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IS TARANJEBIN A PROPHYLACTIC AGENT FOR NEONATAL JAUNDICE?

ZAHRA PANJVANI, HAMED KHARRAZI-SABET, SAID TAWAKKULI, MOHAMMAD REZA RAMAZANI* AND MOHAMMAD TAGHI SARRAF

From the Departments of Pediatrics and Pharmacology, Mashhad University of Medical Sciences, Mashhad, Islamic Republic of Iran.*

ABSTRACT

Taranjebin is a plant resin obtained from camel's thorn, a shrub abundant in desert areas of Iran. It contains saccharose and has been traditionally used by grandmothers to treat neonatal jaundice. This study was conducted to test the effectiveness of taranjebin in reducing bilirubin in physiologic ranges when used prophylactically in normal full-term newborns. 95 term healthy newborns were given 10,20, or 30% taranjebin starting at 4 hours of age for 3 days, while 90 infants were given placebo. Mean serum bilirubin levels were determined on day 5 for both study groups, as were daily transcutaneous bilirubin indices. In the 30% taranjebin group, 5 of 29 treated infants developed jaundice (bilirubin 16 mg per dl) compared to none in the control group ($p< 0.05$).

Taranjebin was thus not found to be effective in preventing hyperbilirubinemia in normal healthy term newborns.

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INTRODUCTION

Jaundice is a common problem of the newborn; two out of three full-term newborns are clinically jaundiced in the first few days after birth, and 20% of Iranian newborns are expected to develop bilirubin levels much higher than the "physiologic" range,[1] necessitating phototherapy. The pediatrician has been troubled by studies that have attempted to show that moderately high levels of bilirubin might be related to hearing loss and low IQ levels.[2] As phototherapy seems innocuous, most pediatricians would use this form of treatment for bilirubin levels of 15 mg/dl or more, which means separating 20% of newborns from their mothers and interrupting nursing for 2-3 days.

Whether moderately high bilirubin levels are indeed neurotoxic or not or whether there is a dose-response relationship between bilirubin levels and neurologic handicap or not are at present controversial issues. However, the notion that lower bilirubin values are preferable to higher ones, is valid. Pharmacologic treatment of hyperbilirubinemia is therefore desirable provided it is safe and effective. Such a drug would indeed be a welcome alternative to phototherapy, as it would not entail separation of the infant from the mother or interruption of nursing.

Taranjebin (a plant resin)[3] has been used to prevent as well as treat jaundice in the newborn by Iranian grandmothers for hundreds of years, but no studies have been done to show if this popular folk medicine is indeed effective. We therefore undertook a study to test this presumption.

MATERIAL AND METHODS

All full-term healthy babies born at Ghaem Hospital from November 30 to March 20, 1991 were eligible to enter the study. However, as most newborns are discharged within 12-24 hours after birth, babies born to primiparous women, who were more likely to have a prolonged hospital stay or those delivered by caesarian section were elected for the study.

Table I. Characteristics of study and control groups

Characteristics	Treatment Group 10 or 20% Taranjebin		Placebo Group (Control)		Significance
Number	66		60		
Mean Birthweight (kg)	3.25		3.12		
Male: Female	35: 31		37: 23		NS
	No/Total	%	No/Total	%	
Delivery:					
Elective C/S	26/66	39.4	28/60	46.7	NS
Emergency C/S	18/66	27.3	13/60	21.7	NS
Vacuum	3/66	4.5	1/60	1.6	NS
Oxytocin	11/50	22.0	10/45	22.2	NS
Apgar Score 5-7	3/66	4.5	3/60	5.0	NS
No. < 2.5 kg	5/66	7.6	8/60	13.3	NS
ABO set up	5/56	8.9	6/51	11.8	NS
Cord Hb > 18 gm/dl	4/36	11.1	4/31	12.9	NS
Cord Hct > 60	2/58	3.4	0	0	NS
Cord Hct < 40	5/58	8.6	9/51	17.6	NS
Cord Bilirubin > 2mg/dl	11/66	16.7	9/59	15.3	NS
Cord Reticulocyte Count > 4	6/57	10.5	8/49	16.3	NS
Feeding type:					
Breastmilk	22/64	34.4	20/59	33.9	NS
Formula	5/69	7.8	1/59	1.7	NS
Mixed	37/64	57.8	38/59	64.4	NS

NS: not significant at 95% confidence limits.

Babies were randomized to receive taranjebin or placebo. Care givers and data collectors were uninformed of the treatment or placebo groups. 10 ml of taranjebin or placebo (water coloured slightly to resemble taranjebin in appearance) was administered orally at 4 hours of age and then every 6 hours thereafter for a total of sixteen doses. Umbilical cord blood samples were obtained for each infant and tested for blood group, Coombs, CBC, reticulocyte count, hemoglobin, hematocrit and bilirubin levels. The mother's blood group was also determined. Daily weight, number and type of feedings per day, and defecation patterns were noted for all infants. Transcutaneous bilirubin (TCB) index was obtained daily using the Minolta Airshield Bilirubinometer and the serum bilirubin level was obtained on the fourth day after finishing the last dose.

Mothers were asked to return on the neonate's seventh day of life when a TCB index was obtained again and a serum bilirubin was obtained only if the baby clinically appeared jaundiced. Babies who became jaundiced on the first two days of life were excluded from the study. Babies who became clinically jaundiced after the second day of life without any pathological cause or those whose serum bilirubin was more than 12 mg/dl on the 4th day or more than 10 mg/dl on the 7th day of life were considered to have significant or exaggerated physiologic jaundice. The treatment group was divided into two groups to receive taranjebin in a concentration of 10 or 20%. As results were similar in the 10 and 20% groups, these two groups were combined for analysis. After analysing the results of these concentrations, the study was repeated using 30% taranjebin for another group of infants born from Aug. 31 to February 23, 1992.

RESULTS

10 or 20% taranjebin

77 subjects were enrolled in the 10 or 20% taranjebin treatment group, of which 11 were excluded; 9 due to insufficient data and 2 due to jaundice developing on the first day of life due to ABO incompatibility.

72 infants received placebo. 12 infants were excluded from this group; 8 due to insufficient data, 2 due to jaundice developing during the first two days of life (one had Rh incompatibility, and the other had hypothyroidism) and 2 infants were excluded because they were not well.

There was no difference between the two groups regarding birthweight, sex, type of delivery, Apgar score,

Table II. Transcutaneous Bilirubin (TCB) Index

	TCB Index	Day 1		Day 3		Day 5		Day 7	
		No	(%)	No.	(%)	No.	(%)	No.	(%)
10 -20% TARANJEBIN	< 12	65/65	(100)	12/64	(18.8)	21/61	(34.4)	16/34	(47)
	12 - 16	—		43/64	(67.2)	23/61	(37.7)	17/34	(50)
	17 - 22	—		9/64	(14)	17/61	(27.8)	1/34	(3)
CONTROL	< 12	55/59	(93)	11/59	(18.6)	15/56	(26.7)	16/30	(53)
	12 - 16	4/59	(7)	38/59	(64.4)	26/56	(46.4)	11/30	(37)
	17 - 22	—		10/59	(17)	15/56	(26.7)	3/30	(10)
NOT SIGNIFICANT									

use of oxytocin during labour, or type of feeding. Cord blood studies were also comparable for both groups (Table I).

Stool characteristics

92.3 and 79.3% of the subject and placebo groups respectively passed their first stool at less than twelve hours of age, with no statistically significant difference. The number of stools per day and the mean weight of stools per day for the four days of the study were not statistically different.

Weight loss between the treatment and control groups was not statistically different; 3.8 and 6.3% of each group respectively lost more than 10% of their birthweight during the study period.

TCB Index

In our newborn population (from previous studies) a TCB index < 12 means no jaundice, a TCB index from 12 to 16 signifies moderate hyperbilirubinemia, and from 17 to 22 significant hyperbilirubinemia. TCB indices on all days were similar in both groups ($p > 0.05$); 100% of subject infants and 93% of placebo infants had a TCB index < 12 on the first day of life; 27.8% and 3.0% of the treatment group and 26.7% and 10% of the control group had a TCB index between 17 and 22 on the 5th and 7th days of life, respectively (Table II). The mean daily TCB indices for all days were exactly the same in both groups.

Jaundice

The mean serum bilirubin on day five was 5.3 (SD 3.6) in the treatment group and 5.4 (SD 3.4) in the control group.

Of the 66 infants in the treatment group 35 had bilirubin levels below 5 mg/dl, 12 between 5 and 8 mg/dl, 10 between 8 and 12 mg/dl, 3 more than 12 mg/dl at 4 days of age, and 6 infants became jaundiced prior to the 4th day requiring phototherapy. In the placebo group of 60 infants, 29 had bilirubin levels below 5mg/dl, 18 between 5-8 mg/dl, 4 between 8-12 mg/dl, 3 above 12 mg/dl, and 6 infants had clinical jaundice prior to the end of the study requiring phototherapy.

Thus, a total of 9 infants in each group had a serum bilirubin of more than 12 mg/dl at 4 days of age. An additional 6 infants in the treatment group and 13 infants in the control group had serum bilirubin levels above 10 mg/dl on the 7th day of life. Thus 15 of the treatment group (22.7%) and 22 of the control group (36.6%) developed significant jaundice. This difference was not statistically significant at 95% confidence limits.

30% taranjebin

A total of 34 infants were enrolled in the treatment group; of these, 4 were excluded due to insufficient data and 1 due to diarrhea, leaving 29 for analysis. The control group consisted of 30 infants after excluding 2 infants that had no bilirubin level on the 4th day of life. Both groups were matched closely in all respects (Table III).

Table III. Characteristics of study and control groups

Characteristics	Treatment Group 30% Taranjebin		Control Group		Significance
Number	29		30		
Mean Birth Weight (kg)	3.14		3.37		NS
Male: Female	15: 14		17: 13		NS
	No/Total	%	No/Total	%	
Delivery:					
Elective C/S	13/29	44.8	15/30	50	NS
Emergency C/S	11/29	37.9	11/30	36.6	NS
Vaginal	4/29	13.8	4/30	13.3	NS
Apgar Score < 5	0	0	0	0	NS
No. < 2.5 kg.	3/29	10.3	1/30	3.3	NS
ABO set up	2/26	7.7	2/27	7.4	NS
Cord Hb > 18 gms/dl	3/26	11.5	0/28	0	NS
Cord Hb < 13 gms/dl	9/26	34.6	6/28	21.4	NS
Cord Hct > 60	2/27	7.4	1/30	3.3	NS
Cord Hct < 40	4/27	14.8	5/30	16.6	NS
Cord Bilirubin > 2mg/dl	2/29	6.9	1/30	3.3	NS
Cord Reticulocyte Count > 4	0/25	0	2/27	7.4	NS
Feeding type:					
Breast milk	1/27	3.7	2/30	6.6	NS
Formula	7/27	25.9	5/30	16.6	NS
Mixed	19/27	70.3	23/30	76.6	NS

The time of passing the first stool, the number of stools per day, and the weight of stools per day were not statistically different in the two groups. However, three babies, all low birth weight, (2150, 2200, and 2250 gms) developed diarrhea and dehydration after receiving 12-15 doses of 30% taranjebin. One of these infants had a weight loss of 15% requiring intravenous hydration and had to be excluded from the study. No serum bilirubin was obtained for this baby as he was not clinically jaundiced. Weight loss in the other two infants was 6.9 and 7.5%; one of these two had a bilirubin level of 16.5mg/dl requiring phototherapy.

46% of the placebo and 32% of the treatment groups had a weight loss of 5-10%, while 3.3% of the placebo and 12.9% of the treatment groups had a weight loss of more than 10%. These differences were not statistically significant.

Day 5 bilirubin

16 of the 29 infants in the treatment group had a serum bilirubin level below 5 mg/dl, two had bilirubin levels from 5- 8 mg/dl, five between 8 -12 mg/dl, and one infant had a bilirubin level above 12 mg/dl.

In the control group of 30 infants, 19 had a serum bilirubin level below 5mg/dl, five between 5-8 mg/dl, three from 8 -12 mg/dl and 3 infants had a bilirubin level above 12 mg/dl. None of these were statistically significant.

However, 5 of the babies who had received taranjebin became clinically jaundiced requiring phototherapy on the 3rd day of life. Their bilirubin values ranged from 16 to 20 mg/dl. None in the placebo group required phototherapy. This difference was significant at $p < 0.05$ (Table IV).

DISCUSSION

Taranjebin is a resin obtained from a plant called the camel's thorn or Alhagi Camelorum fisch.[4] This plant thrives in the desert areas of Iran. It is a spiny branched shrub up to 3 feet tall with simple leaves. Heat or insect activity causes it to exude a resin which hardens and is collected by staking the bush over a cloth spread on the ground.

Agard, Bridel and Villiers thought taranjebin contained melezitose sugar, but Ebert in 1908 and Sadiq Makaddam in 1930 showed the sugar to be saccharose.[5] Taranjebin is used to sweeten medicines. It is also believed to have laxative and expectorant properties.

The spherical particles of taranjebin are boiled with water until dissolved and strained to produce a yellow sweet liquid which is fed to newborns 2-3 times daily. This liquid, being osmolar, is believed to increase the frequency

Table IV. Incidence of significant jaundice in study and control groups

Bilirubin	30% Taranjebin	Control	Significance
Bil. < 12 mg/dl on Day 4	1	3	NS *
Jaundice Requiring Phototherapy	5	0	($p < 0.05$)
Total Jaundiced Infants	6 (20.7%)	3 (10%)	NS
Total Infants Studied	29	30	

* NS: not significant.

Table V. Serum bilirubin values

Bilirubin (mg/dl)	< 5	5 - 8	8 - 12	> 12	Clinical Jaundice + Phototherapy	Total No. of Infants
10% Taranjebin	25	6	10	2	4	47
Placebo	23	12	4	3	2	44
20% Taranjebin	10	6	0	1	2	19
Placebo	6	6	0	0	4	16
30% Taranjebin	16	2	5	1	5*	29
Placebo	19	5	3	3	0	30

* $p < 0.05$

of stools, thereby perhaps increasing the excretion of bilirubin and decreasing its enterohepatic circulation.

Agents that sequester bilirubin in the gut have been used in the newborn to interrupt its enterohepatic circulation and thus influence the course of neonatal hyperbilirubinemia. A reduction of 30% in peak serum bilirubin was observed in term infants fed activated charcoal at 4 hours of life but no effect was seen if it was given at 12 hours of life.[6]

Agar, a colloid laxative, is a polysaccharide extracted from seaweed which binds unconjugated bilirubin in the gut, preventing its reabsorption and increasing its excretion in the stool. When fed to newborns starting at 20 hours of age and continued for 4 days, it prevented the expected rise in bilirubin that occurs on the 3rd to 5th day of life.[7]

We thought taranjebin, also being a polysaccharide and a laxative, might act like agar but our results did not show any difference in the mean number and weight of stools per day in infants fed taranjebin or placebo. Bilirubin excretion in stool however was not studied; it is possible that taranjebin might increase the excretion of bilirubin in stool without increasing the quantity of stool. Indeed it is noteworthy that three low birth weight babies fed 30% taranjebin developed diarrhea. Mothers, upon advice of herbal medicine sellers, dissolve taranjebin to approximately 30% concentration and not uncommonly do we encounter LBW babies with diarrhea and dehydration in the outpatient department following the use of taranjebin by mothers. This was the reason we used 10% taranjebin initially in this study, its specific gravity being close to 5% dextrose water.

The mean maximum serum bilirubin level in white infants is 6 mg/dl by day three which usually declines to less than 3 mg/dl by day seven. Only 3.6% of bottlefed and 12.1% of breastfed white infants will have hiliruhin values exceeding 12 mg/dl. In contrast to this 29.3% of 126 predominantly breastfed infants (treatment and control groups combined) had serum bilirubin values greater than 12 mg/dl by day 4 or above 10 mg/dl by day 7. The transcutaneous bilirubin index also was high in 28% of the same study population by day 5 and 9.5% of the infants required phototherapy. Both serum biliruhinand TCB index are relatively inaccurate tests with wide standard deviations, making it difficult to judge the true incidence of hyperbiliruhinemia in Iranian infants.

However, the limited accuracy of serum bilirubin measurements is not a problem when comparing the number of infants with hyperbilirubinemia in the treatment and control groups. As this was not significantly different (22.7% vs. 36.6%), we can conclude that 10 or 20% taranjebin was not effective in preventing hyperbilirubinemia.

An active enterohepatic circulation does contribute to physiologic neonatal jaundice, but it is difficult to assess its importance in significant neonatal jaundice. Thus it is possible that taranjebin may reduce bilirubin values in the low range but not in the high range.

To assess this, we compared the subject and placebo infants in various ranges of serum bilirubin values (< 5, 5 -

8, 8-12 mg/dl). None of these were significant (Table V) except for the difference in the number of jaundiced infants requiring phototherapy in the 30% taranjebin group. So not only did taranjebin not lower bilirubin values in any range, but in high concentrations it may have had the opposite effect.

If the effect of 10 or 20% taranjebin is small in lowering serum bilirubin levels, a larger number of infants would be needed to show this difference significantly. For example, the association between breast feeding and increased bilirubin levels was missed by several studies because of their limited size (type 2 error).[8]

The wide variation in bilirubin levels among newborns and the unpredictability of the course of hyperbilirubinemia also make it impossible to perform reliable pharmacodynamic studies in babies, requiring a relatively large sample size to demonstrate an effect on bilirubin values.

To summarize, this study compared 95 term healthy newborns who received taranjebin with 90 matched controls and failed to show the effectiveness of taranjebin in preventing hyperbilirubinemia.

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