Int J Clin Exp Med 2019;12(3):2605-2611
www.ijcem.com /ISSN:1940-5901/IJCEM0087668

Original Article

Effect of long-acting nifedipine on blood pressure level, eutocia rate and neonatal health status in patients with pregnancy-induced hypertension

Xiumei Shen[1*], Jingpeng Yan[2*], Anran Ren[1]

[1]*Department of Gynaecology and Obstetrics, Tengzhou Maternal and Child Health Hospital, Tengzhou City, Zaozhuang City, Shandong Province, China;* [2]*Department of Cardiovascular Medicine, Tengzhou Central People's Hospital, Tengzhou City, Zaozhuang City, Shandong Province, China.* [*]*Equal contributors and co-first authors.*

Received October 31, 2018; Accepted December 12, 2018; Epub March 15, 2019; Published March 30, 2019

Abstract: Objective: To investigate the clinical effect of long-acting nifedipine on blood pressure control, full-term birth rate, eutocia rate and neonatal health status in patients with pregnancy-induced hypertension (PIH). Methods: A total of 300 PIH patients were selected and divided into long-acting group and short-acting group according to different treatments, with 150 patients in each group. The short-acting group was treated with short-acting nifedipine, and the long-acting group with the long-acting nifedipine. The blood pressure control level of patients, the full-term birth rate, the eutocia rate and the neonatal health status were observed. Results: There were no significant differences in mean systolic blood pressure (SBP) and mean diastolic blood pressure (DBP) before taking medicine (P>0.05). After treatment, the mean SBP and the mean DBP of the two groups of patients decreased. The long-acting group had a more stable decrease in blood pressure than the short-acting group, with a statistically significant difference (P<0.05). The long-acting group had a higher full-term birth rate than the short-acting group, with a significant difference (P<0.05). The long-acting group had a higher eutocia rate than the short-acting group, with a significant difference (P<0.05). The long-acting group had a significantly better intrauterine distress situation and lower fetal mortality than the short-acting group, with statistically significant differences (all P<0.05). Conclusion: The long-acting nifedipine in PIH patients has a more significant antihypertensive effect and longer duration compared to the short-acting nifedipine, which is more beneficial to fetal eutocia. It protects the neonatal health and is worthy of clinical promotion.

Keywords: Pregnancy-induced hypertension, long-acting nifedipine, short-acting nifedipine, eutocia, neonate

Introduction

Pregnancy-induced hypertension (PIH) is a specific and common disease in pregnant women, clinically characterized by hypertension, edema, proteinuria (PRO), convulsion, coma and renal failure. It is divided into mild, moderate and severe PIH according to severity. Severe PIH is also called pre-eclampsia and eclampsia that refers to convulsion on the basis of hypertension. After 20 weeks of pregnancy, hypertension usually occurs for the first time, with the systolic blood pressure (SBP) ≥155 mmHg (1 mmHg=0.133 kPa) and/or diastolic blood pressure (DBP) ≥105 mmHg, which return/returns to normal within 12 weeks after delivery. And also PRO test is negative [1]. The hypertension, only occurring during pregnancy without substantial organ damage and PRO, is called pregnancy-induced hypertension, referred to as PIH. Hitting the incidence of 5%-12%, PIH, one of causes of maternal and perinatal death, seriously affects the health of mother and infant [2, 3].

At present, the treatment of PIH is to control the condition, prolong the gestational weeks and ensure the safety of mother and child [4]. Its basic principles are rest, sedation, spasmolysis, antihypertension, diuresis, close monitoring on maternal-fetal condition and pregnancy termination at the appropriate time [5]. The goals of depressurization are as follows: those not complicated with organ dysfunction have a SBP controlled at 130-155 mmHg and a DBP at 80-105 mmHg; those complicated with organ dysfunction have a SBP controlled at 130-139 mmHg and a DBP at 80-89 mmHg. The depres-

Table 1. Comparison of general information ($\bar{x} \pm sd$)

	Long-acting group (n=150)	Short-acting group (n=150)	t/χ^2	P
Age (year)	36.2±4.2	35.3±5.3	1.630	0.104
Gestational weeks (week)	26.4±5.3	26.9±5.6	0.794	0.428
Primiparity/multiparity	105/45	108/42	0.065	0.799
Body masss index (kg/m^2)	31.2±4.3	30.5±4.8	1.330	0.184
Time interval between diagnosis of hypertension and inclusion to the study (week)	6.2±2.4	6.4±2.3	0.737	0.462

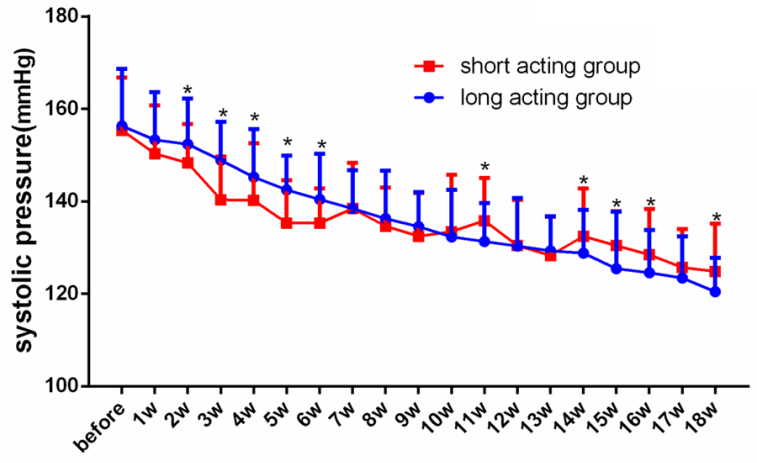

Figure 1. Comparison of SBP. Before: before taking the medicine; 1 w: 1 week after taking the medicine; 2-18 w: 2-18 weeks after taking the medicine. Compared with short-acting group at the same week, *P<0.05. SBP, systolic blood pressure.

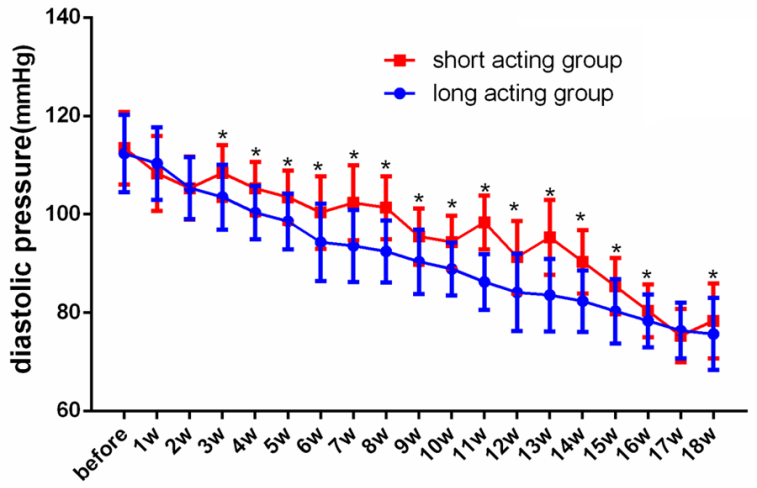

Figure 2. Comparison of DBP. Before: before taking the medicine; 1 w: 1 week after taking the medicine; 2-18 w: 2-18 weeks after taking the medicine. Compared with short-acting group at the same week, *P<0.05. DBP, diastolic blood pressure.

surization process should be stable and not be excessively fluctuating, with a blood pressure more than 130/80 mmHg to ensure uterus-placenta blood perfusion [6].

Nifedipine is the first generation of calcium channel blockers, the clinical application of which has been more than 30 years. It was originally used for treating hypertension, angina pectoris, arrhythmia and hypertrophic cardiomyopathy [7]. It is a good choice for treating mild and moderate hypertension, especially PIH and pregnancy with chronic hypertension [8, 9]. Currently, nifedipine tablets are clinically divided into long-acting and short-acting tablets. In the treatment of hypertensive disorder complicating pregnancy (HDCP), the long-acting nifedipine effectively improves control of the blood pressure level and the clinical treatment. It also has a longer duration of efficacy and higher safety, worthy of the clinical application. However, few studies are about its effect on newborns. Therefore, in this study, the effect of the long-acting or short-acting nifedipine on PIH depressurization, the eutocia rate and the neonatal health status was investigated.

Materials and methods

General information

This study was approved by the Ethics Committee of Tengzhou Maternal and Child

Health Hospital. A total of 300 PIH patients from January 2015 to December 2017 in this department of Tengzhou Maternal and Child Health Hospital were selected and divided into the long-acting group and the short-acting group according to different treatments, with 150 patients in each group. The short-acting group was treated with the short-acting nifedipine, and the long-acting group with the long-acting nifedipine. All patients signed an informed consent form before enrolled in the study.

Diagnosis of HDCP

Hypertension occurs after 20 weeks of pregnancy for the first time, with the SBP ≥155 mmHg (1 mmHg=0.133 kPa) and/or DBP ≥105 mmHg, which return/returns to normal within 12 weeks after delivery. And PRO test is negative. The SBP ≥155 mmHg and/or the DBP ≥105 mmHg are/is diagnosed as severe PIH, in line with the diagnostic criteria for *the Guidelines for the Classification, Diagnosis and Management of Hypertensive Disorder Complicating Pregnancy,* which was developed by the International Research Association of Pregnancy-induced Hypertension in 2018 [10].

Inclusion criteria: Patients without contraindications to nifedipine; patients with the SBP ≥160 mmHg and/or the DBP ≥110 mmHg; patients without PRO, edema, pre-eclampsia, eclampsia and other complications; patient with good treatment compliance.

Exclusion criteria: Patients with PIH heart disease, diabetes mellitus, acute renal failure, placental abruption, idiopathic thrombocytopenic purpura, ascites and other basic diseases or complications.

Treatments

The long-acting group: When diagnosed as PIH, patients were given long-acting nifedipine tablets orally (Baixintong, Qingdao Huanghai Pharmaceutical Co., Ltd., China) 30 mg per time, once a day.

The short-acting group: When diagnosed as PIH, patients were given short-acting nifedipine tablets orally (nifedipine tablets, Tianjin Feiying Pharmaceutical Co., Ltd., China) 20 mg per time, 3 times a day.

Seven days is one treatment course. The weekly blood pressure control level and the blood pressure on the day of delivery were evaluated after taking antihypertensive drugs.

Outcome measures

Main outcome measures: Daily mean SBP and mean SBP when delivery, daily mean DBP and mean DBP when delivery, full-term birth rate (full-term birth: delivery between 37 weeks and less than 42 weeks of pregnancy; preterm birth: delivery between 28 weeks and less than 37 weeks of pregnancy; retarded birth: delivery after 42 weeks of pregnancy and later), eutocia rate and Apgar score.

Apgar score: (1) Skin color: Blue or pale all over as 0 point, blue at extremities as 1 point and body pink as 2 points. (2) Heart rate: absent as 0 point, <100 beats/minute as 1 point and >100 beats/minute as 2 points. (3) Reflex irritability: no response as 0 point, grimacing or feeble cry as 1 point, and grimacing, cough and sneeze as 2 points. (4) Muscule tone: limp as 0 point, slight limbs flexion as 1 point and active movement as 2 points. (5) Respiratory effort: no or slow as 0 point, irregular as 1 point and normal or strong cry as 2 points. Among them, 8-10 points were normal, 4-7 points means mild asphyxia, and 0-3 point(s) severe asphyxia. The score was carried out at 1, 5 and 10 minutes after birth.

Secondary outcome measure: Neonatal mortality.

Statistical methods

SPSS17.0 software was used for analyzing the data. All count data were expressed as case number/percentage (n/%), and chi-square test was used. All measurement data were expressed as mean ± standard deviation ($\bar{x}$ ± sd), and independent sample t-test was used for comparison between groups. When $P<0.05$, the difference is considered to be statistically significant.

Results

General information

There were no statistically significant differences in age, gestational week, body mass index, and Time interval between diagnosis of hypertension and inclusion to the study (week)

Table 2. Comparison of full-term birth rate

	Long-acting group (n=150)	Short-acting group (n=150)	χ^2	P
Full-term birth	122	107		
Preterm birth	16	30		
Retarded birth	12	13		
Full-term birth rate (%)	81.33	71.33	7.587	0.023

Table 3. Comparison of eutocia rate ($\bar{x}$ ± sd)

	Long-acting group (n=150)	Short-acting group (n=150)	χ^2	P
Eutocia	116	95		
Cesarean delivery	34	55		
Eutocia rate (%)	77.33	63.33	7.045	0.008

Table 4. Comparison of apgar scores ($\bar{x}$ ± sd)

	Long-acting group (n=150)	Short-acting group (n=150)	t	P
1 min	7.45±2.33	6.36±2.47	3.932	<0.001
5 min	8.39±1.27	7.27±1.64	6.613	<0.001
10 min	9.37±0.63	8.28±1.24	9.598	<0.001

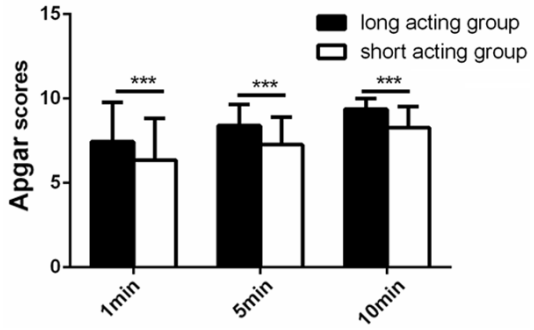

Figure 3. Comparison of apgar scores. 1 min: 1 min after birth; 5 min: 5 min after birth; 10 min: 10 min after birth. Compared with short-acting group at the same week, ***P<0.001.

between the two groups of patients. See **Table 1**.

Comparison of SBP

There was no statistically significant difference in the SBP between the two groups of patients before taking antihypertensive drugs. The long-acting group had a more stable decrease in blood pressure than the short-acting group after 1-18 weeks of taking antihypertensive drugs, with statistically significant differences (all P<0.05). See **Figure 1**.

Comparison of DBP

There was no statistically significant difference in the DBP between the two groups of patients before taking antihypertensive drugs. The long-acting group had a more stable decrease in blood pressure than the short-acting group after 1-18 weeks of taking antihypertensive drugs, with statistically significant differences (all P<0.05). See **Figure 2**.

Comparison of full-term birth rate

The long-acting group had a significantly higher full-term birth rate than the short-acting group, with a statistically significant difference (P<0.05). See **Table 2**.

Comparison of eutocia rate

The long-acting group had a significantly higher eutocia rate than the short-acting group, with a statistically significant difference (P<0.01). See **Table 3**.

Apgar score

The long-acting group had a significantly higher Apgar score than the short-acting group at 1, 5 and 10 minutes after neonatal birth, with statistically significant differences (all P<0.05). See **Table 4** and **Figure 3**.

Comparison of neonatal mortality

The long-acting group had a significantly lower neonatal mortality than the short-acting group, with a statistically significant difference (P< 0.05). See **Table 5**.

Discussion

PIH, as the main cause of maternal and perinatal death, is very common and often complicated with obstetric hemorrhage, infection and convulsion [9]. If not diagnosed and treated in time, it will develop into pre-eclampsia and eclampsia, thereby seriously affecting the maternal and neonatal health [2, 10]. So, early intervention for PIH is essential. At present, PIH is mainly treated by drugs in clinic. However, drugs used during pregnancy will enter the

Table 5. Comparison of neonatal mortality

	Long-acting group (n=150)	Short-acting group (n=150)	t	P
Survival	148	128		
Death	2	22		
Mortality rate	1.33%	14.67%	16.350	0.000

fetus through placental barrier, and some will affect the development of fetal organs, causing fetal malformation and death [11]. Therefore, with regard to a special group, reducing the risk of medication on pregnant women has been concerned by the medical field.

Nifedipine is a drug commonly used in clinical treatment for anti-hypertension and prevention of angina pectoris [12]. Nifedipine tablets are mainly divided into long-acting and short-acting tablets. Short-acting nifedipine tablets are generally maintained for approximately 5 hours, and must be taken 3 times a day. Otherwise they may not have the effective antihypertensive effect. The short-acting nifedipine has a short duration of efficacy but a fast onset and action time, taking only 3-15 minutes. Long-acting nifedipine tablets can maintain the antihypertensive effect for more than 24 hours, usually only once a day. They have a longer action time to achieve the antihypertensive effect, generally taking approximately 7 days [13]. Some literatures show that the short-acting nifedipine has a fast onset time but a short-acting effect, with an excessive fluctuation of blood drug concentration and unstable depressurization. Tsuburaya et al. find that the long-acting nifedipine is not affected by PH value in the body, gastrointestinal peristalsis and food, with slow, steady drug release and lasting, stable depressurization [14]. This study found that the mean SBP and the mean DBP of pregnant women with PIH could be reduced after taking the short-acting nifedipine, while the long-acting nifedipine had a more significant antihypertensive effect and longer duration. The results of this study are consistent with the findings of Tsuburaya. At present, nifedipine sustained-release tablets are gradually used in PIH for depressurization in clinic, which have a longer duration on the vasodilatation of spasm.

The long-acting nifedipine can not only be used for antihypertensive treatment, but also inhibits the excitation-contraction coupling of uterine smooth muscle. Studies show that nifedipine, which can be used in obstetric field, significantly inhibits uterine contraction and protects the fetus [15, 16]. This study found that pregnant women with PIH using the long-acting nifedipine for depressurization had a significantly higher eutocia rate (77.33%) than those using the short-acting nifedipine (63.33%), but a slighter intrauterine distress and lower fetal mortality (1.33% vs 14.67%). Moreover, the long-acting group had a significantly higher full-term birth rate than the short-acting group. The possible reason is that the activity of myometrium is directly related to the free activity of calcium ions, so the reduced calcium ion concentration inhibits the uterine contraction. Nifedipine is a calcium channel blocker. It prevents extracellular calcium ions from flowing into the uterine muscle cell membrane by affecting the voltage-dependent calcium channel on the surface of the muscle cell membrane, thereby reducing the intracellular calcium concentration and relaxing the uterus. As a result, the uterine contraction is inhibited [17, 18]. At the same time, it inhibits the release of oxytocin and prostaglandin. Nifedipine's inhibiting the uterine contraction is comparable to that of β receptor agonists. Many foreign studies conclude that calcium channel blockers, especially nifedipine, are safer and more effective [19-21].

There are many shortcomings in this observation, which need further improvement and research. It is summarized as follows: (1) due to the limited time and small case number in this study, there may be some errors in data statistics. The sample size should be further expanded to minimize statistical errors, so that the results will be more convincing. (2) Due to the limited time and funding support, there are some shortcomings in the number and objectivity of outcome measures in this study. The antihypertensive effect and clinical efficacy of two kinds of nifedipine on different PIH classifications should be complemented in the subsequent research design and the subject. In addition, double-blinded and multi-center studies should be performed to reduce personal errors.

In summary, the long-acting nifedipine in pregnant women with PIH has a more stable antihypertensive effect and longer duration compared to the short-acting nifedipine. Meanwhile, it can effectively improve the eutocia

rate of pregnant women and reduce the incidence of neonatal intrauterine distress and death, protecting the neonatal health, which is worthy of the clinical promotion.

Disclosure of conflict of interest

None.

Address correspondence to: Xiumei Shen, Department of Gynaecology and Obstetrics, Tengzhou Maternal and Child Health Hospital, No.3966 Longquan Road, Tengzhou City, Zaozhuang City 277500, Shandong Province, China. Tel: +86-13793720489; E-mail: shenxiumei0489@163.com

References

[1] Li B, Yang HX, Zhang WY, Shi YD, Qin ST, Wei YM, He YD, Yang WS, Jiang SJ and Jin HY. Gestational Hypertension. Pregnancy Hypertension 2016; 50: 705-10.

[2] Ayansina D, Black C, Hall SJ, Marks A, Millar C, Prescott GJ, Wilde K and Bhattacharya S. Long term effects of gestational hypertension and pre-eclampsia on kidney function: record linkage study. Pregnancy Hypertens 2016; 6: 344-9.

[3] Shen M, Smith GN, Rodger M, White RR, Walker MC and Wen SW. Comparison of risk factors and outcomes of gestational hypertension and pre-eclampsia. PLoS One 2017; 12: e0175914.

[4] Koopmans CM, Bijlenga D, Groen H, Vijgen SM, Aarnoudse JG, Bekedam DJ, van den Berg PP, de Boer K, Burggraaff JM, Bloemenkamp KW, Drogtrop AP, Franx A, de Groot CJ, Huisjes AJ, Kwee A, van Loon AJ, Lub A, Papatsonis DN, van der Post JA, Roumen FJ, Scheepers HC, Willekes C, Mol BW and van Pampus MG. Induction of labour versus expectant monitoring for gestational hypertension or mild pre-eclampsia after 36 weeks' gestation (HYPITAT): a multicentre, open-label randomised controlled trial. Lancet 2009; 374: 979-88.

[5] Bhageerathy P, Thomas V, Regi A and Jose R. Induction of labour versus conservative management for mild gestational hypertension at term. J Matern Fetal Neonatal Med 2017; 689-695.

[6] Gong XJ. Clinical significance by urine microalbumin and serum cystatin C detection in gestational hypertension. Chinese Journal of Modern Drug Application 2017.

[7] Shekhar S, Gupta N, Kirubakaran R and Pareek P. Oral nifedipine versus intravenous labetalol for severe hypertension during pregnancy: a systematic review and meta-analysis. BJOG 2016; 123: 40-47.

[8] Chen Y. Effect of magnesium sulfate combined with nifedipine on hemorheology indexes of patients with gestational hypertension. China Medicine & Pharmacy 2017.

[9] Nobumoto E, Masuyama H, Maki J, Eguchi T, Tamada S, Mitsui T, Eto E, Hayata K and Hiramatsu Y. Comparison of kidney function between gestational hypertension and pre-eclampsia. Acta Medica Okayama 2017; 71: 161.

[10] Magnus MC, Miliku K, Lawlor DA, Felix JF, Jaddoe VWV, Bonilla C and Fraser A. Association of vitamin D concentrations with gestational hypertension and pre-eclampsia: a mendelian randomisation analysis. Lancet 2016; 388: S72.

[11] Guy GP, Ling HZ, Garcia P, Poon LC and Nicolaides KH. Maternal cardiac function at 35-37 weeks' gestation: prediction for preeclampsia and gestational hypertension. Ultrasound Obstet Gynecol 2017; 49: 61-66.

[12] Sharma KJ, Greene N and Kilpatrick SJ. Oral labetalol compared to oral nifedipine for postpartum hypertension: a randomized controlled trial. Hypertension Pregnancy 2017; 36: 44-47.

[13] Ren XP. Comparative analysis of clinical efficacy of short acting and long-acting nifedipine treatment of hypertension in pregnancy. Jilin Medical Journal 2016.

[14] Tsuburaya R, Takahashi J, Nakamura A, Nozaki E, Sugi M, Yamamoto Y, Hiramoto T, Horiguchi S, Inoue K, Goto T, Kato A, Shinozaki T, Ishida E, Miyata S, Yasuda S and Shimokawa H. Beneficial effects of long-acting nifedipine on coronary vasomotion abnormalities after drug-eluting stent implantation: the NOVEL study. European Heart Journal 2016; 3: ehw256.

[15] Yousuf F, Naru T and Sheikh S. Effect of body mass index on outcome of labour induction. J Pak Med Assoc 2016; 66: 598.

[16] Edwards R, Szychowski J, Berger J, Petersen M, Ingersoll M, Braescu AB and Lin M. Foley catheter compared with the controlled-release dinoprostone insert: a randomized controlled trial. Obstet Gynecol 2014; 210: S278-S279.

[17] Kashif M, Manna PP, Akhter Y, Alaidarous M and Rub A. Screening of novel inhibitors against leishmania donovani calcium ion channel to fight leishmaniasis. Infect Disord Drug Targets 2017; 17: 120-129.

[18] Nettey H, Allotey-Babington GL, Nguessan BB, Afrane B, Tagoe M, Ababio A, Botchway P, Darko Y, Sasu C and Nyarko A. Screening of anti-infectives against leishmania donovani. Advances in Microbiology 2016; 6: 13-22.

[19] Muñozpérez VM, Fernándezmartínez E, Poncemonter H and Ortiz MI. Relaxant and anti-inflammatory effect of two thalidomide analogs

as PDE-4 inhibitors in pregnant rat uterus. Korean J Physiol Pharmacol 2017; 21: 429-437.

[20] Kiwilsza A, Milanowski B, Drużbicki K, Jenczyk J, Jarek M, Mielcarek J, Lulek J, Pajzderska A and Wąsicki J. Molecular dynamics and the dissolution rate of nifedipine encapsulated in mesoporous silica. Microporous & Mesoporous Materials 2017; 250: 186-194.

[21] Ebrahimi A, Saffari M and Langrish T. Improving the dissolution rate of hydrophobic drugs through encapsulation in porous lactose as a new biocompatible porous carrier. Int J Pharm 2017; 521: 204-213.