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ORIGINAL ARTICLE

Post-tooth extraction sepsis without locoregional infection – a population-based study in Taiwan

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OBJECTIVE: To investigate the incidence and risk factors of post-tooth extraction sepsis in patients without locoregional infection.

SUBJECTS AND METHODS: We assessed all claim records of the Taiwanese National Health Insurance program in 2005. Admissions for patients aged ≥16 years containing a discharge diagnosis of sepsis, and who received tooth extraction within 14 days before the admission were identified. Patient charts were reviewed to confirm the diagnosis of sepsis and rule out other infection sources. The relationship between postextraction sepsis (PES) and clinical parameters was analyzed.

RESULTS: Thirty-three of the 2 223 971 extraction cases met the criteria of PES, an incidence of 1.48 per 100 000, and seven patients (21.2%) died of the disease. Aging significantly increased the risk of PES ($P < 0.001$). Preexisting comorbidities were found in 20 of the 33 cases, with diabetes mellitus and hematologic diseases the most common. The method, number, and position of extraction had no influence on PES incidence. Blood cultures were positive in 25 patients (75.8%) and isolates included species of the *Streptococcus, Actinomyces, Klebsiella, Bacteroides, Prevotella,* and *Enterococcus* genera.

CONCLUSION: Tooth extraction is associated with a low but significant risk of postoperative sepsis, especially in the elderly and patients with underlying diseases.

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Keywords: tooth extraction; sepsis; odontogenic bacteremia

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Introduction

Sepsis is a complex syndrome that occurs as a result of the systemic manifestation of infection. Pulmonary, gastrointestinal, genitourinary, and primary bloodstream infections account for the majority of infectious sources in septic patients (Bochud *et al*, 2001). As sepsis progresses, organ system dysfunction becomes apparent (severe sepsis) with the final development of fluid refractory cardiovascular dysfunction (septic shock). Despite recent breakthrough, the mortality for sepsis syndrome remains high, ranging from 10% to 15% for sepsis, 17–20% for severe sepsis, and 43–54% for septic shock (Dellinger *et al*, 2004; Marik and Lipman, 2007).

Tooth extraction is a common surgery performed in the oral cavity and generally regarded as a safe procedure. However, locoregional infections occasionally occur following tooth extraction. In most cases, the infections are secondary to contiguous spread of bacteria from the extraction sites. On the other hand, it is well known that tooth extraction *per se* frequently results in bacteremia (Coulter *et al*, 1990; Heimdahl *et al*, 1990; Okabe *et al*, 1995; Roberts *et al*, 1998; Takai *et al*, 2005; Tomas *et al*, 2007, 2008). Although bacteremia from tooth extraction is usually transient in nature, the risks that the microorganisms entering the bloodstream may multiply and cause systemic and distant infections in susceptible hosts still exist. Bacterial endocarditis is a well-known complication of such odontogenic bacteremias and has been a matter of great concern for many decades (Lockhart and Durack, 1999; Rautemaa *et al*, 2007; Wilson *et al*, 2007). Yet there are a number of other organs and body sites that may be affected by focal bacteremic spread associated with tooth extraction (Lockhart and Durack, 1999; Rautemaa *et al*, 2007). Although there are reports implicating tooth extraction as a causal factor for sepsis (Pedersen *et al*, 1993; Ngapeth-Etoundi *et al*, 2001), there are no published data determining the incidence rate of sepsis

associated with tooth extraction in patients without obvious locoregional infection. This may be because of the rarity of cases and the difficulties in establishing a temporal relation between tooth extraction and sepsis since patients may not report their history of dental treatment to the infection treatment team.

In this study, we assessed the incidence of post-tooth extraction sepsis without locoregional infection on the basis of a retrospective population-based survey in Taiwan. Clinical factors associated with the occurrence of postextraction sepsis (PES) were analyzed.

Subjects and methods

Study population and data source

The National Health Insurance Research Database (NHIRD) of Taiwan is a population-based database, which contains comprehensive claim records of the National Health Insurance (NHI) program in Taiwan, and is opened for academic research by the Bureau of National Health Insurance (BNHI). Because of the high coverage rate of the NHI program in Taiwan (97.9% by 2005) and the island was densely populated (23 million in 2005), the NHIRD might be one of the largest health insurance database currently available in the world.

Criteria for case selection

In this study, we assessed the NHIRD for all claim records of outpatient and inpatient care in 2005. All records of admissions for patients aged ≥16, containing a diagnosis of sepsis (ICD-9-CM 038) on discharge, and who received tooth extraction within 14 days before the admission were identified. Four senior oral and maxillofacial surgeons were recruited to review patient charts from the hospitals and dental offices. Each case was first reviewed by two reviewers to verify the diagnosis of sepsis and rule out the existence of other possible infection sources. If there was contradiction between the first two reviewers, the charts were further examined by a third examiner to confirm or rule out the relation between tooth extraction and sepsis. In this study, PES was defined as sepsis after tooth extraction in patients without concomitant locoregional infection and other identifiable infection sources. Before individual chart review, all reviewers met face-to-face to establish a consensus on the criteria for PES. The diagnosis of sepsis should be based on the consensus criteria recommended by the Society of Critical Care Medicine Consensus Conference Committee 1992 (American College of Chest Physicians/Society of Critical Care Medicine Consensus Committee, 1992). Sepsis was defined as suspected or microbiologically proven infection together with SIRS (systemic inflammatory response syndrome). The definition of SIRS was characterized by two or more of the following conditions: (1) temperature higher than 38°C or lower than 36°C, (2) heart rate greater than 90 beats per minute, (3) respiratory rate greater than 20 breaths per minute or $PaCO_2$ lower than 32 Torr, and (4) white blood cell count higher than 12 000 cells per microliter or lower than 4 000 cells per microliter or the presence of more than 10% immature neutrophils or band cells. There should be no symptom and sign of locoregional infection in the area of tooth extraction and no history of trauma, operation or other infectious diseases within 2 months before the appearance of SIRS symptoms.

Data collection

For cases identified as PES, clinical parameters were recorded, which included age, gender, position and preoperative diagnosis of the extracted tooth/teeth, number of tooth/teeth extracted, method of tooth extraction, prescription before/after tooth extraction, time elapsed between tooth extraction and admission for PES, underlying conditions, blood culture results, and outcome of treatment. The methods of tooth extraction were divided into two types, forceps/elevator extraction and odontectomy of impacted tooth, which entailed mucoperiosteal flap reflection with or without bone removal.

Statistical analysis

The association between PES and clinical parameters was analyzed by Chi-square or Fischer's exact test where appropriate. Analysis was performed using the software SPSS (Statistical Program for Social Sciences) version 10 (SPSS Inc., Chicago, IL, USA). *P*-values were two-sided and the significant level was 0.05.

Results

Incidence of PES in Taiwan

In 2005, there were 2 223 971 tooth extraction cases and a total of 2 661 593 permanent teeth extracted among Taiwanese NHI insurants aged ≥16. In 251 patients, sepsis occurred within 14 days of tooth extraction. Among them, the records of 35 patients were incomplete and not eligible for further analysis. Individual chart review found 118 patients had infection sources unrelated to tooth extraction and 65 patients had concomitant cellulitis/abscess in the head and neck region. Therefore, the incidence of PES in cases without concurrent locoregional infections was estimated to be 33/2 223 971, or 1.48 per 100 000.

Demographic characteristics

The 33 cases of PES included 13 women and 20 men. The difference in incidence of PES between men and women was not statistically significant (1.75 *vs* 1.19 per 100 000; $P = 0.358$) (Table 1). The ages of the 33 patients ranged from 23 to 90 years with a median of 66 years and an average of 61.45 ± 19.89 years (mean ± s.d.), and 60.6% of the patients were aged ≥61 years. The PES incidence rates for patients aged ≥61 and ≥81 years were 3.98 and 13.45 per 100 000, respectively. In our study population, PES was not found in patients aged ≤20 years. The age-related differences were statistically significant ($P < 0.001$) (Table 1).

Tooth-related factors

The records for prophylactic antibiotics used before the surgery were incomplete. However, all 33 patients

Table 1 Demographic characteristics and tooth-related factors in patients with postextraction sepsis (PES)

Variable	*Total number of cases (A)*	*Number of PES (B)*	*Incidence of PES per 100 000 (C)*[a]	*P*
Gender				
Male	1 136 465	20	1.75	0.358
Female	1 087 506	13	1.19	
Age (years)				
16–20	131 648	0	0.00	< 0.001
21–30	483 721	3	0.62	
31–40	328 480	2	0.61	
41–50	417 014	5	1.20	
51–60	360 660	3	0.83	
61–70	270 575	7	2.59	
71–80	187 257	7	3.74	
≧ 81	44 616	6	13.45	
Number of tooth/ teeth extracted				
Single	1 794 523	26	1.45	0.955
Multiple	429 448	7	1.63	
Method of extraction[b]				
Forceps/elevator	2 078 325	31	1.49	0.945
Odontectomy	172 633	3	1.74	
Tooth position[c]				
Upper anterior	256 879	5	1.95	0.185
Upper premolar	282 841	2	0.71	
Upper molar	840 351	13	1.55	
Lower anterior	213 155	8	3.75	
Lower premolar	210 985	2	0.95	
Lower molar	847 428	12	1.42	
Supernumerary	9954	0	0	

[a]$C = B/A \times 100\,000$.
[b]The number of cases according to extraction method is higher than the actual number of patients because a single patient may receive two types of extraction simultaneously. In one patient with PES, both types of extraction were performed and were separately counted.
[c]A single patient may receive tooth extractions from different positions. In seven PES cases, the extractions were performed for two different positions and were separately counted.

received prescription of antibiotics, mostly amoxicillin or first-generation cephalosporins, for at least 3 days after the surgery. Among the 33 cases, periodontal disease was the most frequent (20) preoperative diagnosis of the extracted teeth, followed by dental caries or retained root (7), tooth fracture (3), and impaction (3). As for the number of tooth/teeth removed in each case, in 26 patients only a single tooth was extracted whereas the other seven patients received extraction of multiple teeth (range 2–4). The difference in PES incidence between single and multiple extraction cases was not significant (1.45 *vs* 1.63 per 100 000; $P = 0.955$). Forceps/elevator extraction was performed in 30 patients and two patients received odontectomy. In one patient, both types of extraction procedures were performed. The three odontectomies were performed for impacted mandibular third molar in patients aged 20–30 years who had no underlying diseases. The type of extraction technique had no significant influence on the incidence of PES ($P = 0.945$) (Table 1). Regarding the position of extracted tooth, in 17 patients only mandibular teeth were extracted and 14 patients received only maxillary tooth extraction. In two patients, teeth in both jaws were extracted. Extraction of mandibular anterior teeth was associated with the highest incidence of sepsis (3.75 per 100 000), but the differences in PES incidence between tooth position groups were not significant ($P = 0.185$) (Table 1).

Clinical characteristics

Eighteen of the 33 patients (54.55%) were admitted for sepsis within 4 days after tooth extraction and eight patients were admitted more than 10 days postoperatively. The average time elapsed between tooth extraction and admission was 6.03 ± 4.40 days (mean ± s.d.) (Table 2). Fever was the most frequent (19) initial symptom of sepsis among the 33 patients, followed by rigors or chills (13). Pre-existing underlying conditions that might influence immunological competence or wound healing were present in 20 of the 33 cases (60.6%), and in five patients, there were multiple comorbidities (Table 3). Diabetes mellitus was the most commonly found systemic disease (9), followed by hematologic diseases (6), which included four cases of leukemia [all were acute myeloid leukemia (AML)]. Among the four patients with AML, one patient had the disease first discovered after the admission for sepsis, one patient was at myelosuppressive stage of induction chemotherapy and the other two were under postremission consolidation chemotherapy. No comorbidity was found in 13 of the 33 patients (Table 3).

Blood cultures

Among the 33 cases of PES, blood culture was performed in 31 patients but two reports were not

Table 2 Time elapsed between tooth extraction and admission for postextraction sepsis (PES)

Interval between extraction and admission (days)	*Number of patients*
0–2	9
3–4	9
5–6	2
7–8	1
9–10	4
11–12	4
13–14	4

Table 3 Underlying conditions in the 33 patients with postextraction sepsis (PES)

Underlying condition	*Number of patients*[a]
None	13
Diabetes mellitus	9
Renal transplant	3
Liver cirrhosis/hepatoma	5
Head and neck irradiation	1
Hematologic diseases[b]	6
Adrenal insufficiency	1

[a]A total of 20 patients had pre-existing underlying conditions and five of them had two comorbidities.
[b]Hematologic diseases include four cases of acute myeloid leukemia, one case of aplastic anemia, and one case of bone marrow fibrosis with thrombocytopenia and agranulocytosis.

eligible. In four cases, the bacterial cultures remained sterile. Cultures were positive in 25 patients (75.8%) and a total of 52 isolates, including two fungal species, were identified (Table 4). In 20 patients, the cultures were polymicrobial and an average of 2.08 ± 0.64 (mean ± s.d.) isolates (range 1–3) was identified among culture-positive patients. *Streptococcus* spp. were the most frequently identified organisms, accounting for 23.1% of the isolates. *Klebsiella pneumoniae* was identified in three patients with diabetes mellitus. On the other hand, anaerobes were also commonly isolated from blood samples of PES patients, which included species of the *Actinomyces*, *Bacteroides, Prevotell*a, *Enterococcus, Eubacterium,* and *Clostridium* genera, among others.

Outcome of treatment

In 12 patients (36.4%), the disease progressed to severe sepsis and septic shock. Seven patients (21.2%) died of the disease because of multiple organ dysfunction and 26 patients eventually recovered. The average ages in the mortality and recovered groups were 74.14 ± 16.11 and 58.42 ± 19.06 years (mean ± s.d.), respectively, but the difference was not statistically significant (P = 0.055). Comorbidities were noted in three of the seven mortality cases, which included diabetes mellitus, leukemia, and liver cirrhosis with bone marrow fibrosis. The other four mortality cases had no pre-existing underlying disease. They were older than the three patients with comorbidity (83.25 ± 5.19 *vs* 62.00 ± 18.73 years) but the difference was not statistically significant (P = 0.077).

Discussion

In Taiwan, the government launched the NHI program in March 1995 to look after the health of the entire population. Most people in the island enjoyed coverage by the program, which makes the claim record database a very valuable resource for epidemiological studies. To our knowledge, the present study is the first reporting on the incidence of PES in cases without concurrent locoregional infection. The connection between tooth extraction and postoperative sepsis is based on circumstantial evidence but that may be the best we can have. The veracity of the connection can be ascertained only when the same phenotype is isolated preoperatively around the tooth to be extracted and in the blood of the septic patient thereafter, which is impossible for large-scale survey of such a low-incidence disease.

The relationship between focal infections in the oral cavity and systemic diseases has aroused much concern lately (Lockhart and Durack, 1999; Rautemaa *et al*, 2007). It is well known that a number of oral manipulating procedures can give rise to bacteremia with the highest incidence of bacteremia results from tooth extractions, ranging from 39% to 100% depending on the evaluated time intervals and other experimental variables studied (Coulter *et al*, 1990; Heimdahl *et al*, 1990; Okabe *et al*, 1995; Roberts *et al*, 1998; Takai *et al*, 2005; Tomas *et al*, 2007, 2008). Odontogenic bacteremias are usually transient in nature. It can be deduced from previous studies that the bacteremic load peaks within the first few minutes and then gradually declines after 10–20 min (Parahitivawa *et al*, 2009). However, it is important that in spite of an initial steep fall, a few bacteria survive in the circulation after a bacteremic challenge from the oral cavity. These persister cells evade the innate and adaptive defense mechanisms and have the ability to seed target organs and cause systemic and distant infections (Lewis, 2007), especially in immunocompromised hosts. Although the incidence of PES seems not high, the risk is still significant, considering the large number of tooth extractions performed and high mortality of the disease, especially in high-risk patients. Furthermore, the incidence rate reported in this study may be an underestimate because cases with the following conditions were not included: (1) admissions more than 2 weeks after tooth extraction, (2) sepsis not one of the primary or secondary diagnosis on discharge, (3) incomplete records for confirming the diagnosis of sepsis or the exclusion of locoregional infections, and (4) the presence of other possible infection foci. Therefore the true incidence of sepsis related to tooth extraction is likely to be higher than that reported in the study.

The impact of immunosenescence on innate and acquired immunity is associated with relative immunologic depression that may favor the spreading of infection (Grubeck-Loebenstein and Wick, 2002). Interestingly, Okabe *et al* (1995) demonstrated that the frequency of positive postextraction blood cultures was significantly lower in individuals under 20 years of age than in those over 60. In our study, we found that elderly patients had a significantly higher risk of developing PES. The incidence rates of PES were 2.69 and 9.09 times the average for patients aged ≥61 and ≥81 years, respectively. It is noteworthy that all of the six patients aged ≥81 years had no other underlying diseases, supporting the notion that aging *per se* increases the risk of sepsis. As for the prognosis of sepsis in the elderly, previous studies showed that the propensity toward coagulation activation and impaired fibrinolysis, along with enhanced susceptibility to

Table 4 Microorganism identification in 25 postextraction sepsis (PES) patients with positive blood culture

Microorganism	n (%)	*Microorganism*	n (%)
Streptococcus spp.	12 (23.1)	*Morganella morganii*	1 (1.9)
Actinomyces spp.	4 (7.6)	*Proteus mirabilis*	1 (1.9)
Klebsiella pneumoniae	3 (5.8)	*Pseudomonas aeruginosa*	1 (1.9)
Bacteroides spp.	3 (5.8)	*Escherichia coli*	1 (1.9)
Prevotella spp.	3 (5.8)	*Gemella morbillorum*	1 (1.9)
Enterobacter spp.	3 (5.8)	*Propionibacterium acnes*	1 (1.9)
Staphylococcus aureus	2 (3.8)	*Lactobacilli acidophilus*	1 (1.9)
Acinobacter spp.	2 (3.8)	*Peptostreptococcus magnus*	1 (1.9)
Enterococcus spp.	2 (3.8)	*Fusobacterium nucleatum*	1 (1.9)
Eubacterium spp.	2 (3.8)	*Veillonella alcalescens*	1 (1.9)
Clostridium spp.	2 (3.8)	*Candida albicans*	1 (1.9)
Neisseria cinerea	1 (1.9)	*Yeast-like*	1 (1.9)
Corynebacterium xerosis	1 (1.9)		

microbial mediators, contributes to the increased mortality associated with sepsis in elderly patients (Girard *et al*, 2005). In our study, the patients who died had a higher average age than that of patients recovered. However, because of the relatively small number of cases, the difference was not statistically significant.

Pre-existing underlying conditions were noted in 20 of the 33 patients developing PES. One limitation of the study is that it was not possible to identify underlying diseases in all of the 2.2 million tooth extraction cases. Therefore, more reliable statistics cannot be performed to find out the significance of pre-existing diseases to PES and their interactions with aging and other clinical variables. However, diabetes mellitus was found in 27.3% (9/33) of our septic patients, a rate that is much higher than the contemporary prevalence of diabetes (4%) in Taiwan (Tai, 2000). An association between diabetes and bacterial infection has been recognized for many years (Bryan *et al*, 1985). In animal and *in vitro* studies, the host's immune functions were reported to be disturbed by short- or long-term hyperglycemia including neutrophil bactericidal function (Delamaire *et al*, 1997), cellular immunity MacCuish *et al*, 1974), and complement activation (Hostetter, 1990). These defects in the immune system, along with vascular insufficiency, render diabetic patients at higher risk for a variety of severe or invasive infections (Joshi *et al*, 1999). Four (12.1%) of the 33 septic patients had leukemia. Infection is a common cause of morbidity and mortality in patients with leukemia, both after induction therapy and consolidation cytotoxic therapy (Mayer *et al*, 1994; Bishop *et al*, 1996). In a study conducted by Bodey *et al* (1978), septicemia was found during 20% of the febrile episodes in patients with hematologic malignancies. The primary focus, however, was known in only about 60% of septicemias (Schimpff *et al*, 1972; Singer *et al*, 1977; Bodey *et al*, 1978; Greenberg *et al*, 1982). As a possible origin of septicemia in cases with unknown primary focus, the role of oral microflora has been emphasized in previous studies (Greenberg *et al*, 1982; Bergmann, 1998).

The relationship between aggressiveness of surgery and postextraction bacteremia is not conclusive. Some studies showed that the incidence of postextraction bacteremia increased significantly with the number of teeth extracted, the duration of surgery, the amount of bone removal, and the volume of blood loss (Okabe *et al*, 1995; Roberts *et al*, 2006); others found that there was no apparent change in the incidence of bacteremia with increased aggressiveness of the procedures (Takai *et al*, 2005; Tomas *et al*, 2007, 2008). On the contrary, Heimdahl *et al* (1990) demonstrated that a single dental extraction led to a higher frequency of bacteremia than odontectomy of impacted third molar, and they suggested that this might be because of the rich bacterial flora present on the tooth surface and in the gingival sulcus around erupted tooth, and the pumping movements used in the conventional dental extraction technique for erupted teeth (Heimdahl *et al*, 1990; Rajasuo *et al*, 2004). Our study showed that development of PES was not related to the number of teeth extracted or method of extraction (forceps/elevator extraction *vs* odontectomy). Another factor which may lessen the risk of PES is that odontectomy of impacted tooth is more frequently performed in youngsters and patients without major underlying diseases.

Bacterial culture results are useful in guiding antibiotic choices for the prevention and treatment of PES, especially in high-risk patients. Blood cultures were positive in 25 of the 33 septic patients and most of the microorganisms identified are common oral pathogens. *Streptococcus* was the most common bacterial genus identified, consistent with many previous studies showing that streptococci were the predominant organisms isolated in postextraction bacteremias. However, the percentage of streptococcal isolates (23.1%) was much lower in our study than those reported for postextraction bacteremia, in which 60–80% of isolates were streptococci (Heimdahl *et al*, 1990; Roberts *et al*, 1992, 1997; Takai *et al*, 2005; Tomas *et al*, 2007). It is probable that the lower frequency of streptococcal bacteremia in PES is because of their virulence attributes that impede the development of sepsis. Anaerobes were also isolated frequently, indicating the need of anaerobic coverage for prophylaxis before tooth extraction in high-risk patients. Moreover, it is noteworthy that *Klebsiella pneumoniae* was the most common organism identified in patients with diabetes mellitus and all three *K. pneumoniae* isolates were from diabetic patients.

In conclusion, we found that tooth extraction is associated with a low but significant risk of postoperative sepsis. Aging significantly increased the risk of PES and a majority of PES patients had pre-existing immunocompromising diseases such as diabetes mellitus and leukemia. Although the connection between tooth extraction and sepsis is based only on circumstantial evidence, the relationship should not be ignored in view of the high mortality of the disease.

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Conflict of interest

We declare that we have no conflict of interest.

Author contributions

Jang-Jaer Lee handled the study concepts and design, acquisition and analysis of data, and manuscript preparation. Liang-Jiunn Hahn gave advice and content expertise throughout the evolution of the study. Tzu-Pin Kao and Chien-Hsiang Liu gave advice with respect to the use of claims data of the Taiwanese National Health Insurance program. Shi-Jung Cheng, Shih-Lung Cheng, Hao-Hueng Chang, and Jiiang-Huei Jeng reviewed the manuscript for important intellectual content. Sang-Heng Kok handled the study concepts and design, analysis and interpretation of data, and manuscript editing.

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