

Multifetal Pregnancy Reduction: Use of Intra Cardiac Autologous Amniotic Fluid versus Potassium Chloride

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Abstract- Introduction : Feticide in multifetal pregnancy is being practised since last two decades for reduction of multifetal pregnancy or selective fetal termination of anomalous twin. Multifetal pregnancy reduction is particularly gaining importance due to rampant use of Assisted Reproductive Technology world over. However, still there are several issues associated with fetal reduction varying from the its actual requirement to different methods of practising it.

Objective: To compare the efficacy of intracardiac injection of autologous amniotic fluid versus potassium chloride and evaluate the fetomaternal outcome in high order multiple pregnancies (>2), who underwent multifetal pregnancy reduction (MFPR) to twins.

Methods: This was a prospective cohort study conducted in the Department of Maternal and Reproductive Health, Sanjay Gandhi Post Graduate Institute of Medical Sciences. 50 patients were enrolled in the study. Inclusion criteria was High order multiple pregnancy with more than 2 fetuses, Spontaneous conception or conceived via ovulation induction or In-Vitro-fertilization, gestation before 20 weeks. Exclusion criteria was mono chorionicity, even in higher order gestations like quadruplets.

All the reductions were done between 11-13 weeks, triplets were done in single session and quadruplets were done in two sittings. There can be various methods with which reduction can be practised. It can be done transabdominally or transvaginally. We did it transabdominally in the patients. Out of total 50 patients, 25 had instillation of amniotic fluid and 25 had KCl.

Results: We realize that both amniotic fluid and potassium chloride are equally effective agents for fetal reduction, however it appears that there are few advantages with each. The patients exposed to amniotic fluid did not suffer from spontaneous missed abortion. The pricks required to achieve asystole were similar in both the groups. The dosage and time to achieve asystole was significantly less in KCL group.

Conclusion: Multifetal pregnancy has got numerous social, psychological, medical issues. It is a procedure not free of complications. This comparative study demonstrates that, for a multifetal pregnancy reduction, KCl appears to be more effective, less time consuming agent compared from autologous amniotic fluid with similar rates of growth retardation, prematurity and LSCS. Both the groups also had similar mean birth weight and take home baby rates.

Index Terms- Multifetal Pregnancy Reduction (MFPR), Potassium Chloride, Amniotic Fluid

I. INTRODUCTION

Feticide in multifetal pregnancy is being practised since last two decades for reduction of multifetal pregnancy or selective fetal termination of anomalous twin. Multifetal pregnancy reduction is particularly gaining importance due to rampant use of Assisted Reproductive Technology world over. There has been a widespread increase in multifetal pregnancy. Lessons learnt in the past are that higher order pregnancies are associated with an increased risk of maternal complications as well as a high prevalence of prenatal and neonatal morbidity and mortality. However, still there are several issues associated with fetal reduction varying from its actual requirement to different methods of practising it.

The need and efficacy of reduction of high order (more than 2) multifetal pregnancy is proven in the literature. **Van de Mheen et al¹** compared the time to delivery and perinatal mortality in trichorionic triplet pregnancies electively reduced to twins with ongoing trichorionic triplets and primary dichorionic twins. They concluded that in women with a triplet pregnancy, fetal reduction increases gestational age at birth with 3 weeks as compared with ongoing triplets. The procedure is relatively safe, it has a abortion rate of 4 – 6.5%. It does not lead to any increase in rates of IUGR. **Brown et al³** analysed whether the intra-uterine growth performance of a twin pregnancy resulting from MFPR differs from that of an unreduced twin pregnancy. In their retrospective study they found that MFPR does not itself adversely influence intrauterine fetal growth.

Numerous agents exist for the purpose of reduction and there is a constant research to look for which is the preferred one amongst all. Henceforth, this study was planned with the objective to compare the efficacy of intracardiac injection of autologous amniotic fluid versus potassium chloride and evaluate the fetomaternal outcome in high order multiple pregnancies (more than 2), who underwent multifetal pregnancy reduction (MFPR) to twins.

II. MATERIAL AND METHODS

This was a prospective cohort study conducted in the Department of Maternal and Reproductive Health, Sanjay Gandhi Post Graduate Institute of Medical Sciences. 50 patients

were enrolled in the study. Inclusion criteria were high order multiple pregnancies with more than 2 fetuses, Spontaneous conception or conceived via ovulation induction or In-Vitro-fertilization, gestation before 20 weeks.

Exclusion criteria were monochorionicity, even in higher order gestations like quadruplets. The first step began with the counselling and guiding patients when making decisions regarding multifetal pregnancy reduction which included the various risks associated of multifetal pregnancy, the possible medical benefits of multifetal pregnancy reduction, and the complex ethical issues inherent in decisions regarding the use of multifetal pregnancy reduction.

It was the autonomous decision of the patient who must balance the relative importance of the medical, ethical, religious, and socioeconomic determinants and pursue the best course of action for her situation.

All the reductions were done between 11-13 weeks, triplets were done in single session and quadruplets were done in two sittings.

There can be various methods with which reduction can be practised. It can be done transabdominally or transvaginally. We did it transabdominally in the patients. Out of total 50 patients, 25 had instillation of amniotic fluid and 25 had KCl.

The reduction procedure consisted of intrathoracic KCl or autologous amniotic fluid injection into the area of fetal heart. The fetus with largest NT, smallest CRL, any suspicious morphology or obvious defect and farthest from the internal os was the preferred one to be reduced.

Maternal abdomen was prepped and draped, operator and assistant scrubbed and gowned. Ultrasound transducer placed in a sterile probe cover. Ultrasonographic guidance (voluson S8, GE healthcare) was used to insert a heparinised 20 gauge spinal needle into the thorax of the fetus to be aborted, and 0.5 – 2 ml (2 mEq/ml) of KCl was injected. If cardiac activity persisted after initial 0.5 ml, additional KCl was administered.

In the amniotic fluid group, amniotic fluid was aspirated or drained first to fill the puncture needle until 0.5 mL of amniotic fluid¹³ was loaded in a 1-mL syringe. The needle was then advanced into the intrathoracic cavity. We injected 0.1-mL amniotic fluid each time and wait for 2 minutes to repeat until heartbeat ceased immediately.

The dosage of KCl is comparative to other studies^{10,11,12} who also used 4 to 8 mEq KCl.

The fetus was monitored by sonography until its heart stopped beating. Total cessation of heartbeat was observed for 5 min to ascertain asystole before removal of needle. Contrary to other studies¹¹ postoperative oral antibiotics (ampillicin 500mg thrice daily) was given for 5 days. Additionally intramuscular progesterone 500 mg was also given. Ultrasound ere done before discharging the patient the patient from daycare to ensure success of procedure and to evaluate any evidence of sub chorionic bleeding and assessment of viability of remaining foetuses.

Patients returned for follow-up ultrasonography within 1 week of the procedure. The results of the follow-up ultrasound were recorded and pregnancy outcome information was collected in each case.

III. RESULTS

This was prospective cohort study, a total of 50 patients were enrolled in the study. 25 patients had amniotic fluid instillation and 25 had potassium chloride instillation. Both the groups had similar baseline characteristics. Age of the pregnant women varied between 27-33 years with mean age of patients was 33 years. There were 2 quadruplets in amniotic fluid group and 3 in KCl group. Gestational age at time of procedure ranged between 10 weeks \pm 4 days to 13 weeks \pm 4 days with mean gestational age of 11 weeks 4 days in amniotic fluid group and 11 weeks 6 days in potassium chloride group.

We realize that both amniotic fluid and potassium chloride are equally effective agents for fetal reduction; however it appears that there are few advantages with each. The patients exposed to amniotic fluid did not suffer from spontaneous missed abortion. The number of pricks required to achieve asystole were similar in both the groups (Figure2, table 1)

The dosage and the time required to achieve asystole was significantly lesser in potassium chloride group (Figure3, 4, table 2). This appeared probably because of tamponade like affect of amniotic fluid which requires higher dosage compared to KCl which acts with its ion like affect on heart causing cardiac arrest.

Statistical Analysis: Data was analyzed using Statistical Package for Social Sciences (SPSS) version 15.0. Chi-square test and Independent samples 't'-test was used to analyze the data. A "p" value less than 0.05 indicated a significant association.

Follow up of the patients showed three cases of spotting (which was managed conservatively) and one complete abortion (18wk quadruplet, which also had component of cervical incompetence) and no cases of missed abortion in amniotic fluid group. There were two cases of spotting which was managed conservatively and one case of missed abortion in KCl group both of which was not statistically significant. Two cases showed slight atypical presentation, one had irregular heart rate for 1 hr and finally asystole was achieved with additional 0.1ml and total of 0.3 ml. The other case had repeat procedure as fetal heart reappeared after 15min and 0.2ml was again injected.

There rates of were 2 cases of preterm delivery less than 32 weeks, 1 case of intrauterine death and 3 cases of discordant twins with IUGR in amniotic fluid group which was not significantly different from KCl group.

Mean gestational age at delivery was 35 weeks \pm 7 days in amniotic fluid group and 36 weeks \pm 7 days in potassium chloride group and both the groups had almost similar take home baby rate of 85 %. The mean (+/-SD) birth weight was 1.840+/- 200.44 g in amniotic fluid group and 1.832+/- 230.44 g in potassium chloride group (Table 3).

IV. DISCUSSION

Multifetal pregnancy reduction (MFPR) is an effective therapeutic option which reduces the maternal, prenatal, neonatal morbidity and mortality associated with multifetal pregnancies, most important being prematurity.

First trimester transabdominal or transvaginal fetal reduction is a now a recommended and effective alternative for

the management of multifetal pregnancy in assisted reproduction technique. There is constant increment in the literature regarding the methods and agents.

Various agents used are autologous amniotic fluid, potassium chloride, lidocaine and air embolism etc. Furthermore, there are modifications like elimination of use of any agent at all. Embryo aspiration and cardiac puncture have been reported with favorable outcomes, but it may be technically difficult or time-consuming at later gestational ages (4,9). On the contrary, intrathoracic injection of a toxic substance to block fetal blood flow would be less complicated and less time-consuming. Air embolism has been employed in fetal reduction, but the acoustic disturbance makes ultrasound images unclear. In this study, we injected amniotic fluid compared to KCl in efficacy particularly regarding dose and time to achieve asystole.

Mansour RT et al⁹ modified the technique of multifetal pregnancy reduction and studied the outcome. Cases were 75 patients with high-order multiple pregnancies resulting from assisted reproduction. Controls were 40 nonreduced twin pregnancies and 22 high-order multiple gestations. Transvaginal ultrasonically guided multifetal pregnancy reduction was performed. The first 30 cases were done using KCl as a cardiotoxic agent. The modified technique was used for the last 45 cases at an earlier gestational age (approximately 7 weeks) by eliminating the use of KCl and by aspirating the embryonic parts. Using the modified technique, the miscarriage rate was 8.8% and 41 patients delivered between 32 and 39 weeks of gestation (mean \pm -SD, 36.9 \pm -2.45 weeks). The mean (+/-SD) birth weight was 2,450.51 \pm -235.44 g. The miscarriage rate, fetal wastage rate, mean gestational age, and mean birth weight were similar in reduced and nonreduced twins and were significantly better than in non-reduced triplets and quadruplets. According to them, modified technique of multifetal pregnancy reduction by aspiration of embryonic parts significantly improved outcomes, which were similar to those of non-reduced twins resulting from assisted reproduction and significantly better than those of non-reduced triplets and quadruplets.

Intracardiac puncture without injection of any agent has also been reported by **G Iberico et al⁴**, in which they performed an intracardiac embryo puncture until asystole is verified, without the injection of any substances. Any aspiration of embryo tissues or amniotic fluid was avoided. A total of 149 multifetal pregnancies was reduced to twins ($n = 134$) or singletons ($n = 15$) at early gestational age (7.8 ± 0.8 weeks). Eleven cases (7.3%) of miscarriage, two cases (1.3%) of chorioamnionitis, and seventeen cases (11.4%) of transient spotting were recorded as postoperative complications. Vanishing of one embryo occurred in four cases (3.0%) of those reduced to twins. The baby take-home rate was 89.5% for twins and 80.0% for singletons. These studies show that early transvaginal intracardiac embryo puncture is an effective and safe technique.

The said disadvantage of reduction at this early gestation is that at a fact that some foetuses might spontaneously die and vanish without any intervention and additionally at around 11- 12 weeks we get an opportunity to see for nuchal thickness and few malformations which could guide us in choosing the fetus most prone to aneuploidy or malformation.

The use of potassium chloride has been reported in literature both intracardiac and intracranial. **Lembet A et al⁶** for the first

time in 2009 reported case series describing the technique of intracranial injection of potassium chloride during MFPR. In certain cases of MFPR, where difficulty is encountered in reaching the thorax due to the fetal position as well as the location of membranes and placenta, an alternative approach may be the insertion of the needle to the fetal cranium. This approach enables a technically easier procedure than the intrathoracic approach.

Recently in 2013, **Li R et al⁷** assess the effectiveness and feasibility of transabdominal intracranial KCl injection as an alternative to intrathoracic KCl injection for multifetal pregnancy reduction (MFPR) in the early second trimester. Amongst 40 cases who underwent fetal reduction between 12 and 18 weeks of gestation, 16 cases had intracranial injection and 24 cases had intrathoracic injection. These groups were compared for clinical procedures and outcomes. Intracranial injection needed significantly fewer punctures for each fetus than intrathoracic did (1.1 ± 0.2 vs. 1.4 ± 0.6), but both groups received similar doses of KCl (2.6 ± 0.8 ml vs. 2.6 ± 1.2 ml per fetus). All cases succeeded in the first procedure, with no heartbeat recovery. The two groups had similar miscarriage rates and gestational ages at delivery. MFPR by intracranial KCl injection was as effective as, but an easier procedure than intrathoracic KCl injection between 12 and 18 weeks of gestation according to their study.

We performed technique for MFPR by fetal transthoracic intracardiac injection of potassium chloride and autologous amniotic fluid. To our knowledge this kind of comparative study is never reported in the available literature. We found that potassium chloride has significantly lesser dose requirement and shortens time period to achieve asystole compared to amniotic fluid. Other parameters and outcome in both the groups were similar. **Shang-Gwo Horng et al¹³** had reported the only case reports of two triplet pregnancies containing monochorionic twins in which dichorionic twins were successfully preserved after sacrificing one of the monochorionic twins by employing amniotic fluid tamponade. The first case had preterm premature rupture of membranes (PPROM) occurred at 25 weeks of gestation. Both female fetuses failed to survive. In the second case, two healthy babies were delivered by cesarean section at 36 weeks of gestation. The female baby weighed 2100 gm and the male baby 2600 gm, respectively.

Compared to intracardiac amniotic fluid, intracardiac injection of KCl is a modality being practised since long. Long back in 1991, **Donner et al⁸** did multifetal pregnancy reductions during the first trimester of pregnancy in 26 patients. Transabdominal intrathoracic KCl injections were performed in 23 cases, and transcervical aspirations in 3 cases. There were 4 miscarriages (15%) during the second trimester, 18 pregnancies ended in 33 births, 4 pregnancies are going on uneventfully and are beyond 32 weeks. There was no maternal morbidity related to the procedure; fetal morbidity has been mild. Studies have shown an equal efficacy and loss rates between transabdominal versus transvaginal intracardiac KCl injection technique for fetal reduction¹¹.

If we look upon the transabdominal methods, **Berkowitz RL et al¹⁰** presented the outcome of 200 consecutive multifetal pregnancies in whom procedures were performed in the first trimester by the transabdominal injection of potassium chloride. At the time of the procedure 88 women had triplets, 89 had

quadruplets, 16 had quintuplets, and 7 had from 6 to 9 fetuses. These pregnancies were reduced to 189 sets of twins, 5 sets of triplets, and 6 singletons. Reductions to triplets were done at the patient's request, and reductions to singletons were only done for medical indications. There were no cases of chorioamnionitis or other maternal complications attributable to the procedure. A total of 181 women were delivered of one or more live infants after 24 weeks' gestation, and 19 (9.5%) lost all of their fetuses before that time. The mean gestational age for all women delivered after 24 weeks was 35.7 weeks. The mean gestational age at delivery varied inversely with the initial number of fetuses, from 36.1 weeks for women who presented with triplets to 33.8 weeks for those who had 6 or more fetuses. 16 of the 19 complete pregnancy losses occurred more than 4 weeks after the reduction procedure had been performed. The loss rates were 7.9% for those who presented with 3 or 4 fetuses, 12.5% for those with 5, and 42.9% for those with more than 6 and this trend was statistically significant. Two neonates died in the first week of life and one died at 10 months of age as a consequence of the sequel of severe prematurity. Only two surviving infants have shown evidence of chronic morbidity related to early delivery, and all of the others are developing normally. The incidence of intrauterine growth retardation was not increased over that anticipated in a population of twins.

As far as monochorionicity is concerned, it accounts for 30% of multiple pregnancies which occur at a significantly higher rate after ART procedures and could be an important complication after IVF-ICSI treatment. In our study we strictly believed in the fact that agent use to reduce fetus can affect the remaining one in a monochorionic pregnancy owing to the very unique vascular anastomosis seen in majority of monochorionic pregnancies and hence it was considered a contraindication for the procedure. Literature however has case reports for reduction being done in monochorionic pregnancies as well. Li Y et al⁵ reported a dichorionic quadramniotic quadruple gestation with monochorionic triamniotic triplets after intracytoplasmic sperm injection (ICSI) treatment and transfer of two embryos. After extensive counseling, selective reduction of two of monochorionic triamniotic triplets was done and a twin pregnancy remained. Reduction of monochorionic fetuses can be safer in higher order multifetal pregnancies where we actually reduce both twins of monochorionic pair. **Carol B. Benson et al**¹² reduced three quadruplet and two quintuplet gestations, each with a monochorionic pair of fetuses. In all the cases, reduction was performed by injecting one of the monochorionic pair with potassium chloride.

V. CONCLUSION

Multifetal pregnancy has got numerous social, psychological, medical issues. It is a procedure not free of

complications. ACOG has released a new committee statement² in February 2013 replacing the previous one in 2007 which clearly states that Fertility treatments have contributed significantly to the increase in multifetal pregnancies. The first approach to the problem of multifetal pregnancies should be prevention, and strategies to limit multifetal pregnancies, especially high-order multifetal pregnancies, should be practiced by all physicians who treat women for infertility.

This comparative study demonstrates that, for a multifetal pregnancy reduction, KCl appears to be more effective, less time consuming agent compared from autologous amniotic fluid with similar rates of growth retardation, prematurity and LSCS. Both the groups also had similar mean birth weight and take home baby rates.

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Pricks	KCl (n=25)		Amniotic Fluid (n=25)	
	No.	%	No.	%
1	16	64.00	13	52.00
2	8	32.00	10	40.00
3	1	4.00	2	8.00

$\chi^2=0.866$ (df=2); p=0.649 (NS)

Table 1: Comparison of number of pricks required

	Agent	N	Mean	Std. Deviation	
Dose	KCl	25	.3360	.13503	t=5.162; p<0.001 (S)
	Amniotic fluid	25	.5680	.17963	
Time	KCl	23	3.4130	1.22151	t=4.938; p<0.001
	Amniotic fluid	25	5.6400	1.81728	

Table 2: Comparison of dosage and timing

Parameters	Amniotic fluid (n = 25) Delivered N = 18 Aborted / missed/ IUD n = 1	KCL (n = 25) Delivered N = 17 Aborted / missed / IUD n = 1
Mean maternal age at procedure	33.6+/- 3.4	32.6+/- 3.4
Loss of entire pregnancy	1 (4%)	1 (4%)
Inj. Betamethasone coverage	100%	100 %
Gestational age of delivery	< 32wk	2
	32wk1 d -34wk	2
	34wk1d -37wk	11
	>37wk	1
Mode of Delivery	LSCS (10/10)=100%	LSCS (10/10)=100%
Mean Gestational age	35 weeks ± 7 days	35 weeks ± 7 days
20 neonates delivered	Amniotic fluid	Potassium chloride
Neonatal mortality	1 (5%)	1 (5%)
Mean Birth wt.	1.840+/-200.44 g	1.832+/- 230.44 g
Average stay in NICU	6+/-2.5days	7 +/-2.8 days
Requirement of Ventilator	2 (1.1kg bwt.)	2 (1.2 kg)

Table 3 : Outcome (35 out of 50 patients have delivered 15 ongoing pregnancies)

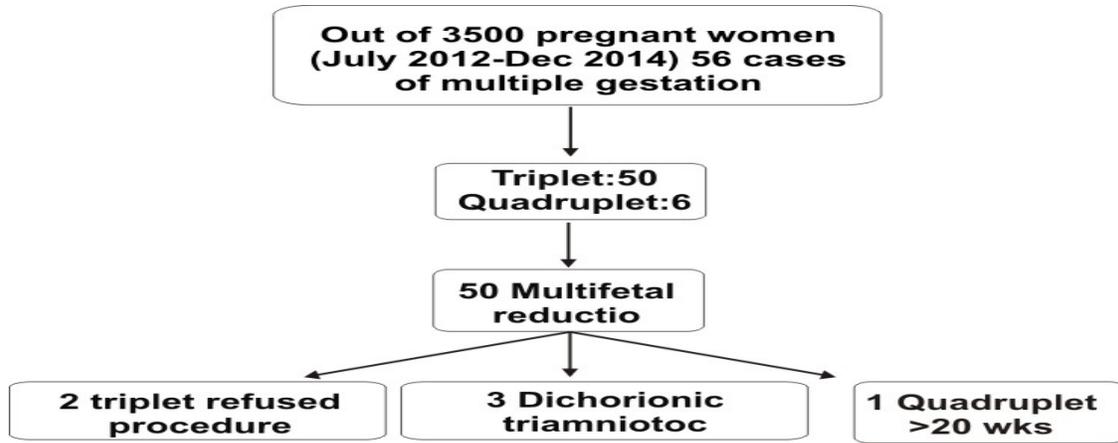


Figure 1. Study Protocol

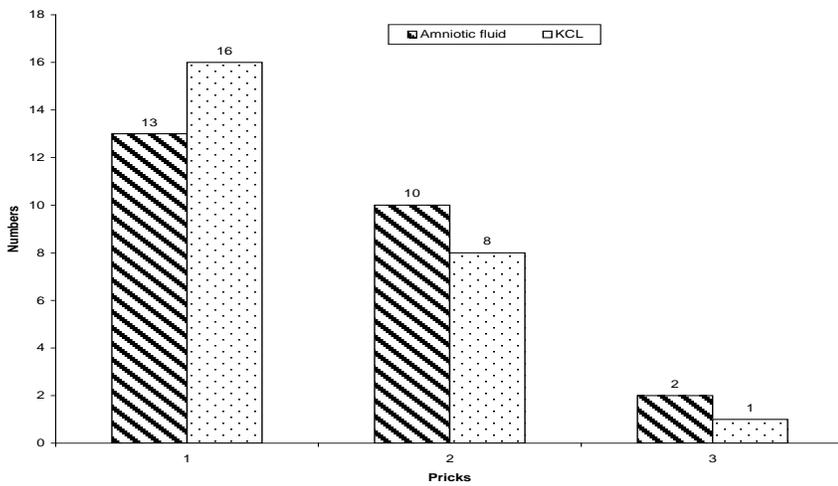


Figure 2: Number of pricks required

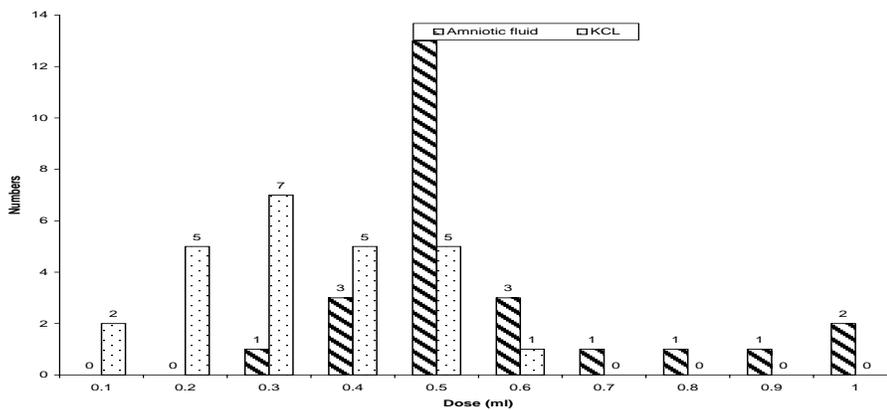


Figure 3. The dosage required to achieve asystole was significantly lesser in potassium chloride group

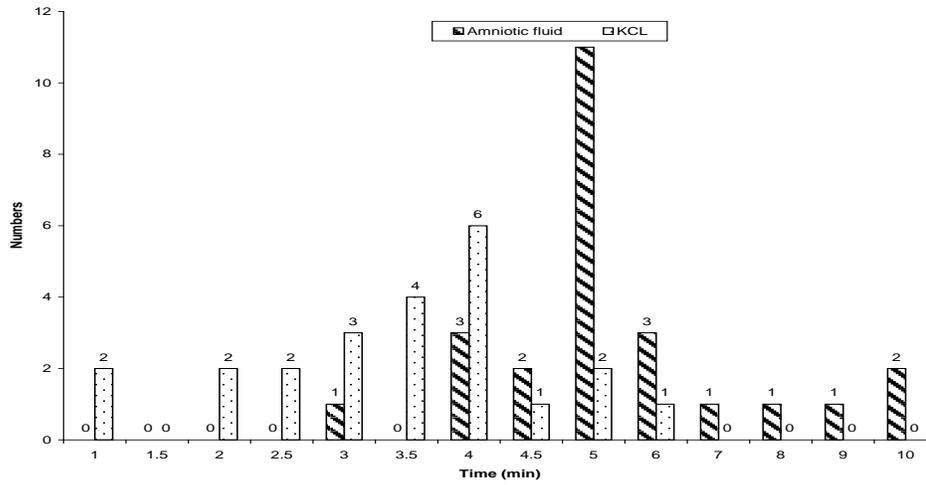


Figure 4. Time required to achieve asystole was significantly lesser in potassium chloride group