Adaptive dose response pilot study of intravaginal Prostaglandin E2 application in free farrowing sows during parturition

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Research

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Abstract

Background

The duration of birth is an important factor influencing the survival of piglets and the health of sows. A prolonged parturition is usually treated with oxytocin, even though several undesirable side effects are described. Therefore, the aim of this study was to evaluate the safety and efficacy of Prostaglandin E2 (PGE2) of different concentrations as an intravaginal applied gel in sows.

Methods

Twelve sows were randomly allocated to one of four treatment groups: Group I (control group) application of placebo gel; Group II application of 2.0 mg PGE2; Group III application of 1.0 mg PGE2; Group IV application of 0.5 mg PGE2. The gel was administered intravaginal after the birth of the fourth piglet. Total duration of birth (time between first piglet and last placenta), piglet interval and placenta expulsion duration (time between first and last placenta) were recorded, and each piglet was scored for meconium staining and vitality. Furthermore, stillborn piglets were categorized into ante-partum and intra-partum deaths.

Results

Although no significant differences between the groups were detected, a beneficial tendency in several parameters was observed in group III. The duration of birth was 284 min (average of 14.3 piglets per litter), whereas in all other groups it was more than 400 min (average of 18.0 piglets per litter). The piglet interval was 10.1 min in group II compared to 10.2 min in group III, 16 min in group IV and 21.4 min in group I. In group III the placenta expulsion duration was 119 min in contrast to the other groups with more than 266 min. Severe meconium staining in more than 10% of piglets was observed in group II and IV. Moreover, piglets of group II showed oedematous and haemorrhagic umbilical cords, lethargy and anoxia, and intra-partum deaths were recorded.

Conclusion

Although the sample size is limited in this study, it is assumed that an application of 1mg PGE2 intra-partum instead of lower or higher dosages has the most beneficial effects on the birth process in sows and on the vitality of piglets. Further investigation is necessary to confirm the positive effect of PGE2 in daily practise.

Introduction

The duration of birth is an important factor for the survival of piglets and the health of the sow (Oliviero et al., 2010). Due to a steady increase in litter size in modern pig production, the duration of birth has increased leading to a negative impact on subsequent fertility in sows (Vanderhaeghe et al., 2010). A prolonged duration of birth increases the risk of postpartal disorders such as post-partum dysgalactia

syndrome (PPDS) and retained placentas (Oliviero et al., 2013). Furthermore, an increased duration of birth results in an elevated number of still- or weak born piglets (Vanderhaeghe et al., 2010). Therefore, a prolonged parturition is usually treated with oxytocin, a potent uterotonic agent, even though several undesirable side effects such as higher amounts of umbilical cord ruptures, meconium staining and weak or stillborn piglets have been described (Mota-rojas et al., 2005, 2006). Due to these reasons, Prostaglandin E2 (PGE2) is used as alternative drug for the induction and assistance of labour in human medicine. PGE2 increases the uterine contractions in intensity but not in frequency unlike oxytocin, which increases intensity and frequency, thus leading to insufficient perfusion of placentae and foetuses. Another very important benefit of PGE2 is the ripening of an unfavourable cervix (Feltovich et al., 2005; Hirsbrunner et al., 2000; Ruan et al., 2011). In addition, PGE2 influences the endogenous oxytocin release and therefore has a direct contractile effect on uterine smooth muscle (Chuck and Huffaker, 1995; Ruan et al., 2011). All these actions result in an increase of Bishop's score (Hostinská et al.), more active labour, fewer failed inductions and less caesarean sections (Chuck and Huffaker, 1995). As every drug provides side effects, seldom-occurring side effects of PGE2 are mainly gastrointestinal disorders such as diarrhoea (Rivière et al., 1991; Wing et al., 1995). Hence, all these effects of PGE2 would be an improvement for the swine industry. Therefore, the aim of this study was to evaluate the safety and efficacy of PGE2 as an intravaginal applicable alternative on the birth process of the sow. In order to elaborate the optimal dosage in daily practice, an adaptive dose response pilot study with three different concentrations (2 mg, 1 mg and 0.5 mg) of PGE2 applied after the fourth piglet was conducted.

Materials And Methods

Twelve crossbred (Large White x Landrace) sows were included in the study and were kept in free farrowing pens. The sows received a commercial diet two times a day via an automated liquid feeding system and had unlimited access to water from a bowl drinker. All sows received straw as rooting and nest building material. To evaluate the effect of PGE2 on the parturition process, following treatment groups were established.

Group I (control, n = 3) intravaginal application of 1.2 mL sterile gel (KY Jelly®, Johnson and Johnson)

Group II (n = 3) intravaginal application of 2 mg of PGE2 in 1.2 mL gel (Prostin®E2, Pfizer)

Group III (n = 3) intravaginal application of 1 mg of PGE2 in 1.2 mL gel (Prostin®E2, Pfizer)

Group IV (n = 3) intravaginal application of 0.5 mg of PGE2 in 1.2 mL gel (Prostin®E2, Pfizer)

The body weight, parity number and the back fat thickness of sows were assessed, when they entered the farrowing unit. Back fat thickness of the sows was measured at the P2-position (6.5 cm off the midline and over the last rib) using an ultra-sonographic devise (iScan, Draminski, Poland). After the expulsion of the first piglet, the data collection for the birth process started. The mean observation time during parturition was 7.9 minutes (Min: 1.5, Max: 10.2). At each observation, new-born piglets were recorded and each piglet was scored for meconium staining (Mota-rojas et al., 2005) and vitality. Furthermore,

stillborn piglets were categorized into type one (greyish, oedematous piglet, ante partum death) or type two (fresh dead piglet, intra partum death) deaths (Mota-rojas et al., 2005). Additionally, the expulsion of placenta parts that had been expulsed at once, were recorded. Within a maximum of 3 minutes after expulsion of the fourth piglet, the group specific treatment was applied. The observation was conducted until expulsion of the last placenta, which was determined retrospectively.

The following parameters were recorded or calculated with regard to each parturition: farrowing duration (time between first and last piglet), total duration of birth (time between first piglet and last placenta), piglet interval (before and after treatment), placenta expulsion duration (time between first and last placenta), first placenta expulsion (expulsion of first placental part relative to last piglet) and last placenta expulsion (expulsion of last placental part relative to last piglet).

Data recording and analysis

Data were collected using structured and standardised data collection forms. All data were entered into a spreadsheet program (Microsoft Office Excel 2016). Continuous variables were first tested for normality and homogeneity of variance using a Shapiro-Wilk normality test. If these assumptions were met, then differences among the four groups were evaluated using a one-way Analysis of Variance (ANOVA) model. The level of statistical significance was considered being $P < 0.05$. Data were analysed using NCSS 12 Data (NCSS 12 Statistical Software (2018). NCSS, LLC. Kaysville, Utah, USA, ncss.com/software/ncss).

Results

In total twelve sows of one farrowing batch, randomly assigned to one of four treatment groups, were included in the study. No significant difference between parameters of the four treatment groups were observed at the beginning of the trial. The mean parity of the sows was 4.1 (SD: ± 2.6), the mean body weight was 255 kg (SD: ± 42.8) and the mean back fat was 13.4 mm (SD: ± 3.7). An overview of all parameters of the different groups is provided in Table 1.

Table 1

Descriptive statistics of the collected parameters in the peripartum period of the four different treatment group containing three animals. No significant differences between the groups could be detected.

	Placebo	0.5 mg PGE2	1.0 mg PGE2	2.0 mg PGE2
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD
Sow traits				
Body weight (kg)	267.3 ± 27.7	250.3 ± 67.2	242.3 ± 55.3	260 ± 3 4.5
Back fat (mm)	10.9 ± 3.3	13.1 ± 6.9	11.9 ± 1.3	9.7 ± 2.4
Litter number (n)	4.6 ± 2.5	4.6 ± 3.5	2.3 ± 2.3	4.6 ± 2.8
Litter weight (kg)	20.9 ± 1.6	21.1 ± 6.1	18.3 ± 1.6	28.5 ± 2.3
Number of total born piglets (n)	16.7 ± 3.8	17 ± 4.4	14.3 ± 2.8	20.3 ± 0.6
Number of still born piglets Typ2 (%)	0	7.9 ± 2.8	0	8 ± 9.8
Farrowing traits				
Farrowing duration (min)	296 ± 166.7	252.7 ± 137.6	139.7 ± 2.1	195.7 ± 109.9
Farrowing + placenta expulsion duration (min)	553.7 ± 114.2	456 ± 167.9	284.7 ± 40.5	404.7 ± 256
Piglets traits				
Piglets interval (min)	17.9 ± 6.0	15.6 ± 6.0	10.8 ± 2.9	9.9 ± 5.3
Piglets interval before treatment (min)	23.5 ± 8.8	11.3 ± 5.1	10.5 ± 4.1	10.6 ± 4.5
Piglets interval after treatment (min)	16 ± 8.3	16.6 ± 6.5	10.7 ± 2.4	9.9 ± 5.4
Number of meconium stained piglets Score 0 (%)	73 ± 8.2	31.7 ± 10.7	70.3 ± 19.1	52.3 ± 10.8
Number of meconium stained piglets Score 1 (%)	29.7 ± 1 0.0	54.0 ± 19.3	23.3 ± 21.7	36.0 ± 5.3
Number of meconium stained piglets Score 2 (%)	4.0 ± 3.6	12.3 ± 21.4	6.7 ± 6.5	11.7 ± 7.6
Placenta expulsion traits				
Placenta expulsion duration (min)	364 ± 120	289 ± 144.1	119 ± 46.13	266.3 ± 180.3
Time from last piglet to first placental part (min)	-111.5 ± 97.25	-85.7 ± 114	26 ± 30.5	-57.3 ± 37.5

	Placebo	0.5 mg PGE2	1.0 mg PGE2	2.0 mg PGE2
Time from last piglet to last placental part (min)	257.7 ± 230.7	203.3 ± 43.7	145 ± 42.0	203.3 ± 152.2
	Median (Min-Max)	Median (Min-Max)	Median (Min-Max)	Median (Min-Max)
Sow traits				
Number of still born piglets (n)	0 (0–1)	1 (1–3)	0 (0–2)	1 (0–4)
Number of still born piglets Typ 1 (%)	0 (0–2)	0 (0-1.9)	0 (0-4.6)	0 (0–0)
Piglets traits				
Reanimation of piglets (%)	0 (0–0)	0 (0–5)	0 (0–0)	5 (4.8–10)
Umbilical cord lesions (%)	0 (0–0)	0 (0-10.5)	0 (0-18.8)	5 (0-23.8)
Placenta expulsion traits				
Expelled placental parts (n)	5 (2–7)	6 (6–7)	5 (4–5)	8 (7–12)

The statistical analysis revealed no significant differences between the four groups in regards to the outcome variables. A trend was observed for the mean farrowing duration, which was shorter in group III compared to all other groups. The same trend was also observed for the total duration of birth. The mean duration of birth was 285 min in group III, and more than 400 min in all other groups. Despite the fact that differences were counted in the number of total born piglets per litter, an overall effect of PGE2 on the piglet-to-piglet interval was observed, when compared to placebo. The shortest average piglet-to-piglet interval was observed in group II, followed by group III with a prolongation of less than 1 minute on average, and group IV and group I with more than 4 minutes longer lasting intervals between two piglets. More detailed information about the piglet interval before and after treatment is provided in Table 1.

The shortest mean placenta expulsion duration was found in group III with more than 170 minutes difference compared to the other groups. Interestingly, group III and I had the same amount of placenta parts (median of five), whereas group II and IV had more than six placenta masses. Further information about the placenta expulsion traits is provided in Table 1.

The results of the different treatment groups regarding the meconium staining are presented in Fig. 1. In addition, umbilical cord lesions in live born piglets, such as oedematous and haemorrhagic umbilical cords, were observed in group II, group III and group IV (Fig. 2). A reanimation procedure due to anoxia and lethargy was only needed in piglets of group II and group IV (Fig. 3)

Discussion

This is the first study describing the effect of PGE2 in farrowing sows and the impact on piglets' health during the birth process. The time point of application was chosen based on a data set of a study describing the influence of time at which oxytocin was administrated during labour in sows (Mota-Rojas et al., 2007). Administration of the drug after expulsion of the fourth piglet had the highest impact on the birth duration and only mild side effects on the piglets' health (Mota-Rojas et al., 2007).

In order to evaluate the effect of PGE2, a proof-of-concept as an adaptive dose response pilot trail was conducted to efficiently gain more information about the dose response in farrowing sows. These data can be utilized for an informed decision, which dosage should be used for further investigations. The small sample size with only three animals per group is a major limitation of this pilot study. However, this study design has been chosen, because it is sufficient to obtain first and novel information about the dose response to PGE2 in sows (Cook et al., 2015; Miller et al., 2014; Smith et al., 2006).

Considering the limitations, this study still showed a trend in dose-dependent effects of PGE2 administered after the fourth piglet on the overall birth process. The shortest farrowing duration and shortest total duration of birth could be detected in the group III with a mean of 140 min and 285 min, respectively. Comparing the results with the group I (farrowing duration: 296 min; total birth duration: 554 min) and the farrowing duration of sows in free farrowing from literature (Oliviero et al., 2008; Hales et al., 2015), this is notably a very short birth duration, which has not been described so far. Taking the effect of PGE2 on duration of birth into account, this might be a good alternative drug to oxytocin, because it is assumed to also decrease the risk for postpartal diseases in sows. Notwithstanding, the most optimal piglet interval (9.9 min) has been observed in the group treated with the highest dose of PGE2, followed by group III (10.8 min), whereas the group with the lowest dose of PGE2 showed no beneficial effect. Based on these findings, we can conclude that PGE2 in the concentrations of 1 mg and 2 mg has an uterotonic effect in sows, as known from human medicine (Chuck and Huffaker, 1995). The intravaginal application route of PGE2, like in women, was chosen to improve animal welfare and to establish a safe and effective route of application that can be used by farmers, when accommodating free farrowing sows. Due to significant similarities between swine and human vaginal mucosa, the swine vaginal mucosa has been proven to be the gold standard as in vitro model for the transmucosal absorption of drugs (Squier et al., 2008). Therefore, it can be assumed, that intravaginal applied PGE2-gel, which was designed for human medicine, can also be absorbed by swine mucosa. However, there is still a species difference and the absorption of certain agents might remain slightly unequal. An example has been described for oxytocin, where the transvaginal absorption is 53% more efficient in the sow compared to the absorption in human vaginal tissue (Eyk and Bijl, 2005). In this pilot study a higher effect in sows when using the human dosage (2 mg PGE2) was observed, which might be related to the effect of absorption as mentioned.

The significant percentage of weak- and stillborn piglets are a major problem of intensive pig production systems and cause ethical discussions in the society (Vanderhaeghe et al., 2010). Therefore, one outcome variable in this dose finding study was piglets' distress. A proven indicator of intrauterine foetal distress is the meconium-stained skin of the piglets after birth (Mota-Rojas et al., 2002). In this pilot study,

severe meconium staining was found in the placebo group and in all PGE2 groups. Some degree of distress caused by foetal hypoxia during birth seems to be physiological due to compression of the umbilical cord when the foetus enters the pelvis. Severe meconium staining in piglets from sows with a placebo treatment were described in a study from Mexico in 1.1% of the born piglets (Mota-Rojas et al., 2002). An explanation for this low percentage compared to group P might be that the average number of total born piglets was just 9.6 compared to 16.7 in this study. Late born piglets are likely to suffer asphyxiation to a greater degree because of the cumulative effects of successive uterine contractions. These piglets have a greater predisposition to get in a hypoxia state which can provoke sever distress and thereby sever meconium-stained skin in piglets (Mota-Rojas et al., 2002). Furthermore, piglets that take longer to be born are more likely to have umbilical cord lesions at birth. The importance of an intact umbilical cord to improve piglets' survival up to three days after birth has been shown in one study (Rootwelt et al., 2013). In the present study, the highest percentage of umbilical cord lesion was recorded in group II. Interestingly, there was no association found between umbilical cord lesions and the meconium scoring or the birth order. In comparison with other studies testing uterotonic substances (Mota-Rojas et al., 2002, 2005, 2006, 2007), we rarely found umbilical cord rupture, which can occur in up to 33% of normal deliveries. The main findings in the PGE2-groups were oedematous and haemorrhagic umbilical cords. Several factors can lead to such changes of the umbilical cord, occurring either prenatal or during the birth process and therefore is still under investigation in human medicine.

Further important clinical parameters for piglets' vitality were 'reanimation of piglets' and 'intra-partum deaths'. Both parameter were only detected in group II and IV. In group II strong uterine contraction in the sows were observed, which might have caused the high number of weak born piglets and intra-partum death. Strong uterine contraction was not observed in group IV. The reason for this high number of intra-partum death of group IV remains unclear and might be just by chance due to the small sample size. Sever hypoxia during delivery originates from the uterus, umbilical cord or placenta. In humans, placental dysfunction is considered the major cause of late foetal death (Mantakas et al., 2018). Because the pig placenta is epitheliochorial, the need for an adequately intimate connection between sow and the piglets is met by the large total surface area of the diffuse placenta. However, there is few data available about the interaction between placenta expulsion and piglets vitality during birth. An interaction may arise, when considering the relationship between the placental parts and the intrapartum death and reanimation in these groups, due to a placental dysfunction during birth.

Conclusion

In a dose finding study, the animal welfare, the beneficial efficiency and the safety of the product are curial factors. Therefore the sample size was limited with three sows per group. This pilot study revealed that an application of 1 mg PGE2 intra-partum has the most beneficial effects on the birth process in sows with only minor sides effect on the piglet vitality. Taking these factors and the results of this study into account, the best outcome for the sows and piglets was achieved with the intravaginal application of

1 mg PGE2 intrapartum after the birth of the fourth piglet. Further investigations are needed to confirm the positive effect of PGE_2 in daily practise.

Abbreviations

PGE2
Prostaglandin E2
PPDS
post-partum dysgalactia syndrome

Declarations

Availability of data and materials

The data supporting the conclusions of this article are available from the corresponding author on reasonable request.

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Contributions

AG and HN participated in study design and manuscript drafting; AG supervised the project; RB and AG collected the samples and performed the main experiments. All authors contributed to the development and the revisions of the manuscript and approved the final version.

Ethics declarations

Ethics approval and consent to participate

This study was conducted according to the Swiss law for Animal Welfare and approved by the cantonal veterinary office under the animal experiment announcement SO05/16.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Figures

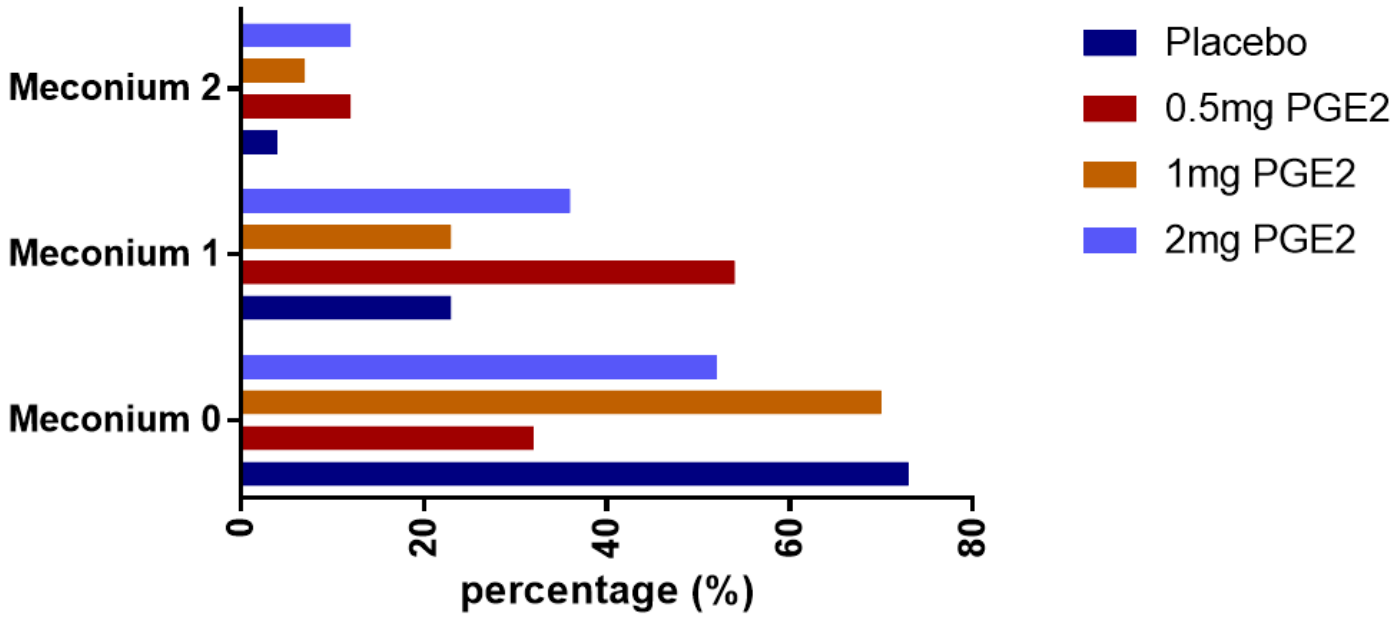

Figure 2

Comparison of the meconium scoring of the different four treatment groups.

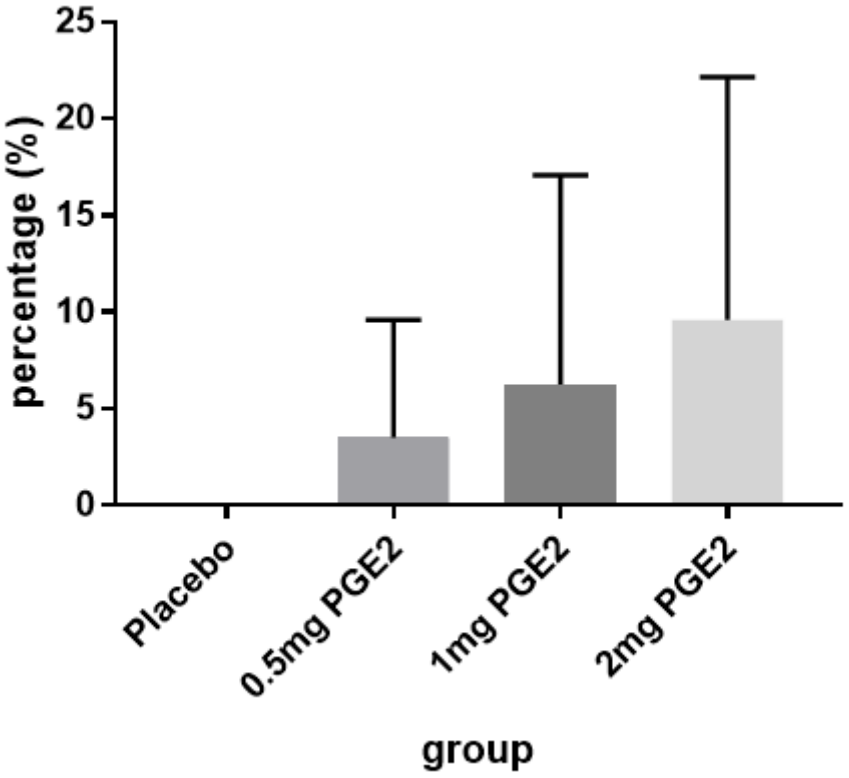

Figure 4

Comparison of the percentage of umbilical cord lesions in the four different treatment groups.

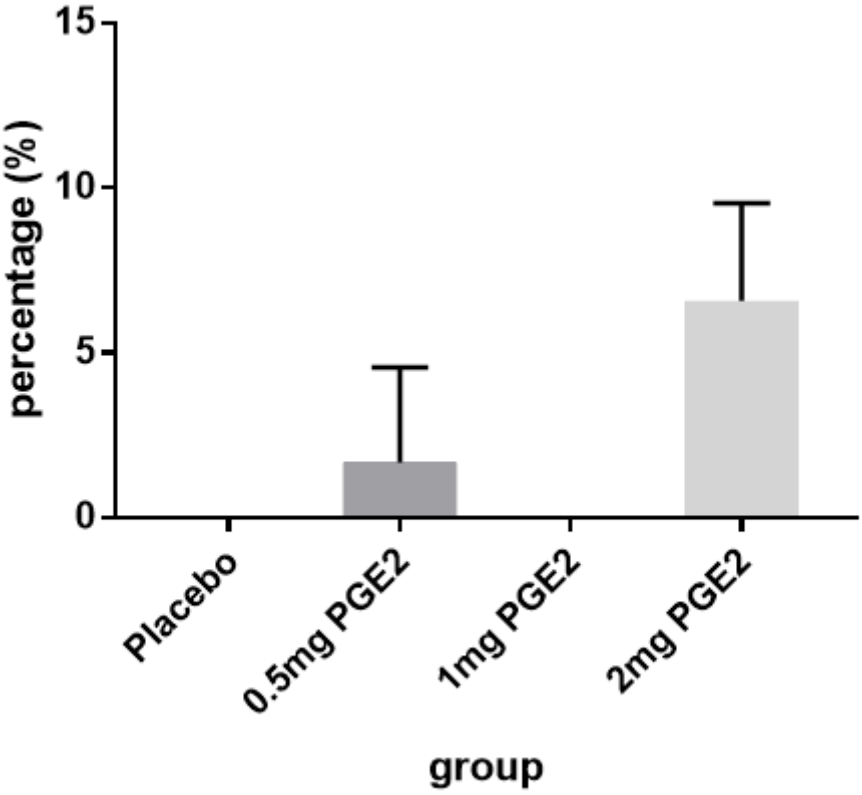

Figure 6

Comparison of the percentage of reanimation in the four different treatment groups.