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Original Research

Effectiveness and Safety of Tokishakuyakusan in Hospitalized Patients With Hypertensive Disorders of Pregnancy: A Nationwide Retrospective Cohort Study Using Japanese Claims Data

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Abstract

Background: Hypertensive disorders of pregnancy (HDP) are life-threatening conditions. Although antihypertensive medications effectively control blood pressure, they do not target the underlying pathophysiology of HDP. Tokishakuyakusan, a traditional Kampo medicine, has demonstrated the potential to improve uteroplacental circulation in experimental HDP models; however, its clinical effectiveness remains unclear. This study investigated the real-world effectiveness and safety of Tokishakuyakusan in hospitalized patients with HDP. **Methods:** This retrospective cohort study analyzed data from the Japanese Diagnosis Procedure Combination database collected between 2014 and 2023. Pregnant women admitted at 20 weeks of gestation or later with a diagnosis of HDP were included if they received oral antihypertensive therapy within the first 3 days of hospitalization. Patients were classified into two groups based on whether they received Tokishakuyakusan within the first 3 days of hospitalization. The primary outcome was the administration of intravenous magnesium sulfate or nicardipine. Secondary outcomes included maternal adverse events and preterm birth. Multivariate logistic regression was performed for statistical analysis. **Results:** Overall, 11,264 women met the inclusion criteria, including 85 who received Tokishakuyakusan in combination with antihypertensive therapy, and 11,179 who received antihypertensive drugs alone. Tokishakuyakusan use was not significantly associated with the primary outcome [adjusted odds ratio (aOR) 1.07, 95% confidence interval (CI) 0.69–1.68], maternal adverse events (aOR: 0.82, 95% CI: 0.52–1.27), or preterm birth (aOR: 0.84, 95% CI: 0.51–1.38). **Conclusions:** Tokishakuyakusan was infrequently prescribed but appeared to be safe in women with HDP. No significant association between reduced disease progression and preterm birth was identified, although the small sample size was a limiting factor.

Keywords: hypertensive disorders of pregnancy; Japan; Kampo medicine; logistic models; Tokishakuyakusan

1. Introduction

Hypertensive disorders of pregnancy (HDP) are serious conditions that can exert profound deleterious effects on both maternal and fetal health. International guidelines emphasize blood pressure control as the primary management [1]. In Japan, oral medications, such as methyldopa, hydralazine, labetalol, and nifedipine, are commonly used. In particular, the use of nifedipine has increased rapidly following guideline updates; however, previous studies using Japanese claims data indicated that these shifts in prescription patterns were not necessarily accompanied by a marked improvement in major pregnancy outcomes [2].

When oral medications fail to control blood pressure adequately, the condition often progresses to severe HDP, which is recognized as a surrogate marker for adverse maternal and perinatal outcomes. International protocols typically recommend intravenous labetalol or hydralazine for such severe cases [1]. However, intravenous nicardipine is preferred in Japanese clinical practice due to its superior titrability and the limited availability of intravenous labetalol in domestic settings [3]. Additionally, magnesium sulfate is required to prevent eclampsia in severe disease [1]. Because delivery is the only definitive treatment for HDP, exploring adjunctive therapies that not only support symptom control but also target the pathological processes underlying HDP is necessary.

Tokishakuyakusan and its primary herbal components are utilized globally for a variety of therapeutic purposes in traditional medicine. In Japan, this formulation is widely prescribed to women before, during, and after pregnancy [4]. Beyond its traditional uses, recent studies suggest it targets the underlying pathophysiology of HDP. Tokishakuyakusan has been shown to improve the angiogenic imbalance by inducing placental growth factor (PlGF) [5] and to protect placental trophoblasts against ischemic stress through active components [6,7]. These biological actions offer a plausible therapeutic strategy for HDP, warranting clinical investigation.

Despite these findings, little is known about the prescription of Tokishakuyakusan for HDP in real-world clinical practice and its influence on maternal or perinatal outcomes and safety. Therefore, this study examined the use of Tokishakuyakusan in hospitalized women with HDP and evaluated its association with disease progression—defined as the need for intravenous magnesium sulfate or nicardipine—as well as maternal outcomes, including preterm birth. In addition, we assessed the safety of Tokishakuyakusan during hospitalization to determine whether it was associated with an increased risk of adverse maternal or perinatal events.

2. Materials and Methods

2.1 Data Source

This retrospective cohort study analyzed data retrieved from the Diagnosis Procedure Combination (DPC), a nationwide inpatient database. Data cannot be made publicly available for ethical reasons, as the data are patient data. The data are available to interested researchers upon request to the corresponding author, pending ethical approval. The DPC database has been described in detail elsewhere [8]. As of 2024, the DPC includes data from 1786 acute-care hospitals. The database contains anonymized discharge summaries and administrative claims data, and has been widely used for epidemiological and health services research [8]. From an obstetric perspective, in addition to International Classification of Diseases, Tenth Revision (ICD-10) codes and Japanese text data, information on pregnancy status (pregnant or not), gestational age at admission, and delivery during hospitalization is also recorded. The database does not contain laboratory data or obstetric examination findings. A previous validation study reported that the diagnostic records in the database generally possess high accuracy, with a respective sensitivity and specificity of 78.9% and 93.2% for primary diagnoses [9].

2.2 Patient Selection

This study included pregnant women admitted at a gestational age of 20 weeks or later and diagnosed with HDP or hypertension between April 2014 and May 2023. The DPC started recording the gestational age from April 2014. Both hypertension and HDP diagnoses were included because the definition of HDP was revised in 2018 to include pregnancies complicated by hypertension [2].

Because the delivery date could not be directly identified from the DPC database, we employed the approach of a previous study and used procedure and prescription records as proxies [10]. The date on which these codes were recorded was designated as the delivery date. The procedures and medications included in this definition are as follows: cervical incision, breech extraction, vacuum extraction, forceps delivery, episiotomy incision and suture, perineal laceration repair, cervical laceration repair, cesarean section, umbilical cord replacement, correction of limb prolapse, bimanual compression of the uterus, manual removal of the placenta, uterine rupture repair, obstetric hysterectomy, and correction of uterine inversion. Procedure and admission dates were used as proxies for uterine dilation, labor induction, and fetal monitoring. Prescription dates were used as proxies for the administration of oxytocin, dinoprost, dinoprostone, ergometrine maleate, methylergometrine maleate, and gemeprost. In particular, for medications or procedures that could span multiple days, such as oxytocin, dinoprost, and fetal monitoring, the most recent recorded date was assumed to represent the delivery date, following the previously validated algorithm [10].

We excluded women with multiple pregnancies or deliveries, placenta previa, chorioamnionitis, amniotic fluid embolism, threatened preterm labor, premature rupture of membranes, or onset of labor at admission. Patients who delivered within 3 days of admission were also excluded to avoid misclassification of outcomes. Women who received magnesium sulfate, nicardipine, ritodrine, or cervical cerclage within 3 days of admission were excluded because these treatments may have been used for indications other than HDP management.

To ensure a consistent exposure definition, we restricted the cohort to women who received antihypertensive therapy within the first 3 days of admission. Patients without such prescriptions were excluded. We further excluded women who had evidence of delivery within 7 days before admission to avoid including postpartum hospitalizations. Cases with an undetermined or implausible gestational age or delivery date were excluded. Finally, patients with missing data on smoking status or ambulance transport were excluded from the analysis.

2.3 Exposure and Control

The exposure group was defined as women who received antihypertensive drugs (methyldopa, hydralazine, labetalol, or nifedipine) combined with Tokishakuyakusan within the first 3 days of hospitalization. The control group included women who received antihypertensive drugs (methyldopa, hydralazine, labetalol, or nifedipine) alone within the first 3 days of hospitalization.

2.4 Outcome

The primary outcome was intravenous administration of either magnesium sulfate or nicardipine during hospitalization. According to the clinical guidelines for HDP, magnesium sulfate is administered in severe cases, particularly when the blood pressure is markedly elevated or preeclampsia-related symptoms are present. Nicardipine is used when urgent blood pressure control is required [3]. Since both medications are typically administered to patients with severe HDP, their use was considered an indicator of progression to severe disease and designated as the primary outcome.

The secondary outcomes were adverse maternal events and preterm birth. Maternal adverse events included any of the following: emergency cesarean section, placental abruption, abnormal postpartum hemorrhage, admission to an intensive care unit or maternal–fetal intensive care unit, renal failure, liver dysfunction, stroke, and pulmonary edema. For the analysis of preterm birth, we restricted the study population to women who were hospitalized at ≤36 weeks of gestation.

2.5 Covariates

The following covariates were included in the analysis: maternal age at admission (categorized as ≤19, 20–24, 25–29, 30–34, 35–39, or ≥40 years), gestational age at admission (<34 or ≥34 weeks), body mass index (BMI) was calculated using height and body weight measured at admission and categorized into four groups: <18.5, 18.5–24.9, 25–29.9, and ≥30 kg/m^2, and the number of concomitant antihypertensive agents. Based on the diagnostic codes, HDP was classified into gestational hypertension, chronic hypertension, preeclampsia, and superimposed preeclampsia. In the HDP subtype, gestational hypertension was used as the reference category. Patients were stratified based on gestational age at admission: <34 weeks and ≥34 weeks. This categorization was adopted in accordance with the consensus statement by the International Society for the Study of Hypertension in Pregnancy (ISSHP) [11]. Additional covariates included smoking status, teaching hospital status, hospital volume, ambulance transport at admission, and level of consciousness at admission, which was determined using the Japan Coma Scale (JCS score 0 vs. ≥1). Comorbidities, which were assessed using ICD-10 codes, included gestational diabetes mellitus, diabetes mellitus, epilepsy, mental and behavioral disorders due to tobacco use, mental and behavioral disorders due to alcohol use, chronic kidney disease, autoimmune diseases, antiphospholipid syndrome, and dyslipidemia. The fiscal year of admission was also included as a covariate. A list of the codes is provided in **Supplementary Table 1**.

2.6 Statistical Analysis

The normality of continuous variables was assessed using the Shapiro-Wilk test. Since the continuous variables, including age and BMI, showed non-normal distributions ($p < 0.001$), they have been expressed as median (interquartile range [IQR]). However, to provide a standardized measure of balance and ensure comparability with the existing literature, standardized mean differences (SMDs) were calculated from the means and standard deviations for all continuous covariates.

Categorical variables are expressed as numbers and percentages. We compared the baseline patient characteristics between the two groups using SMDs. An absolute SMD of <0.1 indicated a negligible difference between the groups [12]. The SMD for categorical variables was calculated using the following formula [13]:

$$SMD = \frac{(p_1 - p_2)}{\sqrt{\frac{p_1(1-p_1)+p_2(1-p_2)}{2}}}$$

Pearson's chi-squared test was used to compare the outcomes between groups. Multivariate logistic regression analysis was performed to evaluate the association between the exposure and the primary and secondary outcomes. Missing data were handled using complete case analysis.

We also conducted subgroup analyses by repeating the analysis among women aged 35 years or older at admission, and those with a diagnosis of preeclampsia at admission.

In the sensitivity analysis for adverse maternal outcomes (secondary outcome), we redefined postpartum hemorrhage based on recorded blood loss of ≥1000 mL in the claims data. Furthermore, to test the robustness of our time-window definition, we conducted an additional sensitivity analysis in which exposure was defined as the use of medicine at any time during the hospitalization period. Additionally, robust Poisson regression was used to estimate the adjusted risk ratio (RR) for more interpretable effect sizes, given that the primary outcome was not rare.

Multicollinearity was assessed using the variance inflation factor (VIF). Model fit was evaluated using the Hosmer-Lemeshow goodness-of-fit test. A post-hoc power analysis was also performed to evaluate the statistical power of the study, given the small sample size of the Tokishakuyakusan group. No formal adjustment for multiple comparisons was performed, because the secondary, subgroup, and sensitivity analyses were considered exploratory. All statistical analyses were conducted using Stata/MP 18.0 (StataCorp, College Station, TX, USA).

3. Results

Based on the eligibility criteria, after excluding 1010 women with missing smoking or ambulance transport data, 85 women who received antihypertensive drugs combined with Tokishakuyakusan within the first 3 days of hospitalization and 11,179 women who received antihypertensive drugs alone within the first 3 days of hospitalization were included (Fig. 1). Compared with the control group, women in the Tokishakuyakusan group were older and more likely to be smokers. The proportion of preeclampsia was also higher in the Tokishakuyakusan group (Table 1).

Table 2 shows the numbers and proportions of outcomes obtained from the main analyses. The incidence of primary or adverse maternal outcomes did not differ significantly between the Tokishakuyakusan and control groups.

Table 3 shows the proportion of preterm birth in both groups. The analysis included 72 women from the Tokishakuyakusan group and 8232 from the control group, all of whom were admitted at ≤36 weeks' gestation.

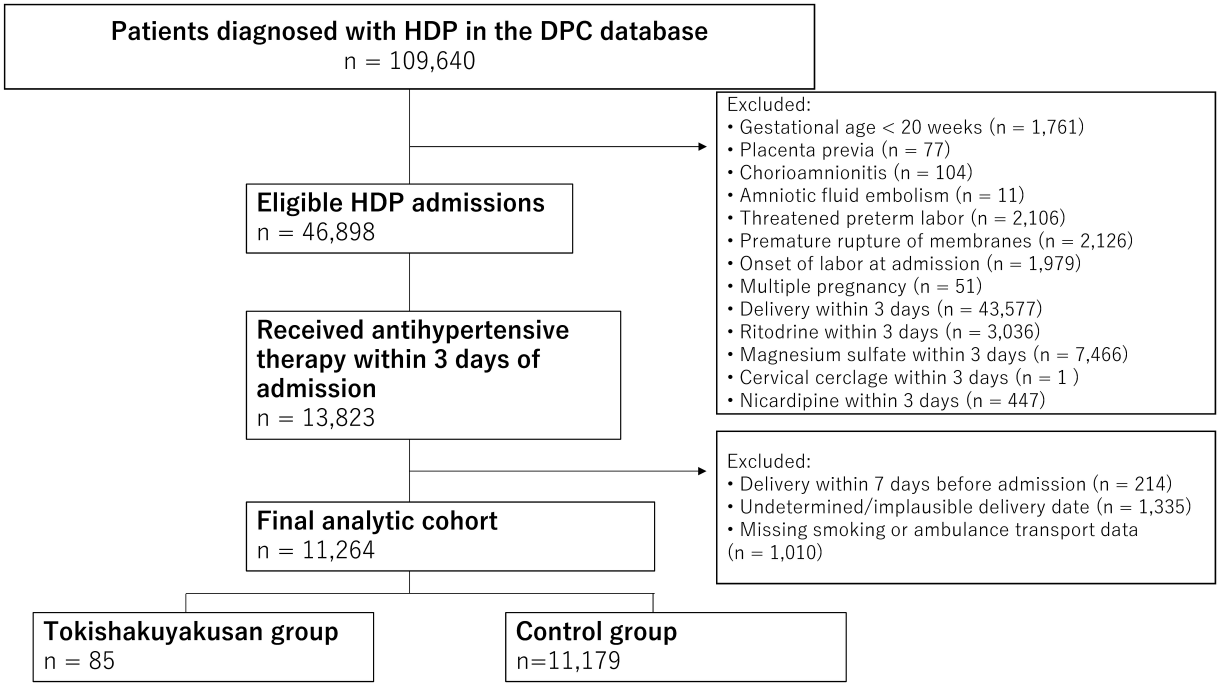

Fig. 1. Flowchart of patient selection for the study cohort. HDP, hypertensive disorders of pregnancy; DPC, Diagnosis Procedure Combination.

Table 4 shows the results of multivariate logistic regression in the main analysis. Tokishakuyakusan use was not associated with the primary outcome [adjusted odds ratio (OR): 1.07, 95% confidence interval (CI): 0.69–1.68]. Similarly, Tokishakuyakusan use was not associated with adverse maternal events (adjusted OR: 0.82, 95% CI: 0.52–1.27) or preterm birth (adjusted OR: 0.84, 95% CI: 0.51–1.38). To ensure the validity of our statistical models, we assessed multicollinearity and model fit. Mean VIF = 1.04, indicating no significant multicollinearity. Furthermore, the Hosmer-Lemeshow goodness-of-fit test confirmed that all models had a good fit (p = 0.390 for the primary outcome, p = 0.487 for adverse maternal outcomes, and p = 0.381 for preterm birth).

Similar results were observed in the subgroup analyses limited to women aged 35 years or older and those diagnosed with preeclampsia. In addition, the association remained insignificant in the sensitivity analysis based on the definition of postpartum hemorrhage recorded as blood loss ≥1000 mL. In another sensitivity analysis, we redefined the exposure group to include the use of Tokishakuyakusan and antihypertensive agents at any time during hospitalization. In this expanded cohort (n = 254), the results remained consistent with our primary analysis; the 95% CI for all outcomes crossed 1.0, indicating no significant association between Tokishakuyakusan use and an increased risk of the primary outcome, adverse maternal outcomes, or preterm birth. The number and proportion of the outcomes in the subgroups and sensitivity analyses are shown in **Supplementary Table 2**. The results of the subgroup analysis, with preterm birth as the outcome, restricted to women admitted at ≤36 weeks, are shown in **Supplementary Table 3**. Table 5 shows the results of multivariate logistic regression performed for the subgroup and sensitivity analyses. In all cases, Tokishakuyakusan use was not associated with a higher risk of adverse outcomes and resulted in lower numbers of preterm births, but the difference was not statistically significant.

To further assess the robustness of our findings, we conducted a sensitivity analysis using robust Poisson regression. The adjusted RR for the primary outcome, adverse maternal outcomes, and preterm birth was 1.03 (95% CI: 0.81–1.31), 0.90 (95% CI: 0.71–1.14), and 0.91 (95% CI: 0.71–1.16), respectively.

4. Discussion

This study investigated the effectiveness and safety of Tokishakuyakusan combined with antihypertensive therapy in patients hospitalized with HDP. To the best of our knowledge, this is the first study to evaluate the clinical impact of Tokishakuyakusan in this population using a nationwide claims database. Our findings revealed that while its prescription was not common, Tokishakuyakusan was utilized in real-world clinical practice. No significant associations were observed with disease progression, maternal adverse events, or preterm birth.

Notably, the robustness of these findings was supported by several sensitivity analyses using different expo-

Table 1. Baseline characteristics.

	Tokishakuyakusan group n = 85	Control group n = 11,179	SMD
Age (years), median (IQR)	37.0 (32–40)	35.0 (31–39)	0.235
BMI (kg/m^2), median (IQR)	27.2 (24.3–30.7)	26.9 (24.0–30.8)	0.032
BMI category (kg/m^2), n (%)			0.092
Underweight (<18.5)	0 (0.0)	96 (0.9)	
Normal (18.5–24.9)	26 (30.6)	3681 (32.9)	
Overweight (25.0–29.9)	31 (36.5)	4091 (36.6)	
Obesity (≥30.0)	28 (32.9)	3311 (29.6)	
Number of concomitant antihypertensive agents, n (%)			0.080
1	67 (78.8)	9130 (81.7)	
2	17 (20.0)	1982 (17.7)	
3	1 (1.2)	67 (0.6)	
Gestational hypertension, n (%)	28 (32.9)	3844 (34.4)	0.030
Chronic hypertension, n (%)	5 (5.9)	656 (5.9)	0.001
Preeclampsia, n (%)	51 (60.0)	6190 (55.4)	0.094
Superimposed preeclampsia, n (%)	6 (7.1)	741 (6.6)	0.017
Fiscal year, n (%)			0.103
2014	5 (5.9)	1037 (9.3)	
2015	5 (5.9)	1004 (9.0)	
2016	11 (12.9)	1139 (10.2)	
2017	7 (8.2)	1187 (10.6)	
2018	13 (15.3)	1293 (11.6)	
2019	8 (9.4)	1357 (12.1)	
2020	17 (20.0)	1337 (12.0)	
2021	7 (8.2)	1372 (12.3)	
2022	12 (14.1)	1453 (13.0)	
Smoking, n (%)	16 (18.8)	1321 (11.8)	0.195
Emergency Transport, n (%)	5 (5.9)	937 (8.4)	0.097
Consciousness disturbance (JCS > 0), n (%)	0 (0.0)	15 (0.1)	0.052
Gestational diabetes, n (%)	10 (11.8)	1518 (13.6)	0.054
Diabetes mellitus, n (%)	1 (1.2)	180 (1.6)	0.037
Dyslipidemia, n (%)	0 (0.0)	66 (0.6)	0.109
Epilepsy, n (%)	0 (0.0)	29 (0.3)	0.072
Chronic kidney disease, n (%)	0 (0.0)	54 (0.5)	0.099
Autoimmune disease, n (%)	6 (7.1)	774 (6.9)	0.005
Antiphospholipid syndrome, n (%)	0 (0.0)	50 (0.4)	0.095
Teaching hospital status	78 (91.8)	9967 (89.2)	0.089
Hospital volume, n (%)			0.230
Low	36 (42.4)	3653 (32.7)	
Middle	28 (32.9)	3835 (34.3)	
High	21 (24.7)	3691 (33.0)	

Continuous variables are presented as median (IQR) because they were not normally distributed ($p < 0.001$ by the Shapiro–Wilk test). The SMD was calculated from the means and SD to assess the balance between the two groups. Categorical variables are presented as numbers and percentages. Percentages may not total exactly 100% because of rounding. Percentages of HDP subtypes may exceed 100% because the subtype categories are not mutually exclusive, and more than one diagnostic code may have been recorded for some patients during hospitalization.

Fiscal year was defined as the period from April to March of the following year.

IQR, interquartile range; SMD, standardized mean difference; SD, standard deviation; BMI, body mass index; JCS, Japan Coma Scale.

Table 2. Outcomes of the main analysis: number and proportion of events.

Outcomes	Tokishakuyakusan group (n = 85)	Control group (n = 11,179)	*p* value
Primary outcome	37 (43.5%)	4587 (41.0%)	$p = 0.641$
Adverse maternal outcomes	37 (43.5%)	5541 (49.6%)	$p = 0.267$

Table 3. Number and proportion of preterm birth outcomes.

Outcomes	Tokishakuyakusan group (n = 72)	Control group (n = 8232)	*p* value
Preterm birth	32 (44.4%)	4147 (50.4%)	$p = 0.316$

Table 4. Results of logistic regression for the main analysis and preterm birth outcomes.

Outcomes	Crude OR (95% CI)	Adjusted OR (95% CI)
Primary outcome	1.11 (0.72–1.70)	1.07 (0.69–1.68)
Adverse maternal outcomes	0.78 (0.51–1.20)	0.82 (0.52–1.27)
Preterm birth	0.79 (0.49–1.25)	0.84 (0.51–1.38)

Values represent ORs with 95% CIs. Adjusted for maternal characteristics and comorbidities (see Methods). Primary outcome: intravenous use of magnesium sulfate or nicardipine. Adverse maternal outcomes: emergency cesarean section, placental abruption, postpartum hemorrhage, ICU/MFICU admission, renal failure, liver dysfunction, stroke, or pulmonary edema. Preterm birth was assessed among women admitted at ≤36 weeks of gestation.

OR, odds ratio; CI, confidence interval; ICU, intensive care unit; MFICU, maternal-fetal intensive care unit.

Table 5. Results of logistic regression for the subgroup and sensitivity analyses.

Outcomes	Tokishakuyakusan group Event n/N (%)	Control group Event n/N (%)	Crude OR (95% CI)	Adjusted OR (95% CI)
Subgroup analysis				
Maternal age ≥35 years				
Primary outcome	24/56 (42.9)	2603/6121 (42.5)	1.01 (0.59–1.72)	0.96 (0.56–1.67)
Adverse maternal outcomes	23/56 (41.1)	3092/6121 (50.5)	0.68 (0.39–1.16)	0.68 (0.39–1.19)
Preterm birth	22/47 (46.8)	2294/4689 (48.9)	0.93 (0.51–1.71)	0.93 (0.50–1.71)
Preeclampsia				
Primary outcome	25/51 (49.0)	3082/6190 (49.8)	0.96 (0.55–1.68)	0.96 (0.55–1.67)
Adverse maternal outcomes	26/51 (51.0)	3457/6190 (55.8)	0.82 (0.47–1.42)	0.87 (0.49–1.52)
Preterm birth	24/43 (55.8)	2380/4753 (50.1)	0.85 (0.46–1.57)	0.92 (0.50–1.72)
Sensitivity analysis				
Redefinition of adverse maternal outcomes (Hemorrhage defined as ≥1000 mL)	35/85 (41.2)	5296/11,179 (47.4)	0.77 (0.50–1.19)	0.81 (0.51–1.26)
Medicine use during the entire hospitalization period				
Primary outcome	122/254 (48.0)	9090/19,902 (45.7)	1.10 (0.86–1.41)	1.07 (0.83–1.39)
Adverse maternal outcomes	154/254 (60.6)	11,142/19,902 (56.0)	1.21 (0.94–1.56)	1.28 (0.98–1.65)
Preterm birth	111/206 (53.9)	7404/13,592 (54.5)	0.98 (0.74–1.29)	0.98 (0.73–1.31)

Values represent ORs with 95% CIs. Adjusted for maternal characteristics and comorbidities (see Methods). Subgroup analyses: women aged ≥35 years or with preeclampsia.

Sensitivity analysis:

a. Postpartum hemorrhage was redefined as recorded blood loss ≥1000 mL.

b. Exposure was defined as medication use during the entire hospitalization period.

sure definitions and statistical models, all of which yielded consistent results. Although the Tokishakuyakusan group showed numerically lower incidences of certain adverse events, these differences were not statistically significant. This lack of significance is likely due to the limited number of patients in the Tokishakuyakusan group, which resulted in wide 95% confidence intervals for the primary and secondary outcomes. Such wide intervals suggest a high risk of Type II error, meaning the study may have been underpowered to detect clinically meaningful differences.

A previous study reported that approximately 8% of pregnant women in Japan were prescribed Tokishakuyakusan [4]. However, the effectiveness and safety profile of Tokishakuyakusan are unknown, because it is impossible to investigate the effectiveness of Tokishakuyakusan prescribed in outpatient settings without establishing a cohort.

Tokishakuyakusan may possess therapeutic potential for HDP, supported by a multifaceted biological rationale from pharmacological studies. In a screening of 74 Kampo formulas, Tokishakuyakusan was identified as an inducer of PlGF production [5], suggesting that it could restore angiogenic activity even in the presence of soluble Fms-Like Tyrosine Kinase-1(sFlt-1), potentially addressing maternal endothelial dysfunction. Interestingly, a component analysis within the same study noted that Paeoniae Radix (Shakuyaku) and Poria (Bukuryo)—both components of Tokishakuyakusan— were commonly found in many of the top formulas that promoted PlGF production, suggesting their role in PlGF induction [5]. Furthermore, Paeoniae Radix extract has been reported to exhibit endothelium-dependent vasodilator effects, which may be mediated by nitric oxide (NO) production via its active component, gallotannin [14].

In addition to maternal vascular effects, Tokishakuyakusan might also target placental dysfunction, which underlies HDP. Cnidii Rhizoma (Senkyu), identified as a component specific to Tokishakuyakusan among the top PlGF-inducing formulas [5], may play a distinct role. Recent evidence suggests that ligustrazine (tetramethylpyrazine), a major bioactive component of Cnidii Rhizoma, inhibits apoptosis and promotes proliferation and invasion in ischemia-reperfusion injured trophoblasts, possibly via activation of the Wnt/β-catenin signaling pathway [6,7].

Moreover, Tokishakuyakusan appears to possess antioxidant properties and scavenge reactive oxygen species (ROS), which are known to contribute to endothelial damage in the ischemic placenta [15]. Thus, it is conceivable that Tokishakuyakusan exerts a comprehensive effect on the pathophysiology of HDP through the synergistic action of its components.

Despite these theoretical mechanisms targeting both placental and maternal pathologies, our clinical data did not demonstrate a statistically significant benefit of Tokishakuyakusan in ameliorating HDP exacerbation. This could be due to limited statistical power, as only a small number of patients received Tokishakuyakusan in our study cohort.

Limitations

This study has some limitations. First, the Tokishakuyakusan group had a small sample size (n = 85). The 95% confidence intervals for the primary and secondary outcomes were wide, indicating substantial statistical uncertainty. Accordingly, the absence of statistically significant associations should not be interpreted as evidence of no effect, because the study may have been prone to Type II error.

Second, the primary outcome was the intravenous administration of magnesium sulfate or nicardipine, which was used as a proxy for progression to severe HDP. Although the initiation of these medications may potentially be influenced by institutional practices or physician preference, the management of HDP in Japan is highly standardized according to national clinical guidelines, thereby minimizing the influence of individual physician preference on treatment decisions. Nevertheless, the lack of granular clinical data, such as longitudinal blood pressure measurements or laboratory values, may have led to some degree of misclassification of disease severity. Furthermore, because the pathogenic mechanisms of different HDP subtypes are distinct, we conducted a subgroup analysis restricted to preeclampsia to account for this distinct pathophysiology. Therefore, baseline disease severity and subtype-specific characteristics could not be fully adjusted for, and residual confounding may remain.

Third, the DPC database is an administrative claims database primarily designed for reimbursement. Thus, discrepancies may exist between clinical records and coded diagnoses. Additionally, because our identification of the delivery date relied on specific diagnostic and procedure codes, physiological deliveries without recorded medical interventions might have been excluded, introducing a selection bias toward cases requiring more intensive medical management.

Fourth, we used complete case analysis and excluded patients with missing smoking status or ambulance transport data. Although these variables are routinely collected in the DPC database, it was not possible to determine whether the missingness was completely at random; therefore, some degree of selection bias cannot be excluded. In addition, no formal adjustment for multiple comparisons was performed, and the findings from the secondary, subgroup, and sensitivity analyses should therefore be interpreted cautiously as exploratory. Furthermore, no propensity score-based or other additional analyses were performed, which should also be taken into consideration when interpreting the findings.

Fifth, due to the study's retrospective design, we lacked detailed information on the treatment course or med-

ications prescribed in the outpatient setting prior to admission.

Despite these limitations, our findings provide preliminary real-world evidence regarding the clinical benefits of Tokishakuyakusan in hospitalized patients with HDP. Tokishakuyakusan was not associated with an increased risk of adverse maternal or neonatal outcomes, indicative of its safety.

5. Conclusion

In this retrospective cohort study of hospitalized women with HDP, the use of Tokishakuyakusan in combination with antihypertensive drugs was not associated with disease progression or maternal adverse outcomes. Although clear clinical benefits were not demonstrated, no major safety concerns were observed. Further prospective studies are needed to clarify the effectiveness and potential role of Tokishakuyakusan as an adjunctive therapy for HDP.

Availability of Data and Materials

The raw data underlying this study are not publicly available due to privacy restrictions imposed by the ethics committee. However, where there is a reasonable justification, requests submitted to the corresponding author may be carefully reviewed.

Author Contributions

HG, OH, YS, HY, MF, MN, YE, RT, MH, YH contributed to the study concept and made substantial contributions to the interpretation of the data and findings. HG and YS conducted the data analysis. HG was a major contributor to drafting the manuscript. All authors contributed to critical editorial revisions and intellectual content of the manuscript. All authors read and approved the final version of the manuscript. All authors agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

This study was conducted in accordance with the principles of the Declaration of Helsinki. The dataset used in this study was obtained from a database approved by the Ethics Committee of University of Tokyo. Ethical approval for access and use of this database was granted under approval number 3501-5, which covers the general use of the database for research purposes. For the present analysis, ethical compliance was ensured under an additional ethics approval associated with the same research framework and study objectives, under approval number 3501-46. All data were anonymized prior to analysis, and no identifiable personal information was accessed. Therefore, the informed consent received exemption from the ethics committee.

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Conflicts of Interest

The authors declare no conflicts of interest. Osamu Wada-Hiraike is serving as one of the Editorial Board members/Guest editors of this journal. We declare that Osamu Wada-Hiraike had no involvement in the peer review of this article and has no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to handling editor.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.31083/CEOG49468.

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