



A new and more effective feticide technique in late termination of pregnancy: potassium chloride injection into the interventricular septum of the fetal heart

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Abstract

Objective This study sought to compare the efficacy and outcomes of fetal intracardiac intraventricular and interventricular septal potassium chloride (KCl) injections during the induced fetal demise process in a cohort of pregnant women with severe fetal abnormality who opted for late termination of pregnancy (TOP).

Materials and methods This study consisted of 158 pregnant women who requested late TOP for severe fetal abnormality between 22 and 36 weeks of pregnancy. Participants were randomly assigned with the simple randomization procedure to one of two feticide procedure groups: the intraventricular KCl injection group and the interventricular septal KCl administration group. We studied the clinical outcomes of both the feticide procedures.

Results The median total dose of strong KCl was significantly lower in the interventricular septal KCl administration group (3 mL) than in the intraventricular KCl injection group (5 mL, $p < 0.001$). The median time to reach asystole and the median total duration of the procedure was significantly shorter in the interventricular septal KCl administration group (42 s and 85 s, respectively) than in the intraventricular KCl injection group (115 s and 150 s, respectively, $p < 0.001$). We detected a statistically significant correlation between the gestational week at feticide and the total dose of KCl ($r = 0.705$, $p < 0.001$), time to reach asystole ($r = 0.653$, $p < 0.001$), and total duration of the procedure ($r = 0.683$, $p < 0.001$).

Conclusion KCl administered directly into the interventricular septum induces immediate and permanent fetal cardiac asystole with a 100% of success rate without comprising maternal safety. We did not observe any maternal complications related to the procedure in our cases. Since the consequences of failed feticide procedure are challenging for both parents and healthcare providers, and providers are also concerned about potential legal implications regarding an unintended live birth, it is crucial to guide a strict protocol to confirm permanent fetal cardiac asystole.

Keywords Feticide · Late termination of pregnancy · Potassium chloride · Interventricular septal injection

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What does this study add to the clinical work

Feticide could be performed successfully by the interventricular septal KCl injection, without compromising maternal well-being. In addition, significantly smaller doses of KCl were required to achieve fetal cardiac asystole by the interventricular septal route compared to the intraventricular route.

Introduction

As a result of the advances in high-resolution ultrasound (US) technology, the introduction of prenatal screening tests and diagnostic procedures, and the improved access to prenatal diagnostic centers by many families worldwide, fetal abnormalities are increasingly being diagnosed throughout the different stages of gestation. The identification of an abnormal fetus is a stressful experience for the pregnant woman, her spouses, and healthcare professionals, and decision-making concerning termination of pregnancy (TOP) includes numerous medical, ethical, religious, and emotional issues [1]. Some of the fetal abnormalities are frequently diagnosed late in pregnancy or fetal prognosis could predict evidently as the pregnancy progresses, and thus late TOP is suggested [2, 3]. TOP for fetal abnormalities is solely carried out when there is a substantial risk of either death or survival with a severe and irreversible mental or physical handicap or disorder as a consequence of the anomaly diagnosed along with certainty about the diagnosis [4].

The probability of a live birth following a pregnancy termination increases with progressing weeks of pregnancy. The pregnant woman, her family, and healthcare providers are concerned about the possibility of live birth after late TOP when the fetus is viable [5]. Critical care decisions in neonatal medicine should be performed if these infants are delivered alive and the standard of palliative care should be provided for as long as the neonate survives [6]. Royal College of Obstetricians and Gynaecologists strongly recommended that late TOP should not end in a birth of a living infant that then dies for reasons other than the indication of TOP, and thus, a neonatal death taking place after a live birth from a TOP should be prevented [7]. Hence, by providing fetal death before the abortion process, unintended live birth cannot arise, thereby avoiding completely the difficulty that faces the healthcare providers and the pregnant woman if the patient were to deliver the infant with life signs [8]. Feticide is suggested to be carried out before all terminations irrespective of the reasons for late TOP at the gestational

age of more than 21^{6/7} weeks to confirm that a viable fetus is born dead [6]. Providers might also prefer induced fetal demise before a late TOP for several indications, including shortening the induction to abortion time for medical abortion in the later weeks of gestation, allowing for autopsy and other investigations of the fetus following abortion which provides appropriate counseling concerning subsequent pregnancies, avoiding extramural delivery with live birth, and patient preference [9, 10].

Different methods and various pharmacologic agents have been introduced to induce fetal demise before late TOP. The most commonly used method for a fetus with a severe abnormality is the transabdominal intracardiac potassium chloride (KCl) injection performed with ultrasound guidance. Intracardiac KCl injection has still been widely used to induce fetal death by producing asystole [11]. For cases who decide to terminate their pregnancies complicated with severe fetal abnormality at later weeks of gestation, the efficacy and safety of the procedure utilized to induce fetal demise should be well established. However, to the best of our knowledge, no study to date has compared whether there was a difference between the safety, efficacy, required dose, and required time to achieve fetal asystole regarding the site of fetal intracardiac KCl administration.

This study sought to compare the efficacy and outcomes of fetal intracardiac intraventricular and interventricular septal KCl injections during the induced fetal demise process in a cohort of pregnant women with severe fetal abnormality who opted for late TOP.

Materials and methods

This prospective randomized control trial (RCT) was carried out with all pregnant women presenting for induced fetal demise by fetal intracardiac KCl injection before late TOP at Kanuni Sultan Süleyman Training and Research Hospital, which was a fetal diagnosis and treatment center in Turkey, between January 2021 and June 2022. We included all cases after providing signed informed consent. The Ethics Committee's approval was obtained before the study was taken place (Approval Number: 2021-01-10). The data regarding all pregnant women who experienced induced fetal demise with KCl administration before late TOP in our hospital during the study period were retrieved from the hospital's well-maintained ultrasound (US) database system and patient files. The inclusion criteria included singleton pregnant women diagnosed with severe fetal abnormality at > 22 weeks of gestation. The exclusion criteria for all pregnant women were multiple pregnancies, and maternal indications for late TOP in which continuation of the current pregnancy significantly threatens the physical or mental health of the pregnant woman. Pregnant women who

had fetuses with major fetal cardiac abnormality were also excluded. We demonstrated the consort flow diagram in Fig. 1.

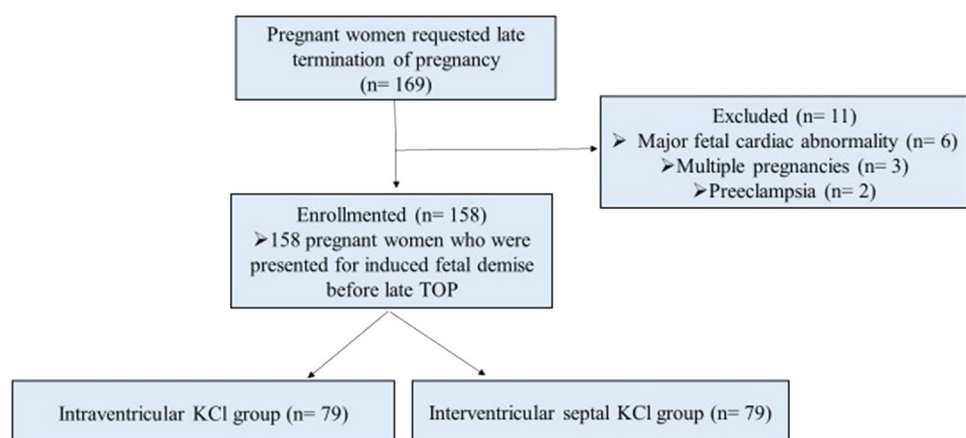
All US examinations are conducted by maternal–fetal medicine specialists utilizing the ARIETTA 850 US machine (Hitachi, Ltd., Tokyo, Japan). A severe fetal anomaly was diagnosed according to the second-trimester US anomaly scan findings, with or without confirmatory examinations including karyotype analysis and fetal magnetic resonance imaging (MRI). The diagnosis of a severe fetal malformation necessitating the option of late TOP was based on the consensus expert opinion by a multidisciplinary team, which included an obstetrician, maternal–fetal medicine specialist, medical ethicist, geneticist, and other specialists based on the type of the disorder such as a pediatric surgeon, and neurosurgeon. Pretermination counseling, including a detailed explanation of the risks and benefits of feticide to avoid a live birth with a severe fetal abnormality, was offered to all cases. All interventions were conducted at the pregnant woman’s request.

All interventions are conducted by maternal–fetal medicine specialists under continuous transabdominal sonographic (ARIETTA 850 US machine [Hitachi, Ltd., Tokyo, Japan]) visualization. Fetal lie, presentation, position, and placental location were recorded. The feticide procedure was taken place using a free-hand technique without maternal sedation or local anesthesia. The aseptic method was utilized to minimize the procedure-related infection risk as the mother’s abdominal skin was cleaned with povidone-iodine and draped. Participants were randomly assigned the following simple randomization procedure (computerized random numbers) to one of two feticide procedure groups: intraventricular KCl injection group and interventricular septal KCl administration group. A 15 cm, 20-Gauge spinal needle was inserted through the anterior wall, maneuvered into the fetal thoracic cavity into the left ventricle of the fetal heart. For the intraventricular KCl injection group, the correct location of the needle was proved by aspirating 1 ml of fetal blood.

For the interventricular septal KCl administration group, following the aspiration of fetal blood, the needle was moved forward and inserted into the fetal cardiac interventricular septum. The correct location of the needle was proved by the inability to aspirate the fetal blood in the septal KCl administration group. Following the correct placement confirmation in both of the groups, 2 ml of strong KCl (15%, 20 mM/10 ml) was slowly injected into the fetal heart. The fetal heart was monitored visually for the documentation of fetal asystole. An additional dose of 1 ml of strong KCl was injected every 30 s until permanent fetal asystole was achieved, and the duration of the procedure was recorded. Once a fetal arrest has been confirmed, the fetal heart continued to monitor for at least 30 s to ensure the persistence of asystole with the needle in situ. The needle was removed after confirming the fetal heart arrest. After the procedure, the patient was invited to rest in a comfortable position in a silent room and her vital signs were assessed for an average of 1 h. Then, the patient was rescanned 1 h after the procedure to confirm the permanent fetal asystole. The fetal blood specimen was analyzed for Rh blood type and karyotyping. Anti-D immunoglobulin prophylaxis was given to all RhD-negative pregnant women with RhD-positive fetuses. After the feticide procedure, the clinical approach was similar to that of pregnancies presenting with a spontaneous intrauterine fetal demise after 22 weeks of pregnancy. All the participants were suggested a postmortem autopsy and additional relevant examinations after feticide for a severe fetal abnormality to provide precise counseling concerning future pregnancies.

We studied maternal demographic and clinical characteristics and maternal and neonatal outcomes of the participants. Maternal characteristics were maternal age, parity, a gestational week at the time of feticide, indications for feticide, time to reach asystole, the total duration of the procedure, amount of KCl utilized to achieve permanent asystole, and procedure-related complications. The time to reach asystole was calculated from the time of starting the injection of KCl into the

Fig. 1 Flow chart of the patients included in the study



ventricle or interventricular septum to the permanent fetal asystole. The total duration of the procedure was calculated from the time of the needle insertion to the time of the needle being removed from the patient's abdomen. Procedure-related complications included failed feticide resulting in a live birth, maternal procedure-related infections, maternal sepsis, and maternal cardiac arrest. The estimated fetal weight (EFW) was calculated by the sonographic measurements of fetal biparietal diameter, head circumference, AC, and femur length in the week before the procedure [12].

Statistical analysis

Sample size calculation

For the prospective randomized study investigating the difference in the time to reach asystole in the administration of potassium KCl from the interventricular septum or into the left ventricle, the time to reach asystole was used as the primary outcome variable. In this sense, we used 17 patients who were given potassium KCl to the interventricular septum as pilot study data and the result we obtained was 47.88 ± 22.47 seconds. We calculated the sample size that would find a significant difference of 20% between the groups, using double-sided hypothesis control, Student's *t*-test, and 5% type I error (minimum power 0.80). As a result, we calculated the number of subjects for groups as 76 (a total number of 152 cases), and considering the dropouts, we decided to include 79 patients in each group in our study. Random Allocation Software (RAS) version 1.0.0 was used to perform randomization in assigning patients to groups, and the double-block randomization method was applied.

The data were statistically analyzed using IBM SPSS Statistics for Windows, Version 20.0. (Armonk, NY: IBM Corp.) package program. Data were summarized as mean \pm standard deviation and median (minimum–maximum) for continuous variables. Mann–Whitney *U* test was used for the independent group (left ventricle and interventricular septum) comparisons, depending on the distributional properties of the data based on groups (according to results of the Shapiro Wilk test). The degree of association between variables such as the gestational week at feticide versus total KCl dose, time to reach asystole, and total duration of the procedure, were calculated using nonparametric Spearman's rho correlation coefficients. For all statistical analyses, any *p* value less than 0.05 was considered statistically significant.

Results

During the study period between January 2021 and June 2022, a total of 169 pregnant women requested late TOP for severe fetal abnormality between 22 and 36 weeks of

pregnancy. Three cases were multiple pregnancies. Six cases had a fetus with major cardiac abnormality. In 2 cases, the indication for late TOP was severe preeclampsia. These 11 cases were excluded from the study before the final analysis. A total of 158 pregnant women who were presented for induced fetal demise before late TOP completely fulfilled the inclusion criteria described in the study project.

We demonstrated the indications for late TOP in Table 1. All terminations in this study took place for fetal indications. The most common indication for late TOP was central nervous system abnormalities ($n = 71$, 44.9%). Thirty-nine of these cases were neural tube defects. Of the neural tube defects, 30 were spina bifida. Chromosomal abnormalities were the second most common indication for feticide in our cohort ($n = 35$, 22.2%). Of these, 15 were trisomy 21, and 7 were trisomy 18.

We presented the demographic features and KCl procedure characteristics of the participants in Table 2. We performed the feticide procedure by intraventricular KCl injection in 79 women, and by interventricular septal KCl administration in 79 cases. The groups were similar regarding maternal age, gravidity, and parity. The mean gestational age at feticide in the intraventricular KCl injection group (26.95 ± 3.29 weeks, ranging between 22 and 35 weeks) was similar to that of the interventricular septal KCl administration group (26.59 ± 3.46 weeks, ranging from 22 to 36 weeks, $p = 0.106$). The EFW in the intraventricular KCl injection group (1027.16 ± 545.28 g, range from 380 to 2470 g) was not significantly different from that of the interventricular septal KCl administration group (995.47 ± 533.19 g, range between 370 and 2670 g, $p = 0.147$). We obtained complete cessation of heart activity in all participants. No cases required an additional needle insertion. The median total dose of strong KCl was significantly lower in the interventricular septal KCl administration group (3 mL) than in the intraventricular KCl injection group

Table 1 Indications for late termination of pregnancy

Indication	<i>n</i> (%)
Central nervous system	71 (44.9%)
Neural tube defects	39 (24.7%)
Other	32 (20.2%)
Chromosomal abnormalities	35 (22.2%)
Trisomy 21	15 (9.5%)
Trisomy 18	7 (4.5%)
Trisomy 13	1 (0.6%)
Other	12 (7.6%)
Musculoskeletal abnormalities	22 (13.9%)
Urogenital abnormalities	15 (9.5%)
Multiple abnormalities	14 (8.9%)
Respiratory system abnormalities	1 (0.6%)

Table 2 Demographic features and KCl procedure characteristics of the participants

	Left intraventricular KCl group (<i>n</i> = 79)		Interventricular septal KCl group (<i>n</i> = 79)		<i>p</i> value
	Mean ± Std	Median (min. – max.)	Mean ± Std	Median (min. – max.)	
Maternal age, years	30.86 ± 4.8	31 (22–41)	30.38 ± 4.63	31 (22–41)	0.555
Gravidity	2.1 ± 1.09	2 (1–5)	2.13 ± 1.14	2 (1–5)	0.952
Parity	0.84 ± 0.93	1 (0–3)	0.85 ± 0.92	1 (0–3)	0.910
Gestational week at feticide	26.95 ± 3.29	27 (22–35)	26.59 ± 3.46	27 (22–36)	0.106
Estimated fetal weight, g	1027.16 ± 545.28	870 (380–2470)	995.47 ± 533.19	750 (370–2670)	0.147
KCl dose, mL	5.32 ± 1.35	5 (3–8)	3.28 ± 0.89	3 (2–6)	<0.001
Time to reach asystole, seconds	115.94 ± 40.7	115 (45–202)	48.97 ± 24.76	42 (8–135)	<0.001
Total duration of the procedure, seconds	153.61 ± 40.53	150 (85–250)	91.52 ± 24.42	85 (45–175)	<0.001

Table 3 Correlational relationship between the gestational week at feticide and the total dose of KCl, time to reach asystole, and total duration of the procedure

	Total dose of KCl (mL)	Time to reach asystole (seconds)	Total duration of the procedure (seconds)
Gestational week at feticide			
Spearman's rho	0.705	0.653	0.683
<i>p</i> value	<0.001	<0.001	<0.001

(5 mL, $p < 0.001$). The total dose of KCl did not exceed 6 mL in any case in the interventricular septal KCl administration group, and 8 mL in the intraventricular KCl injection group. The median time to reach asystole and the median total duration of the procedure was significantly shorter in the interventricular septal KCl administration group (42 s and 85 s, respectively) than in the intraventricular KCl injection group (115 s and 150 s, respectively, $p < 0.001$). Fetal cardiac asystole was achieved in all cases within 135 s of interventricular septal KCl administration and 202 s of intraventricular KCl injection. No maternal complications were reported in both the groups. All cases continued to a TOP and all of them delivered stillbirths.

The correlational relationship between the gestational week at feticide and the total dose of KCl, time to reach asystole, and total duration of the procedure were demonstrated in Table 3. We detected a statistically significant correlation between the gestational week at feticide and the total dose of KCl ($r = 0.705$, $p < 0.001$), time to reach asystole ($r = 0.653$, $p < 0.001$), and total duration of the procedure ($r = 0.683$, $p < 0.001$) in our study cohort (Figs. 2, 3, 4).

Discussion

In the current study, we compared the outcomes of intraventricular KCl injection and interventricular septal KCl administration for achieving feticide. We demonstrated that feticide

could be performed successfully by both intraventricular and interventricular septal KCl injection, without compromising maternal well-being. However, significantly smaller doses of KCl were required to achieve fetal cardiac asystole by the interventricular septal route compared to the intraventricular route. In addition, we found a significantly shorter mean procedure time to reach asystole and total processing time in those who received interventricular septal KCl injection when compared to those who received intraventricular KCl injection. The amount of strong KCl required to induce fetal cardiac asystole was significantly correlated with the gestational age and estimated fetal weight at the time of the procedure in all fetuses. Strong KCl could be safely utilized to reach fetal cardiac asystole in amounts up to 8 mL for the intraventricular route and 6 mL for the interventricular septal route.

The decision-making process regarding TOP is further challenged when an abnormal fetus is diagnosed in the later weeks of pregnancy [1]. The subject of late TOP for fetal malformations is debatable as laws regarding this issue differ from one country to the other both in respect of indications and gestational week [5]. Fetal viability is currently thought to be reached from 22 weeks onwards. In several countries, including Turkey, late TOP for fetal anomalies can be conducted from the edge of viability to term for a high risk of severe, non-treatable, and lethal fetal disorders [13]. The main causes for late TOP included missed diagnosis on an earlier scan, delayed diagnosis and establishment of prognosis due to the nature of the malformation, additional investigations being performed, delay in referral to a maternal–fetal medicine center, and late decision of the parents [3, 6]. Inducing fetal demise before induction TOP prevents signs of life at the time of delivery that might have favorable legal, ethical, and emotional consequences [8].

Practitioners have been utilizing pharmacologic agents before TOP over the years with the procedure becoming increasingly popular [10, 14]. In addition, an RCT of intra-amniotic fetidical agents for late TOP found that subjects reported a 92% of preference for fetal demise before the

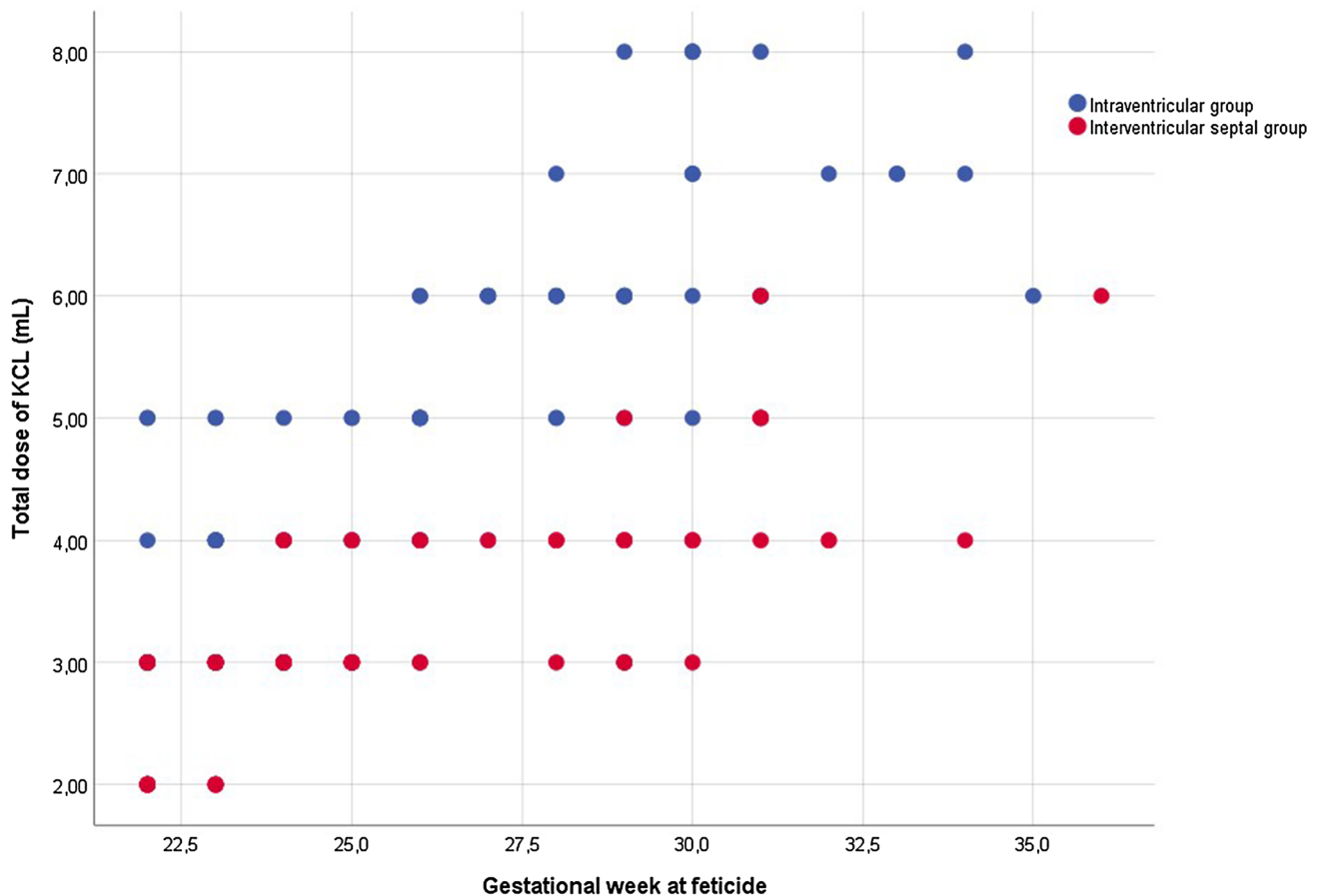


Fig. 2 The relationship between the gestational week at feticide and the total dose of KCl according to Spearman's correlation coefficient

abortion procedure [15]. Many techniques for inducing fetal demise before TOP have been widely utilized since the early 1980s. KCl was first described as a fetocidal agent in 1988, and from then on KCl has been widely utilized to induce fetal cardiac asystole by either umbilical cord or intracardiac injection [11]. Asystole is commonly detected within a few minutes of KCl administration with both of the sites. Cordocentesis requires to be carried out following rigid rules and increases hypothetical worries regarding fetomaternal KCl passage and maternal well-being. In addition, the umbilical cord administration requires higher technical expertise than the intracardiac injection, frequently takes a long time to carry out, and might be complicated by needle displacement, and patient discomfort [3]. Gill et al. and Bhide et al. reported a success rate of 86.7% and 95.2%, respectively, with intrafunicular KCl injection to produce fetal demise. Both of the studies stated one case of failed feticide following the umbilical cord KCl administration that ended with live birth. In addition, 4.8–13.3% of cases required further intracardiac KCl injection [16, 17]. These findings might have tremendous emotional consequences for parents and economic impacts on the healthcare providers concerned.

Pasquini et al. and Govender et al. reported a success rate of 100% with intracardiac KCl administration to induce fetal cardiac asystole [3, 6]. Likewise, in our study, quick and efficient fetal heart cessation was obtained in all participants (a success rate of 100%) with a volume of KCl that did not compromise maternal safety. Thus, the modality of feticide utilizing intracardiac KCl seems to be more effective and safe than the umbilical cord KCl administration.

When performing the feticide procedure before the late TOP, the smallest effective dose of the selected fetocidal agent should be utilized [8]. There is a paucity of data regarding the most effective site for KCl administration. Increased extracellular potassium decreases the excitability of cardiac myocytes by suppressing both pacemaker and conduction tissues. Bhide et al. proposed that a bolus of strong KCl administered by the intraventricular site is pumped quickly away from the ventricles, with only a part of KCl being provided to the coronary arteries. In addition, KCl pumped away from the ventricles would be swiftly taken up by fetoplacental unit cells when administered by the intraventricular site, ending in comparatively low KCl doses returning to the fetal heart [17]. As known, the electrical

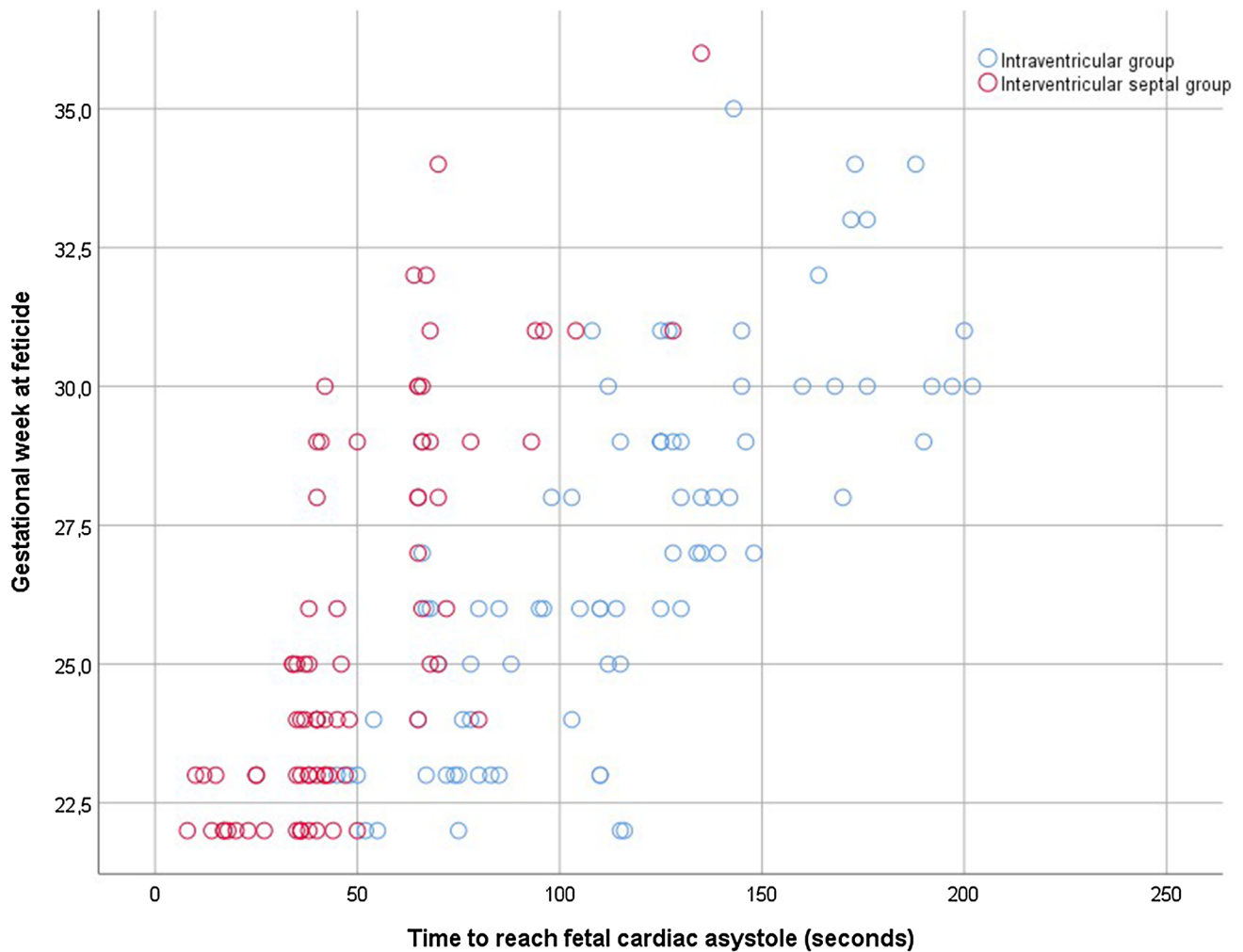


Fig. 3 The relationship between the gestational week at feticide and time to reach fetal cardiac asystole according to Spearman's correlation coefficient

impulse moves from the sinus node to the atrioventricular node, then travels the conduction pathway via the bundle of His on the interventricular septum [18]. By giving KCl to the interventricular septum, we aimed to directly block this conduction pathway with a minimum dose of KCl. In this way, we hypothesized that we can achieve fetal cardiac asystole in a shorter time with a lower dose than intraventricular KCl injection. Previous studies found that on average 5–12 mL of strong KCl is required to induce fetal demise by intraventricular administration [3, 6, 11, 19]. Our study indicated the utilization of 5.32 ± 1.35 mL of strong KCl on average within 45–202 s of injection to produce permanent fetal cardiac asystole by the intraventricular injection. However, fetal cardiac asystole was achieved in all cases within 8–135 s of interventricular septal KCl injection with an average volume of 3.28 ± 0.89 mL. The duration and the volume of KCl required to achieve fetal cardiac asystole were significantly lower in the septal group than in the intraventricular group

($p < 0.001$). Since the prolongation of the procedure may lead to needle displacement and patient discomfort, shortening the procedure time will be beneficial for the emotional health of the mother who will experience fetal demise and subsequently an abortion procedure. In addition, no patients experienced any maternal complications associated with the procedure, and permanent rapid fetal cardiac was achieved in all cases. Thus, our data highly recommend the use of strong KCl by the intraventricular septal site to induce fetal demise before late TOP.

Lee et al. concluded that the capacity for functional pain perception can arise only after thalamocortical fiber connections begin to function, which may occur about 29 to 30 weeks of gestation [20]. The use of fetal analgesia and anesthesia during feticide mainly improves outcomes of the procedure by inhibiting the fetal physiologic stress response and minimizing fetal movement [21]. However, analgesic agents might destabilize the fetal cardiovascular system by

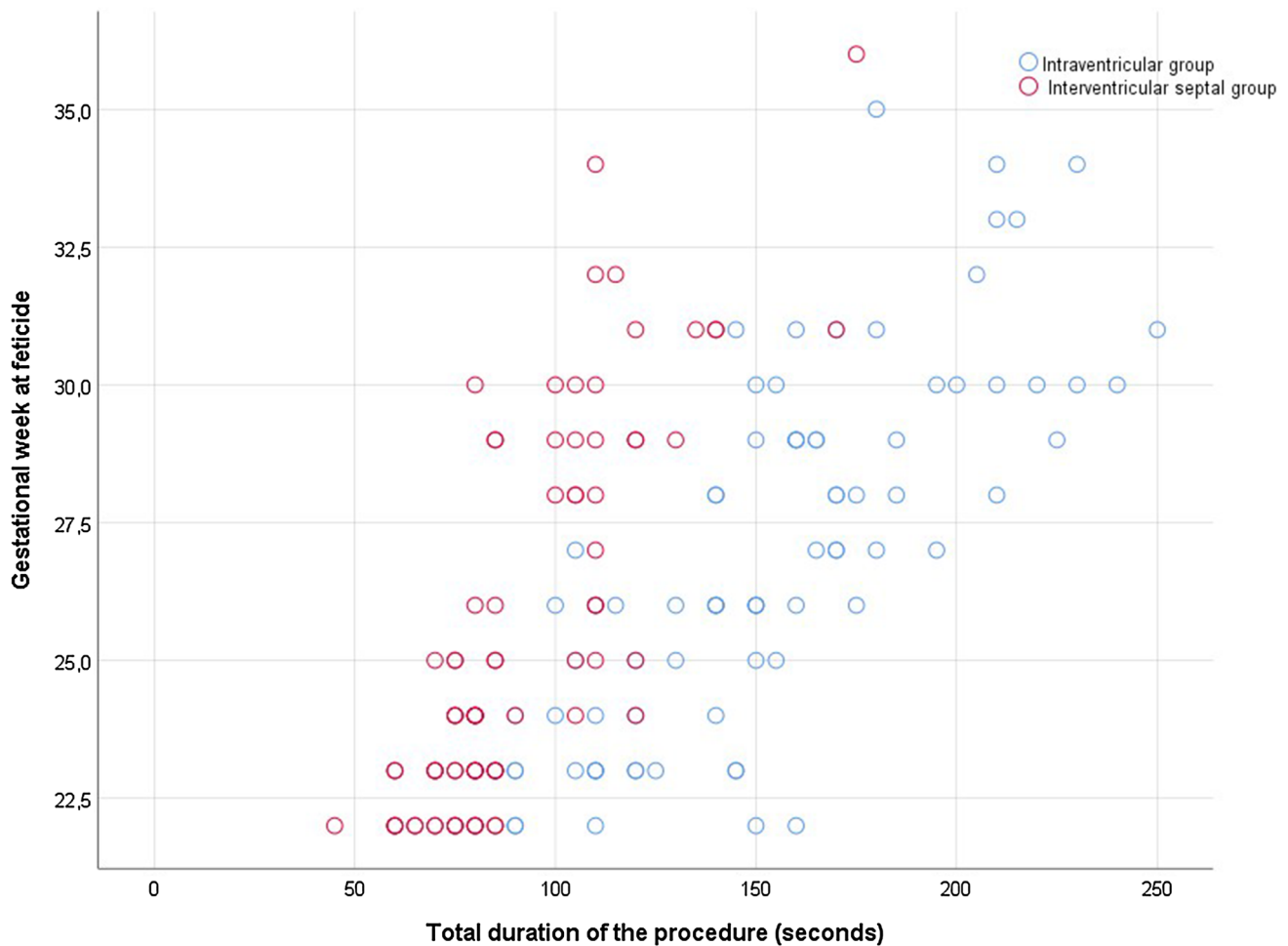


Fig. 4 The relationship between the gestational week at feticide and the total duration of the procedure according to Spearman's correlation coefficient

causing direct fetal myocardial depression [22]. As the dose of KCl, time to reach asystole, and the total duration of the procedure might vary with this cardiac effect, we did not perform fetal analgesia which could introduce potential bias to the outcomes of our study.

The main strength of the study is that, as far as is known, there has been no RCT in the literature comparing the sites of fetal intracardiac concentrated KCl administration. This is the first research on feticide with the strong KCl injection to the fetal intraventricular and interventricular sites.

Conclusion

KCl administered directly into the interventricular septum induces immediate and permanent fetal cardiac asystole with a 100% of success rate without comprising maternal safety. We did not observe any maternal complications related to the procedure in our cases. Since the consequences of

failed feticide procedure are challenging for both parents and healthcare providers, and providers are also concerned about potential legal implications regarding an unintended live birth, it is crucial to guide a strict protocol to confirm permanent fetal cardiac asystole.

Declarations

Conflict of interest The authors have no conflict of interest to declare.

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