintain SpO_2 > 89%.

- Xray of the lung: endothelial disease from grade II or higher.

2.2. Exclusion criteria

- The newborns must be placed a ventilator or ventilation bag from the time they started hospitalization.

- The newborns have severe birth defects.

2.3. INSURE method

- Insert intubation and surfactant administration via endotracheal tube (ET).

- Remove endotracheal tube when patient's condition is stable, SpO2> 90%.

- Follow up the patients clinically and subclinically after 6 hours, 24 hours, 48 hours.

- Criteria for success: The newborns maintained CPAP breathing with FiO_2<60%, PEEP <5cmH_2O and SpO_2> 90% after surfactant administration until CPAP withdrawal and did not use the ventilator within 48 hours later.

3. RESULTS

From January 2014 to October 2016, we had 30 premature infants with the acute respiratory distress syndrome treated with INSURE, including 15 males. There were 07 (23.3%) newborns with gestational age of 28-30 weeks, 16 (53.6%) newborns with gestational age of 30-32 weeks. Their average birth weight was 1103.3 ± 196g (900g -1700g). Most 28 newborns had an Apgar score of less than 6 minutes in the first minute; of those, 33.3% had a score of 0-3 only and 80% had an Apgar score of 4-6 at the 5th minute. There were 13 (43.3%) Caesarean cases.

Almost 25 (83.3%) mothers suffered from the diseases, of which 11 mothers suffered

from preeclampsia, 7 mothers suffered from diabetes, 3 mothers suffered from kidney failure, 2 mothers suffered from lupus, 1 mother suffered from heart disease and 1 mother suffered from sepsis. 14 (46.7%) mothers received antenatal cortioid prophylaxis with the last injection before giving birth> 24 hours. There were 14/30 (46.7%), 12 (40%) and 4/30 (13.3%) newborns were administered the surfactant before 6 hours; within 6-12 hours and after 12 hours after the delivery.

After insertion of endotracheal tube and surfactant administration, 24/30 (80%) newborns were withdrawn the tube and breathed nCPAP. There were 6/30 (20%) newborns were not withdrawn the tube and they continued to be ventilated. Of the 24 newborns who were withdrawn the endotracheal tube and continued to follow up after 24 hours, there were 4 newborns to be re-inserted the endotracheal tube for mechanical ventilation and after 48 hours there were 3 to be re-inserted the endotracheal tube; so, a total of 7/24 cases were re-inserted the endotracheal tube for mechanical ventilation. Thus, the success rate of the INSURE method was 17/30 (56.7%).

Pediatric progression during INSURE method

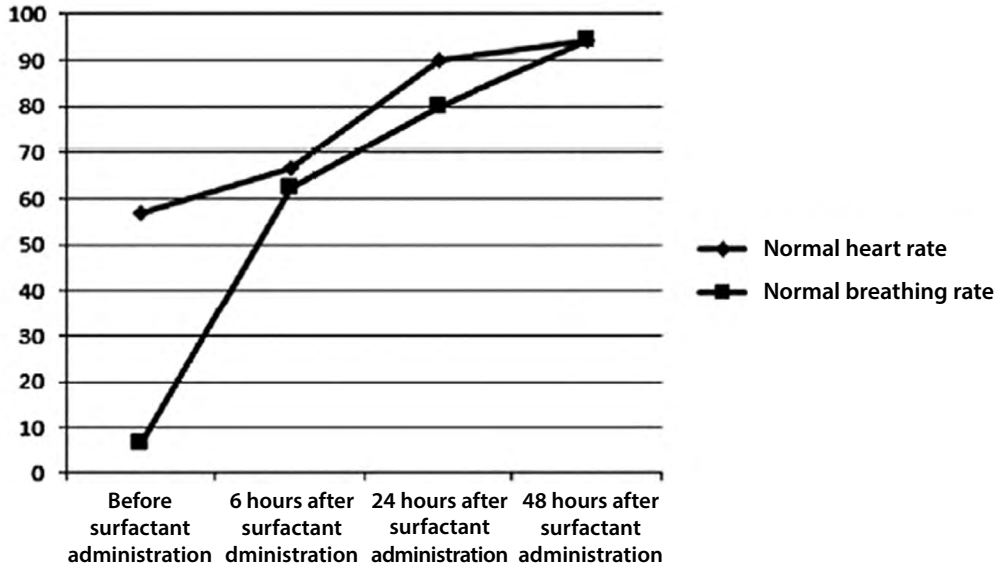

Figure 1. Change in heart rate and breathing rate to normal rate before and after surfactant administration

The curve in figure 1 shows that before the surfactant administration, only 2/30 (6.7%) newborns had normal breathing rate. This rate increased to 62.5% at 6 hours, 80% at 24 hours and 94.1% after 48 hours of surfactant administration. Likewise, the rates over time to return to normal heart rate were 56.7%; 66.7%; 90% and 94.1% respectively (Figure 1).

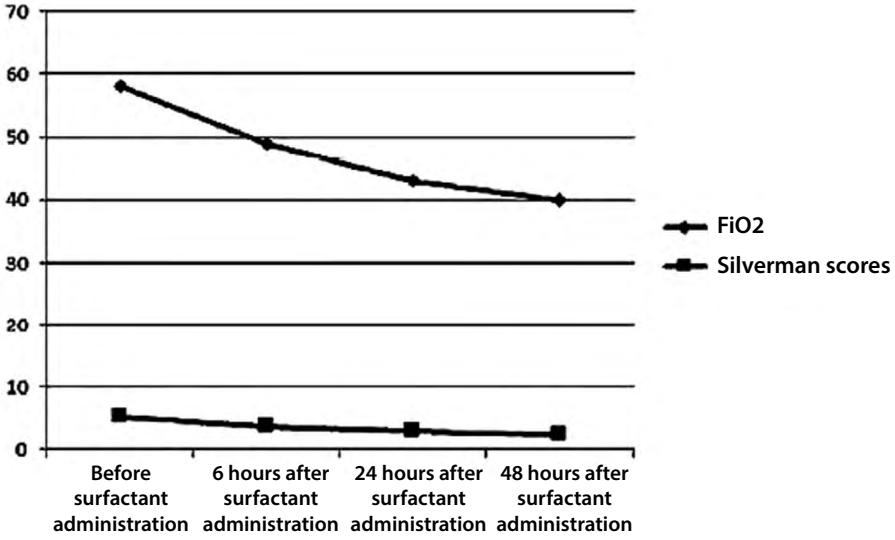

Figure 2. Change in FiO_2 and Silverman score before and after surfactant administration

The need for oxygen intake decreased gradually over time; before the surfactant administration, the newborns needed to breathe with the average FiO2 of 58% then gradually decreased to 49% after 6 hours, 43% after 24 hours, and after 48 hours, the newborns only needed to breathe with the average FiO2 of 40%. The Silverman index decreased 6 hours after surfactant administration, and after 48 hours, it dropped to the average of 2.37 score (Figure 2).

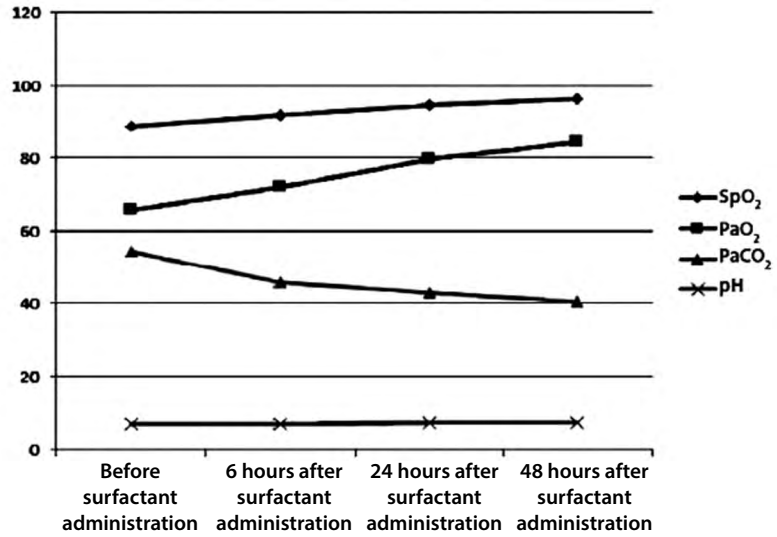

Figure 3. Change in SpO_2, PaO_2, $PaCO_2$ and pH before and after surfactant administration

The SpO_2 and PaO_2 indexes increased significantly after 24 hours of treatment especially after 48 hours, the average pH before INSURE was 7.29 ± 0.07, after 6 hours of surfactant administration, the pH was improved very quickly to 7.36 ± 0.05 while the $PaCO_2$ decreased gradually after the surfactant administration (Figure 3).

Table 1. Change in Xray grades before and after INSURE treatment

Chest Xray	Before treatment	After 6 hours	After 24 hours (1)	After 48 hours (2)
Normal	**0**	**0**	**7(35)**	**15(88,2)**
Grade I	0	10 (41,7)	10(50)	2 (11,8)
Grade II	14 (46,7)	12 (50)	3 (15)	0
Grade III	10 (33,3)	2 (8,3)	0	0
Grade IV	6 (20)	0	0	0
P		<0,01*	<0,01*	<0,01*

(1) After 24 hours, 2 patients used the Xray machine, (2) After 48 hours, 3 patients used the Xray machine

According to Table 1, before the treatment, on straight line chest radiograph, all 30 (100%) patients had an RSD of grade II or higher, of which 6/30 (20%) were lesions at grade 4. After 6 hours of treatment. there were no patients with grade 4 lung lesions and 10 patients returned to grade 1. After 24 hours of treatment, there were no patients at grade 3 and 7 patients with pneumothorax returned to normal. After 48 hours of treatment, 15 patients with the chest Xray results returned to normal condition.

Table 2. Risk factors for failure of the INSURE method

Risk factors		Successful group n = 17	Failed group n=13	OR (95%CI); P
Diabetic mother	Yes	14	9	2,07 (0,37-11,5)
	No	3	4	P=0,407
Mother with antenatal corticosteroid administration	Yes	14	5	5,6 (1,15 - 27,07)
	No	4	8	P=0,029
Method of delivery	Cesarean section	8	5	1,42 (0,32 - 6,17)
	Vaginal delivery	9	8	P=0,643
Gestational age	> 30 weeks	16	5	22,4 (1,86-107,06)
	<30 weeks	1	7	P=0,002
Apgar in the first minute	7-10 scores	2	0	-
	0-6 scores	15	13	P=0,208
Apgar in the 5th minute	7-10	10	0	-
	0-6	7	13	P=0,000
Birth weight	>1000g	16	4	36 (3,47 - 373,1)
	<1000g	1	9	P=0,000
Silverman score	3-5 scores	8	1	10,6 (1,12-101,3)
	>5 scores	9	12	P=0,021
Heart rate (times / minute)	100-160	16	1	192 (10,87-3390,1)
	<100 or >160	1	12	P=0,000
SpO_2(%)	> 90%	17	4	38,25 (3,70-395,3)
	< 90%	1	9	P=0,000
BMT grading on x-ray	Grade I-II	13	1	39 (3,80-399,8)
	Grade III-IV	4	12	P=0,000
Surfactant administration time (hours)	< 6 hours	2	1	1,6 (0,129-19,83)
	> 6 hours	15	12	P=0,717

The results in Table 2 show that the risk factors for failure of the INSURE method include: mother had no antenatal corticosteroid administration (OR = 5.6 (1.15 - 27.07); P = 0.029); gestational age less than 30 weeks (OR = 22.4 (1.86-107.06); P = 0.002); Apgar at the 5th minute below 7 (P=0.000); birth weight less than 1000g (OR = 36 (3.47 - 373.1); P = 0.000); Silverman score> 5 (OR = 10.6 (1.12-101.3); P = 0.021); heart rate <100 or> 160 beats/ minute (OR = 10.6 (1.12-101.3); P=0.021); SpO2 <90% (OR = 38.25 (3,70-395,3); P=0,000); Xray with membrane of grade III-IV (OR = 39 (3.80-399.8); P = 0.000).

Three children had complications; of those, 2/30 (6.7%) had pulmonary hemorrhage and 1/30 (3.3%) had pneumothorax.

4. DISCUSSION

4.1. For the gestational age and birth weight

The average gestational age of patients in our study was 30.9 ± 1.83 (28-35) weeks, similar to other studies. Study by Pham Nguyen To Nhu et al [2] showed that the average gestational age was 30.6 ± 2.6 weeks. According to other studies in the world also using the INSURE method, the gestational age of newborns was mainly 30-32 weeks. The study results of Dani C et al showed that the newborns with 30-32 weeks gestation accounted for 34% [6].

The average birth weight of the newborns in our study was 1103 ± 196.1 (900 -1700g). The study of Cherif A et al showed that more than half of the pediatric patients weighed from 1000 to 1500g (57.1%) [5], similar to the study of Ngo Xuan Minh; weighing from 1000-1500g accounted for the highest rate of 56.6% [1].

4.2. Medical state of the mothers during pregnancy

In our study, 11/30 (36.7%), 7/30 (23.3%), 2/30 (6,7%), 2/30 (6,7%), 1/30 (3,3%) and 1/30 (3,3%) of newborns whose mothers suffered from the preeclampsia, diabetes, kidney failure, lupus, heart disease and infected bacteremia, respectively. The rate of mothers with the diseases was very high compared to other studies and this is also a characteristic of the Department of Obstetrics of Bach Mai Hospital, which many obstetric cases have been treated.

Meanwhile, according to Pham Nguyen To Nhu, in 30 studied newborns, there was no newborn whose mother suffered from the diabetes [2], while according to Cherif A et al, only 3.8-4.5% of newborns whose mother suffered from the diabetes. [5]. This rate is lower than our study.

4.3. Mothers in the prevention of the respiratory distress syndrome (RDS) with antenatal administration of betamethasone

There is evidence that intramuscular injection of 2 doses of betamethasone 12mg 12 hours apart to the mothers reduces the severity of RDS, complications of cerebral hemorrhage, ductus arteriosus, pneumothorax and necrotizing enterocolitis in preterm infants. In our study, 14/30 (46.7%) of mothers received the antenatal corticosteroid administration. This rate is lower than 70% of study of Pham Nguyen To and 50% -53.8% [2], [5] study of Cherif A et al.

4.4. Treatment results and risk factors for failure of the INSURE technique

Studies have shown that the INSURE method has many advantages: reducing the need for and the time of mechanical ventilation, reducing the time of oxygen therapy and incidence of chronic lung disease, and reducing complications such as emphysema and cerebral hemorrhage and death [7], [8], [9], 12]. Our treatment success rate is 56.7% which is lower than that of some other studies of Naseh A et al [11] which has a success rate of 74% and that of Jun Miyahara et al [10] which has a failure rate of 2/15 (13.3%) and that of Cherif A et al [5] which has failure rate of 32.1%.

In our study, the factors related to INSURE failure were the mothers' failure to receive the antenatal corticosteroid administration, the 5th

minute Apgar <7 scores, birth weight <1000g, Silverman score> 5, heart rate < 100 or> 160 times/ minute, SpO_2 <90% and chest Xray with hyaline membrane from grade 3 or higher. Cherif A et al. studied on 109 newborns and showed that the risk factors related to failure of INSURE were $PaCO_2$ a/ APO_2 and disease severity on radiograph [5]. Brix N et al. studied on 322 newborns and showed that the risk factors for INSURE failure were low gestational age, the 5th minute Apgar <7 scores, Hb <8.5mmol / L, oxygen demand> 50%, pCO_2> 53mmHg, pH <7.3 and lactate> 2.5mmol / L [4]. The study of Koh JW et al on 84 children only found that the a/ APO_2 ratio in the failed group was statistically significantly smaller than the successful group, the ratio was 0.45 ± 0.19 compared to 0.28 ± 0.13 (p = 0.001) [8]. According to Dani C (2012), the prognostic factors for failure of INSURE are weight <750g, gestational age <30 weeks and arterial blood gas of pO_2 / FiO_2 <218 and a / APO_2 <0.44 [6].

A recent study by Awaysheh F et al [3] on 63 newborns showed that the risks for failure of INSURE method were gestational age <28 weeks, weight <1000g, mothers not receiving antenatal corticosteroid administration, Hb <14mg /dl, the 5th minute Apgar <7 scores and umbilical cord blood pH<7.2. Although each study had its own risks for failure, they were generally similar to our study.

4.5. Complications of the INSURE method

Our study experienced 1 (3.3%) patient with the pneumothorax complication, 2 (6.7%) patients with pulmonary hemorrhagic complications. The rates of these complications are similar to other studies. Nguyen Pham To Nhu experienced 3.3% patients with the pulmonary hemorrhage and pneumothorax complications [2]. A Cherif A et al experienced patients with 5.7% of pulmonary hemorrhage, 1.4% patients with pneumothorax complications [11a]. Dani C commented that the group with INSURE treatment had a lower complication rate than the group with mechanical ventilation [6].

5. CONCLUSIONS

- INSURE is a good treatment for preterm infants with a success rate of 56.7%, and a low complication rate where the pneumothorax is 3.3% and pulmonary hemorrhage is 6.7% and there is no chronic lung disease complication.

- The risk factors for failure of the INSURE method are mothers not receiving the antenatal corticosteroid administration, the 5th minute Apgar <7 scores, birth weight < 1000g, Silverman score > 5 scores, heart rate <100 or above 160 times/ minute, SpO_2 <90% and chest Xray with hyaline membrane from grade 3 or higher.

REFERENCES

1. Ngo Xuan Minh. Hiệu quả của kỹ thuật INSURE trong điều trị suy hô hấp ở trẻ đẻ non. Y học thành phố Hồ chí Minh. Ho Chi Minh City Medicine, Volume 8, 2007; pp.151-161.

2. Pham Nguyen To Nhu. Mô tả kết quả điều trị bệnh màng trong ở trẻ sinh non bằng surfactant qua kỹ thuật INSURE. Ho Chi Minh City Medicine, Volume 14, 2010, pp. 155-161.

3. Awaysheh F, Alhmaiedeen N, Al-Ghananim R, Bsharat A, Al-Hasan M. Criteria for Using INSURE in Management of Premature Babies With Respiratory Distress Syndrome. Med Arch, 73 (4), 240-243 Aug 2019.

4. Brix N, Sellmer A, Jensen MS, Pedersen LV, Henriksen TB. Predictors for an unsuccessful INtubation-SURfactant-Extubation procedure: a cohort study. BMC Pediatr. 2014 Jun 19;14:155.

5. Cherif A, Hachani C, Khrouf N. Risk Factors of the Failure of Surfactant Treatment by Transient Intubation During Nasal Continuous Positive Airway Pressure in Preterm Infants. Am J Perinatol, 25 (10), Nov 2008: 647-52.

6. Dani C, Corsini I, Poggi C. Risk factors for intubation - surfactant - extubation (INSURE) failure and multiple INSURE strategy in preterm infants. Early Hum Dev. 2012 Mar;88 Suppl 1: S3-4.

7. Kirsten GF, Kirsten CL, Henning PA, Smith J, Holgate SL, Bekker A, Kali GT, Harvey J. The outcome of ELBW infants treated with NCPAP and InSurE in a resource-limited institution. Pediatrics. 2012 Apr;129(4): e952-9.

8. Koh JW, Kim JW, Chang YP. Transient intubation for surfactant administration in the treatment of respiratory distress syndrome in extremely premature infants. Korean J Pediatr. 2018 Oct;61(10):315-321.

9. 6.a Leone F, Trevisanuto D, Cavallin F, Parotto M, Zanardo V. Efficacy of INSURE During Nasal CPAP in Preterm Infants With Respiratory Distress Syndrome. Minerva Pediatr, 65 (2), Apr 2013: 187-92.

10. Miyahara J, Sugiura H, Ohki S. The evaluation of the efficacy and safety of non-invasive neurally adjusted ventilatory assist in combination with INtubation-SURfactant - Extubation technique for infants at 28 to 33 weeks of gestation with respiratory distress syndrome. SAGE Open Med. 2019 Mar 15;7:2050312119838417.

11. Naseh A, Yekta BG. INSURE method (INtubation - SURfactant-Extubation) in early and late premature neonates with respiratory distress: factors affecting the outcome and survival rate. Turk J Pediatr. 2014 May-Jun; 56(3): 232-7.

12. Nayeri FS, Shirvani TS, Aminnezhad M, Amini E, Dalili H, Bijani FM. Comparison of INSURE Method With Conventional Mechanical Ventilation After Surfactant Administration in Preterm Infants With Respiratory Distress Syndrome: Therapeutic Challenge. Acta Med Iran; 52 (8), 596-600; 2014.