

## Intravenous tocolysis with *Bryophyllum pinnatum* is better tolerated than beta-agonist application

Nathalie Plangger<sup>a</sup>, Lukas Rist<sup>b</sup>, Roland Zimmermann<sup>a</sup>, Ursula von Mandach<sup>a,\*</sup>

<sup>a</sup>Zurich University Hospital, Department of Obstetrics, Frauenklinikstrasse 10, CH-8091 Zurich, Switzerland

<sup>b</sup>Paracelsus Hospital Richterswil, Switzerland

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### Abstract

**Objective:** To compare tolerability and tocolytic outcome between i.v. infused plant extract, *Bryophyllum pinnatum*, and beta-agonists. **Study design:** In a retrospective study, 67 pairs of pregnant women in preterm labor treated with intravenous *B. pinnatum* or beta-agonists were closely matched for maternal age, gestational age at tocolysis, CTG recorded contractions, cervical effacement, preterm premature rupture of the membranes, and history of preterm labor. Endpoints were prolongation of pregnancy, gestational age at delivery, pre- and postpartum duration of hospitalization, maternal tolerability, neonatal outcome and morbidity. **Results:** Pregnant women with *B. pinnatum* and beta-agonists were equal in the prolongation of pregnancy (6.2 versus 5.4 days, NS), the gestational age at delivery (38.0 versus 37.1 weeks, NS) and the duration of hospitalisations, but had less adverse effects (34.3 versus 55.2% with palpitation or dyspnea,  $P = 0.02$ ). The neonatal outcome and morbidity in the *B. pinnatum* group were equal or better (oxygen use 10.4 versus 44.8%,  $P < 0.001$ ; respiratory distress syndrome 4.5 versus 19.4%,  $P = 0.01$ ). **Conclusion:** In the management of preterm labor *B. pinnatum* is no less effective than beta-agonists, but is significantly better tolerated.

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**Keywords:** *Bryophyllum pinnatum*; Beta-agonists; Tocolysis; Tolerability; Preterm labor

### 1. Introduction

Extracts of *Bryophyllum pinnatum*, a plant with a variety of common names in English (life plant, air plant, resurrection plant, Canterbury bells, cathedral bells, Mexican love plant) have been used by modern physicians mainly as a psychiatric sedative. Identified active ingredients include bufadienolides, flavonoids, glycosides, steroids and organic acids [1–5], while in vitro effects in rodent tissue include sedation, positive inotropism, antimicrobial activity and H<sub>1</sub> antagonism (ileum, peripheral vasculature, bronchial muscle) [6–8].

*B. pinnatum* was first used to treat preterm labor in 1970 as a 5% aqueous tincture for intravenous (i.v.) infusion at a maximal dose of 580 mg/h. However, because of its

exclusive use in anthroposophical medicine, there have been only two reports of clinical applications [9,10], describing an outcome similar to that with the beta-agonist fenoterol. We recently provided the first in vitro confirmation that *B. pinnatum* inhibits human myometrial contractility: it decreases the amplitude of spontaneous contraction (although increasing its frequency), while decreasing both the amplitude and frequency of induced contraction [11].

Conventional labor inhibitors can have important and well-documented adverse effects, notably on the cardiovascular system, in both mother and child. No such effects have been reported for *B. pinnatum*. However, the relevant studies have been scientifically inadequate [9,10]. As a preliminary to a prospective study, we therefore undertook a retrospective matched-pair study in the management of tocolysis to compare tolerability and pregnancy and newborn outcomes between *B. pinnatum* and beta-agonists.

\* Corresponding author. Tel.: +41 1 255 51 36; fax: +41 1 255 44 30.  
E-mail address: [ursula.vonmandach@usz.ch](mailto:ursula.vonmandach@usz.ch) (U. von Mandach).  
URL: <http://www.geburtshilfe.usz.ch/>

## 2. Materials and methods

### 2.1. Design and patients

Two treatments for preterm labor (*B. pinnatum* and beta-agonists) were compared in a matched-pair study of patients admitted between January 2000 and December 2003 by two Swiss and two German centers. The study was approved by the institutional review board of the Departments of Obstetrics and Urology, Zurich University Hospital.

The inclusion/exclusion criteria corresponded to a standardized protocol for all study patients. Inclusion criteria were intrauterine singleton pregnancy, gestational age  $\geq 25.0 \leq 35.0$  weeks, gravida I or II, caucasian, preterm labor, age  $> 18$  years, pre-pregnancy BMI  $< 30$ . Gestational age was calculated from the first day of the last menstrual period and first trimester ultrasound; dates were corrected to the ultrasound data where appropriate. Preterm labor was defined as CTG recorded and painful contractions  $> 2/h$  and cervical effacement detected either clinically by vaginal examination or by vaginal ultrasound scanning (cervical portio length  $< 2.0$  cm) with or without intact membranes. The exclusion criteria were multiple pregnancy, cervical dilation  $> 3$  cm, vaginal bleeding, preeclampsia and/or pregnancy-related hypertension (diastolic pressure  $> 90$  mmHg after 20.0 weeks of gestation with or without proteinuria and edema), fever ( $> 37.5$  °C), urinary tract infection (positive nitrite and microbiological culture), placental abnormality, fetal malformation, intrauterine growth retardation, serious maternal disease, alcohol or drug abuse, pretreatment with other tocolytics, and participation in a clinical trial in the preceding month.

*B. pinnatum* patients (group 1) were recruited from Herdecke Community Hospital (Germany), Filderstadt Hospital (Germany), and Paracelsus Hospital (Richterswil, Switzerland). In these three institutions operating anthroposophical medicine i.v. tocolysis with *B. pinnatum* (Weleda AG, D-73525 Schwäbisch Gmünd, 5%, 10 ml ampoules for i.v. use) was performed according to the following standardized protocol: the infusion was started and maintained to a maximal dose of 600 mg/h (corresponding 30 mg of plant) for at least 48 h and until cessation of contractions. If the therapy was ineffective after 48 h, *B. pinnatum* was supplemented by a parenteral beta-agonist for subsequent tocolysis. After cessation of contractions, treatment was switched to oral 50% *B. pinnatum* at a mean dose of 200 mg 2-h (corresponding 100 mg of plant).

These patients were closely matched to women from the Department of Obstetrics, Zurich University Hospital (group 2). Because centers carrying out anthroposophical medicine do not use beta-agonists alone and our hospital does not yet use *B. pinnatum*, the matching of patients was not possible within the same center. In the Zurich University Hospital women received an i.v. beta-agonist infusion with fenoterol, to 4  $\mu\text{g}/\text{min}$ , or hexoprenaline, to 0.3  $\mu\text{g}/\text{min}$ . After cessation of contractions, treatment was switched to an

oral beta-agonist (fenoterol, to 40 mg/24 h, or hexoprenaline, to 4 mg/24 h). The match variables were maternal age, gestational age on starting tocolysis, frequency of CTG recorded and painful contractions, cervical effacement (length of cervical portio vaginalis), PPRM, and a history of preterm labor or delivery.

In both groups patients received supplemental magnesium sulfate during the parenteral phase of their tocolytic therapy (mean daily dose: 33 g, equivalent to 54 mmol  $\text{Mg}^{2+}$ ) and magnesium aspartate during the oral phase (mean daily dose: 20 mmol  $\text{Mg}^{2+}$ ). According to the clinical protocols additional parenteral antibiotics and/or corticosteroids (betamethasone i.m. two 12 mg doses 24 h apart) were administered for suspected amniotic/fetal infection and fetal lung maturation, respectively.

### 2.2. Data collection and endpoints

Maternal and neonatal data were collected from the medical records.

Primary endpoints were i.v. tocolysis duration, gestational age at delivery, prolongation of pregnancy, requirement for supplemental beta-agonists (group 1), antibiotics and corticosteroids, adverse events (unwanted signs or symptoms recorded in the medical records during i.v. tocolysis) and duration of pre- and postpartum hospitalization.

Secondary endpoints were neonatal mortality (intrauterine death and death to 7 days postpartum), outcome (birth weight, sex, Apgar at 1, 5, 10 min) and morbidity including the following parameters: bradycardia ( $< 80/\text{min}$  for preterm), hypoglycemia  $< 1$  h postpartum ( $< 2.0$  mmol/l), hyperbilirubinemia 48 h postpartum or at least once during hospitalisation (healthy term  $> 2500$  g:  $> 300$   $\mu\text{mol}/\text{l}$ ; ill term  $> 2500$  g:  $230 \leq 300$   $\mu\text{mol}/\text{l}$ ; term  $< 2500$  g:  $\leq 240$   $\mu\text{mol}/\text{l}$ ; preterms:  $\leq 240$   $\mu\text{mol}/\text{l}$ ), respiratory distress syndrome ( $\geq 2$  of the following parameters: respiratory rate  $> 60/\text{min}$ , cyanosis in room air, inspiratory retractions, expiratory grunting, nasal flaring, use of oxygen therapy), intracranial hemorrhage, cerebral palsy, necrotizing enterocolitis and systemic infection needing antibiotic treatment.

### 2.3. Statistics

Power was calculated using StatSoft Statistic Power Analysis for WinXP based on the hypothesis that mean gestational age at delivery with a standard deviation of  $\pm 2.5$  weeks did not differ ( $< 1.0$  week) between the two groups: the minimal sample size was  $n = 64/\text{group}$  ( $\alpha = 0.05$ ;  $\beta = 0.8$ ). The data were entered into Excel and analyzed in Stat View 5.0.1 for Windows XP. Means, standard deviations and medians were calculated. Normality was tested using the Kolmogorov–Smirnov test. Primary and secondary endpoints were compared between treatment groups: continuous data were tested using the unpaired two-tailed *t*-test if normally distributed (and log-transformed),

and the Mann–Whitney *U*-test if non-normally distributed. Fisher's exact test was used for nominal data. A significance value  $<0.05$  was used in all tests.

### 3. Results

#### 3.1. Maternal data at admission

Sixty-seven patient pairs met the inclusion and matching criteria. The groups did not differ significantly in maternal data at admission (Table 1).

#### 3.2. Pregnancy outcome

There were no significant differences between the two groups in gestational age at admission, at start, end and duration of tocolysis. Gestational age at start of tocolysis equalled gestational age at admission. Mean gestational age at delivery was non significantly higher in group 1 (38.0, range: 34.3–41.3 weeks) than in group 2 (37.1, range: 26.6–42.3 weeks;  $P = 0.051$ ); prolongation of pregnancy did not differ (6.2 days in group 1 versus 5.4 days in group 2) (Table 2).

#### 3.3. Maternal outcome

Additional beta-agonists in group 1:  $6.8 \pm 9.6$  (median 4.0) days after starting *B. pinna*tum (i.e. at a gestational age of  $32.8 \pm 2.1$  weeks, median 33.0 weeks), 19 patients received a supplemental parenteral beta-agonist (intravenous fenoterol to 4  $\mu\text{g}/\text{min}$ ,  $n=16$ ; intramuscular ritodrine to 60 mg/24 h,  $n = 3$ ) for persistent preterm labor. Six patients received an oral beta-agonist as a supplemental boost for a mean 1 day (fenoterol:  $n = 4$ , to 40 mg/24 h; hexoprenaline:  $n = 2$ , to 4 mg/24 h) (Table 2).

Table 1

Maternal data at admission (all differences NS)

	Group 1 ( $n = 67$ ) ( <i>B. pinna</i> tum)	Group 2 ( $n = 67$ ) (Beta-agonists)
Age (y)	$31.0 \pm 4.6$	$30.9 \pm 4.6$
Parity ( $n$ )	$1.5 \pm 0.7$	$1.6 \pm 0.7$
Gravidity ( $n$ )	$1.9 \pm 1.3$	$1.9 \pm 0.9$
Gestational age (w)	$31.8 \pm 2.5$	$31.7 \pm 2.5$
Range	25.3–35.0	25.0–34.9
Cervical length (cm)	$1.6 \pm 0.6$	$1.5 \pm 0.7$
Cervical dilation (cm)	$0.5 \pm 0.6$	$0.6 \pm 0.6$
Contraction frequency (n/h)	$7.5 \pm 5.0$	$8.2 \pm 4.7$
PPROM (yes/no)	3/64	3/64
Positive history <sup>a</sup> (yes/no)	17/50	17/50

Continuous values: mean  $\pm$  S.D. ( $n$ ) numeric values:  $n$ ; PPRM: preterm premature rupture of the membranes.

<sup>a</sup> Preterm labour or preterm delivery.

Parenteral antibiotics and corticosteroids: Antibiotics were administered in two patients of group 1 (co-amoxiclav 1.2 g/d *tid*) and in 24 patients of group 2 (co-amoxiclav,  $n = 22$ , 1.2 g/d *tid*; erythromycin,  $n=1$ , clindamycin,  $n = 1$ ) ( $P < 0.001$ ). Betamethasone was given for fetal lung maturation in four group 1 patients and thirty-two group 2 patients ( $P < 0.001$ ) (Table 2).

Maternal adverse effects: They were less frequent in group 1 (23 patients, 34.3%) than in group 2 (37 patients, 55.2%) ( $P = 0.02$ ); 4 (6%) patients of group 1 versus 16 (23.9%) patients of group 2 had  $>1$  adverse effect ( $P = 0.006$ ). Dyspnea was absent in group 1 but present in seven patients (10.4%) in group 2 ( $P = 0.01$ ). Palpitations (incorporating tachycardia) and dyspnea were also less pronounced ( $P < 0.05$ ) in group 1 patients with *B. pinna*tum alone (without additional beta-agonists,  $n = 48$ ) (Table 2 and Fig. 1).

Hospital stay: One group 1 patient was readmitted twice and three group 2 patients were readmitted once for tocolysis; the groups did not differ in mean prepartum hospital stay.

Table 2

Pregnancy and maternal outcome

	Group 1 ( $n = 67$ ) ( <i>B. pinna</i> tum)	Group 2 ( $n = 67$ ) (Beta-agonists)	$P^*$
GA at end of tocolysis (w)	$33.6 \pm 2.5$ (34.4)	$33.8 \pm 2.7$ (34.7)	NS
Range	27.7–37.3	25.9–37.0	
Duration of tocolysis (w)	$1.8 \pm 1.8$ (1.3)	$2.2 \pm 2.3$ (1.3)	NS
GA at delivery (w)	$38.0 \pm 1.8$ (38.1)	$37.1 \pm 3.3$ (37.4)	NS
Range	34.3–41.3	26.6–42.3	
Prolongation of pregnancy (w)	$6.2 \pm 3.4$ (5.7)	$5.4 \pm 3.6$ (5.3)	NS
Prolongation $\geq 7$ days	64 (95.2)	56 (83.6)	NS
Additional parenteral $\beta$ -agonists	19 (28.4)	–	–
Additional i.v. antibiotics	2 (3.0)	24 (35.8)	$<0.001$
Betamethasone <sup>a</sup>	4 (6.0)	32 (47.8)	$<0.001$
Women with adverse effects	23 (34.3)	37 (55.2)	0.02
Women with $>1$ adverse effect	4 (6.0)	16 (23.9)	0.006
Antenatal hospital stay (d)	$19.9 \pm 15.4$ (13.0)	$18.6 \pm 15.1$ (12.0)	NS
Postnatal hospital stay (d)	$4.8 \pm 2.2$ (4.0)	$5.6 \pm 2.5$ (6.0)	NS

Continuous values: mean  $\pm$  S.D. (median); numeric values:  $n$  (%); d: days; GA: gestational age; w: weeks.

<sup>a</sup> For fetal lung maturation.

\* vs. group 2 (Fisher's exact test)

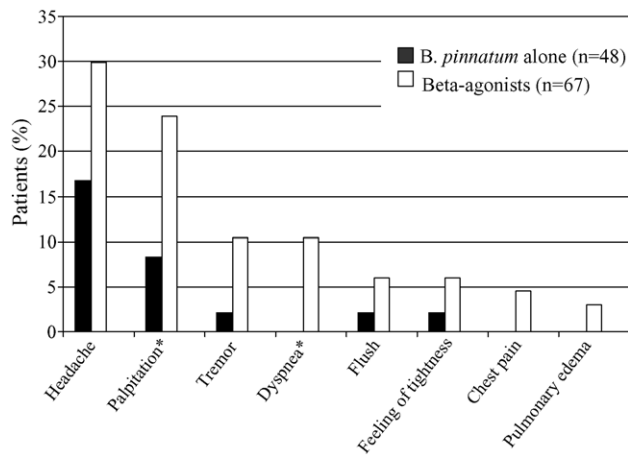


Fig. 1. Women (%) with adverse effects from tocolysis with *B. pinnatum* alone ( $n = 48$ ) and beta-agonists ( $n = 67$ ). \* $P < 0.05$  vs. beta-agonists (Fisher's exact test).

### 3.4. Neonatal outcome

**Table 3** There were no intrauterine or postnatal inpatient deaths. The proportion of preterm births was similar: 22 (32.8%) in group 1 versus 31 (46.3%) in group 2 ( $P = 0.16$ ). Two deliveries (both group 2) were at  $<28$  weeks. Apgar scores at 1, 5 and 10 min were higher ( $P < 0.001$ ) (the two  $<28$ -week infants had Apgar scores  $<7$  at 5 min) and oxygen use lower in group 2 than in group 1 ( $P < 0.001$ ). Overall morbidity was lower in group 1 ( $P = 0.008$ ) due to higher preterm morbidity in this group ( $P = 0.01$ ). Individual parameters showed less respiratory distress syndrome in group 1 (4.5 versus 19.4%,  $P = 0.01$ ). There were no cases of necrotizing enterocolitis or cerebral palsy. No differences in morbidity of neonates from mothers in group 1 with *B.*

*pinnatum* alone versus *B. pinnatum* combined with beta-agonists were found.

## 4. Discussion

Pregnancy and newborn outcomes in preterm labor treated with *B. pinnatum* were similar to those associated with beta-agonist therapy. They were even better in Apgar scores, oxygen use and neonatal morbidity (RDS). Maternal adverse effects were significantly decreased. These effects were also more marked in the subgroup receiving *B. pinnatum* alone. No variable was to the disadvantage of *B. pinnatum* group.

The close matching procedure using multiple variables and the clear definition of premature labor in the inclusion criteria ensured a similar starting point for the risk of premature delivery in both groups. This gives our study clear strengths over previous comparisons of *B. pinnatum* with beta-agonists [9,10,12]. However, there are several points to be discussed.

We were not able to separate the effects of magnesium, whether as the sulfate or aspartate. Magnesium should optimize tocolytic efficacy and minimize cardiovascular side effects. As our study shows, maternal adverse effects were more pronounced in the beta-agonist group. This prompted the decision, based on several studies [13,14], to abandon use of magnesium sulfate in preterm labor on the combined grounds of inefficacy and poor tolerability.

Comparison of our results with the recent multicenter prospective study of the oxytocin antagonist atosiban versus beta-agonists (terbutaline or ritodrine) using similar inclusion/exclusion criteria [15] shows similar prolongation of

Table 3  
Neonatal outcome and morbidity

	Group 1 ( $n = 67$ ) ( <i>B. pinnatum</i> )	Group 2 ( $n = 67$ ) (Beta-agonist)	$P$
<b>Outcome</b>			
Female/male	30/37	33/34	NS
Preterm ( $\leq 37.0$ w)	22 (32.8)	31 (46.3)	NS
Birth weight (g)	3096 $\pm$ 490 (3010)	2900 $\pm$ 666 (2980)	NS
Range	1900–4430	1020–4300	
Apgar at 5 min	Median: 10	Median: 9	$<0.001^*$
Range	7–10	4–10	
Oxygen use	7 (10.4)	30 (44.8)	$<0.001^\dagger$
<b>Morbidity</b>			
Newborn with $\geq 1$ event	9 (13.4)	23 (34.3)	0.008 $^\dagger$
Preterm with $\geq 1$ event	6 (9.0)	18 (26.9)	0.01 $^\dagger$
Bradycardia	0	4 (6.0)	NS
Hyperbilirubinemia	4 (6.0)	8 (11.9)	NS
Hypoglycemia	1 (1.5)	2 (3.0)	NS
Respiratory distress syndrome	3 (4.5)	13 (19.4)	0.01 $^\dagger$
Intracranial hemorrhage	0	2 (3.0)	NS
Systemic infection	1 (1.5)	0	NS

Continuous values: mean  $\pm$  S.D. (median); numeric values:  $n$  (%).

\* vs. group 2 (unpaired two-tailed  $t$ -test).

$^\dagger$  vs. group 2 (Fisher's exact test).

pregnancy (mean 5.5 weeks; our study: mean 5.4 weeks (median 5.3) in the beta-agonist group and 6.2 weeks (median 5.7) in the *B. pinnatum* group (Table 2). These results give strength to the reliability of the results in our study compared to others and also within our study groups irrespectively of the retrospective design. However, the better neonatal outcome of the *B. pinnatum* group leads to the hypothesis that the (non significantly) lower preterm morbidity has contributed to these results. For this aspect it has to be taken into account, that our results depend not only on the possibly different effect/action of *B. pinnatum* and beta-agonist, but also on the different topics of medicine carried out in the centers with/without anthroposophical medicine. As pregnancy outcome (Table 2) has shown, corticosteroids (betamethasone) and antibiotics were less used in the *B. pinnatum* than in the beta-agonist group. Centers with anthroposophical medicine use these substances more restrictively. Thus, we cannot conclude, that in the *B. pinnatum* group threatened preterm labour or infections were lower as in our hospital. Moreover, for the latter aspect, it has to be considered that *B. pinnatum* has antimicrobial activity (in vitro inhibition of *Escherichia coli*, *Staphylococcus aureus*, *Bacillus subtilis* and *Pseudomonas aeruginosa*) which may also help to avert preterm labor [16]. For conclusion, the lower neonatal morbidity rate in the *B. pinnatum* group cannot be explained satisfactorily and has to be reevaluated in a further prospective study.

Beside the tocolytic effectiveness, the tolerability of *B. pinnatum* has also briefly to be discussed. *B. pinnatum* tocolysis has fewer maternal adverse effects, notably palpitations (tachycardia) and dyspnea because, unlike beta-agonists, it does not stimulate cardiac beta<sub>1</sub>-adrenoceptors. However, the bufadienolides found in many *B. pinnatum* preparations are potentially cardiotoxic, as veterinary reports have testified following the ingestion of large amounts of fresh plant [17,18]. It is thus important to note that analysis by the manufacturer, Weleda, revealed no toxic bufadienolides in our test preparation (100% aqueous leaf extract). Other sources have confirmed that bufadienolide concentrations in aqueous solution are much lower than in fresh roots or non-aqueous extracts [7,19].

Finally, the uterorelaxant effect of *B. pinnatum* is a point which needs to be clarified. In a recent in vitro study we could demonstrate for the first time, that *B. pinnatum* relaxes spontaneous and oxytocin-induced contraction in human myometrium [11]. Animal studies have revealed an H<sub>1</sub>-receptor antagonist in the pressed juice of *B. pinnatum* [20]. Given the in vitro evidence that histamine increases human myometrial activity [21], this could account for the preparation's uterorelaxant effect.

For summary, this study confirms the in vitro relaxant effect of *B. pinnatum* in human myometrium. Moreover, the good tolerability justifies the conduct of a prospective controlled trial of *B. pinnatum* within the same center. Dose-finding studies and further in vitro investigations to clarify its uterine cellular action are also necessary.

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