

Correcting hypokalaemia in a paediatric patient with Bartter syndrome through oral dose of potassium chloride intravenous solution

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Abstract

Bartter syndrome is a rare autosomal recessive disorder characterized by hypokalaemia. Hypokalaemia is defined as low serum potassium concentration <3.5 mmol/L, which may lead to arrhythmia and death if left untreated. The aim of this case report was to normalize serum potassium concentration without the need for intravenous intervention. A 5-month-old male of 2.7 kg body weight diagnosed with Bartter syndrome was admitted to the general paediatric ward with acute severe hypokalaemia and urinary tract infection. The main challenge was the inability to administer drugs through intravenous route due to compromised body size. Therefore, we shifted the route of administration to the nasogastric tube/oral route. A total of 2 mL of concentrated intravenous potassium chloride (4 mEq potassium) were dissolved in distilled water and administered through nasogastric tube. Serum potassium concentration was rapidly normalized, which culminated in patient discharge. In conclusion, shifting drug administration from intravenous to oral route in a paediatric patient with Bartter syndrome includes numerous advantages such as patient convenience, minimized risk of cannula-induced infection, and reduced nurse workload.

Keywords

Bartter syndrome, hypokalaemia, paediatrics, kidney, case report

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Introduction

Bartter syndrome (BS) is a rare autosomal recessive disorder initially reported in 1962, when two patients were reported with hypokalaemia and hyperaldosteronism with normal blood pressure.¹ BS is attributed mainly to genetic mutations in the ascending loop of Henle, hence disrupting salts reabsorption that leads to severe loss of ions.² Genotypic phenotypic studies have categorized BS into four major types: (1) antenatal BS type I or hyper-prostaglandin E2 syndrome, where *SLC12A1* gene mutations contribute to abnormal function of furosemide-sensitive sodium-potassium-chloride cotransporter-2 (NKCC-2). Infants are usually born prematurely, with early signs of hyposthenuria (urine of low specific gravity) associated with lethargy and poor feeding. Hypokalaemia develops from the first week; (2) antenatal BS type II, where *KCNJ1* gene mutations contribute to abnormal function of the renal outer medullary potassium

channel (ROMK). Infants are usually born prematurely, with early signs of hyposthenuria associated with lethargy and poor feeding. However, hypokalaemia is less frequent than in BS type I, and transient hyperkalaemia is observed in the first days of life, which may be attributed to the immaturity of the sodium-potassium-ATPase (Na + K + ATPase) pump;

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(3) BS type III, where *CLCNKB* gene mutations contribute to the abnormal function of basolateral chloride channels (CLC-Kb). The onset of such type of BS is in early childhood; therefore, it is not considered as antenatal. In addition to hypokalaemia, the main characteristic of BS type III is hyperchloremic alkalosis; (4) BS type IV is sub-grouped into two groups; BS type IVa, where *BSND* gene mutations contribute to abnormal function of barttin subunit of CLC-Ka and CLC-Kb, while BS type IVb is attributed to mutations in both *CLCNKA* and *CLCNKB* genes. Infants are usually born prematurely, with early signs of hyposthenuria, hypokalaemia, and hyperchloremic alkalosis.^{2,3}

Hypokalaemia is a common complication of BS and is defined as low serum potassium concentration (normal range: 3.5–5.0 mmol/L).^{1,2,4} Severe and life-threatening hypokalaemia is defined when potassium levels are <2.5 mmol/L. If left untreated, hypokalaemia may lead to mental retardation and irregular heart rhythm, which might be aggravated to syncope and sudden death.⁴

Case report

Here, we report a 5-month-old male diagnosed with antenatal BS Type I, born of preterm 32 weeks gestational age through normal vaginal delivery. At birth, he was 1.7 kg weight and currently weighed 2.7 kg. While in the neonatal intensive care unit (NICU), hypokalaemia was controlled through oral solution potassium chloride (1 M: 1 mEq/ml) 3.5 mL every 2 h and spironolactone 1.7 mg twice daily, with hyponatremia controlled through oral sodium chloride (1 M: 1 mEq/mL) 2 mL every 2 h. Moreover, as the patient showed improvement in serum potassium concentration, his potassium level was maintained through receiving 2 mL of oral solution potassium chloride (1 M: 1 mEq/mL) before being discharged.

The patient was readmitted to the general paediatric department at Al Adan Hospital as a case of BS with severe metabolic alkalosis, hypokalaemia, and hyponatremia, urinary tract infection, and undiagnosed congenital heart syndrome. The main challenge of controlling our patient's condition was the inability to administer drugs through the intravenous (IV) route due to compromised body size. Therefore, we shifted the route of administration to the intramuscular route and oral drugs, including nasogastric tube (NGT) rather than IV route. The initial serum electrolyte concentrations were as shown in Table 1.

Based on the electrolyte levels at admission in NICU, and since potassium concentration was low, the patient was administered 3.5 mL of potassium chloride (1 M) of 1 mEq/mL every 2 h by NGT, spironolactone 1.7 mg twice daily, and sodium chloride (1 M: 1 mEq/mL) 2 mL every 2 h by NGT. The patient was stable and hence was moved to the general ward within 4 months of admission. The patient showed severe hypokalaemia with serum potassium concentration reaching 2.5 mmol/L, while the concentrations of other electrolytes were normal, as shown in Table 1. The patient

received concentrated IV KCl through NGT. Despite the initial normalization of potassium concentration, the patient started developing signs of gastritis, such as vomiting.

Accordingly, it was essential to correct potassium levels. However, as mentioned, the main obstacle towards such a vital step was the inability to administer potassium chloride intravenously. We discussed possible alternatives with a hospital pharmacist, who suggested administering potassium chloride (15%: 2 mEq/mL) through NGT rather than the designated IV route of administration. Such a suggestion was based on calculating the milliequivalents (mEq) of potassium chloride (KCl) solution. Since oral KCl 1 mL of (1 M) was of 1 mEq/mL KCl, we aimed to provide equivalent oral KCl through IV KCl solution of 2 mEq/mL. After detailed calculations, it was concluded that the IV solution should be diluted in a 1:1 ratio with distilled water. Since BS is characterized by abnormal excretion of ions through urine, it was suggested in-ward to dilute the IV KCl solution with oral electrolyte solution (Pedialyte from Abbott containing sodium (1.02 mg/mL), total carbohydrate (25 mg/mL), potassium (0.8 mg/mL), zinc (0.008 mg/mL), and chloride (1.2 mg/mL) (Table 1).

However, the next day, the patient developed gastritis, vomiting and diarrhoea (GIT side effects) in addition to fluctuation in potassium concentration. The hospital pharmacists notified the nurse to re-prepare the IV KCl solution using distilled water as a diluent in a 1:1 ratio to yield 1 mEq/mL concentration, which is equivalent to the concentration of the extemporaneously prepared oral solution the patient previously received while in NICU. After 24 h, the patient developed stable potassium concentration without developing GIT side effects, as shown in Table 1.

Such a protocol was continued and showed less fluctuation in serum potassium concentration (Figure 1(a)), accompanied by a significant increase ($p = 0.02$) in potassium concentration, as shown in Figure 1(b). The mean serum concentration of potassium = 4.9 ± 0.42 mmol/mL when IV concentrated KCl was diluted in distilled water, while mean serum concentration of potassium = 3.6 ± 0.2 mol/mL when IV concentrated KCl was diluted in oral rehydration solution (Pedialyte).

Moreover, using distilled water as a diluent for IV concentrated KCl showed less fluctuation in serum chloride concentration (Figure 2(a)) accompanied by a significant increase ($p = 0.004$) in chloride concentration, as shown in Figure 2(b). The mean serum concentration of chloride = 103.6 ± 1.4 mmol/mL when IV concentrated KCl was diluted in distilled water, while the mean serum concentration of chloride = 100.9 ± 3.7 mol/mL when IV concentrated KCl was diluted in oral rehydration solution (Pedialyte).

Furthermore, using distilled water as a diluent for IV concentrated KCl showed less fluctuation in serum sodium concentration (Figure 3(a)) and an insignificant effect on sodium concentration as shown in Figure 3(b) ($p = 0.06$). The mean serum concentration of sodium = 139.2 ± 1.1 mmol/mL when IV concentrated KCl was diluted in distilled water,

Table 1. Serum electrolyte concentration measured through 5 days after admission throughout 114 h. The patient received spironolactone 1.7 mg every 12 h through NGT in addition to the therapeutic regimen in the table: KCl, NaCl and initial IV intervention.

Hours	Serum potassium concentration (mmol/L) Reference (3.5–5)	Serum chloride concentration (mmol/L) Reference (98–110)	Serum sodium concentration (mmol/L) Reference (135–150)	IV	NGT KCl	NaCl (1 mEq/ml)
Admission	2.5	87	136			
Zero	2.5	82	136	0.45% DNS + 12 mL KCl (15%; 2 mEq/mL)	3.5 mL (1 mEq/mL) every 2 h	2 mL every 2 h
4	2.6	80	133	0.45% DNS + 12 mL KCl (15%; 2 mEq/mL)	2 mL (15%; 2 mEq/mL) every 2 h	2 mL every 2 h
8	2.4	82	133	0.45% DNS + 15 mL KCl (15%; 2 mEq/mL)	2 mL (15%; 2 mEq/mL) every 2 h	2 mL every 2 h
12	3.7	92	138	0.9% DNS + 12 mL KCl (15%; 2 mEq/mL)	2 mL (15%; 2 mEq/mL) every 2 h	2 mL every 2 h
18	4.4	99	144	0.9% DNS + 12 mL KCl (15%; 2 mEq/mL)	2 mL (15%; 2 mEq/mL) every 4 h	2 mL every 6 h
Day 1 serum electrolyte concentration (Mean ± SEM)	3.12 ± 0.4	85 ± 4.9	138.8 ± 2.04			
24	3.2	107	146	0.9% DNS + 12 mL KCl (15%; 2 mEq/mL)	2 + 2 mL Pedialyte every 2 h	2 mL every 8 h
28	4	114	146	0.45% DNS + 12 mL KCl (15%; 2 mEq/mL)	2 + 2 mL Pedialyte every 2 h	1 mL every 8 h
34	4	121	147	0.45% DNS + 10 mL KCl (15%; 2 mEq/mL)	4 + 4 mL Pedialyte every 4 h	1 mL every 8 h
40	4.3	116	152	0.45% DNS + 10 mL KCl (15%; 2 mEq/mL)	4 + 4 mL Pedialyte every 4 h	1 mL every 8 h
42	5.1	108	147	0.45% DNS + 10 mL KCl (15%; 2 mEq/mL)	4 + 4 mL Pedialyte every 6 h	1 mL every 8 h

(Continued)

Table 1. (Continued)

Hours	Serum potassium concentration (mmol/L) Reference (3.5–5)	Serum chloride concentration (mmol/L) Reference (98–110)	Serum sodium concentration (mmol/L) Reference (135–150)	IV	NGT KCl	NaCl (1 mEq/ml)
Day 2 serum electrolyte concentration (Mean ± SEM)						
48	4.12 ± 0.31	113.2 ± 2.6	147.6 ± 1.12			
52	3.5	113	148	0.45% DNS + 10 mL KCl (15%; 2 mEq/mL)	4 + 4 mL Pedialyte every 4 h	1 mL every 8 h
56	3.5	111	151	0.45% DNS + 10 mL KCl (15%; 2 mEq/mL)	2 + 2 mL Pedialyte every 4 h	1 mL every 8 h
71	3.8	109	150	0.45% DNS + 10 mL KCl (15%; 2 mEq/mL)	2 + 2 mL Pedialyte every 4 h	1 mL every 8 h
	4	107	143	0.45% DNS + 10 mL KCl (15%; 2 mEq/mL)	4 + 4 mL Pedialyte every 4 h	2 mL every 8 h
Day 3 serum electrolyte concentration (Mean ± SEM)						
84	3.7 ± 0.12	110 ± 1.29	148 ± 1.78			
90	3.5	97	138	0.45% DNS + 7 mL KCl (15%; 2 mEq/mL)	4 + 4 mL distilled water every 4 h	2 mL every 8 h
	5.2	99	138	0.45% DNS + 5 mL KCl (15%; 2 mEq/mL)	2 + 2 mL distilled water every 4 h	2 mL every 8 h
Day 4 serum electrolyte concentration (Mean ± SEM)						
96	4.35 ± 0.85	98 ± 1.0	138 ± 0.00			
102	6.3	104	138	Discontinued	4 + 4 mL distilled water every 4 h	2 mL every 8 h
108	4.1	102	137	Discontinued	3 + 3 mL distilled water every 4 h	2 mL every 8 h
114	4.8	107	143	Discontinued	2 + 2 mL distilled water every 4 h	2 mL every 8 h
	4	106	140	Discontinued	2 + 2 mL distilled water every 4 h	2 mL every 8 h
Day 5 serum electrolyte concentration (Mean ± SEM)						
	4.8 ± 0.53	104.75 ± 1.11	139.5 ± 1.32			

IV: intravenous; NGT: nasogastric tube; SEM: standard error of the mean.

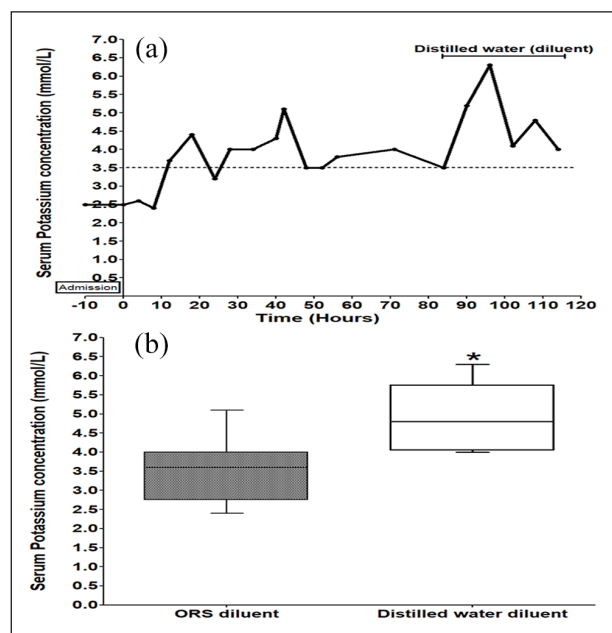


Figure 1. Serum potassium concentration and the effect of using distilled water as a diluent for the concentrated intravenous solution of potassium chloride. (a) Timescale graph showing stabilized and normalized potassium concentration when diluting concentrated intravenous potassium chloride with distilled water after it was diluted with oral rehydration solution (ORS). (b) The mean serum concentration of potassium was significantly higher when concentrated intravenous potassium chloride was diluted in distilled water compared to concentrated intravenous potassium chloride diluted in the oral rehydration solution (ORS). The dashed line represents minimum normal concentration. Data presented as mean \pm SEM. Significance presented as * $p < 0.05$ analysed through paired Student's t-test (CI = 95%).

while mean serum concentration of sodium = 143.0 ± 1.6 mol/mL when IV concentrated KCl was diluted in oral rehydration solution (Pedialyte).

Discussion

BS is a rare autosomal recessive disorder characterized mainly by hypokalaemia and hyperaldosteronism. Therapeutic strategies essentially focus on correcting electrolytes, especially potassium levels. Although KCl was available as an IV solution, it was challenging to administer KCl through the IV route because of the patient's compromised body weight and size. Therefore, based on our experience in treating paediatric patients with small body size and low body weight,⁵ IV KCl administration was shifted to oral based on the patient's need for potassium. The IV KCl concentration is 2 mEq/mL, which is more concentrated than the extemporaneously prepared oral solution (1 mEq/mL) that was previously administered to the patient while in the NICU. Therefore, the hospital pharmacists suggested the administration of KCl IV solution through oral route by mixing the IV solution with distilled water to yield a final

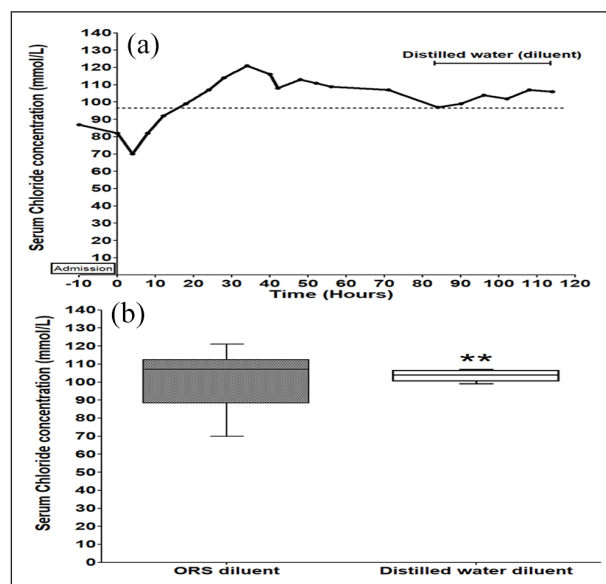


Figure 2. Serum chloride concentration and the effect of using distilled water as a diluent for the concentrated intravenous solution of potassium chloride. (a) Timescale graph showing stabilized and normalized chloride concentration when diluting concentrated intravenous potassium chloride with distilled water after it was diluted with oral rehydration solution (ORS). (b) The mean serum concentration of chloride was significantly higher when concentrated intravenous potassium chloride was diluted in distilled water when compared with concentrated intravenous potassium chloride diluted in ORS. The dashed line represents minimum normal concentration. Data presented as mean \pm SEM. Significance presented as ** $p < 0.01$ analysed through paired Student's t-test (CI = 95%).

concentration of 1 mEq/mL. This concentration did not cause GIT upsetting and side effect. Moreover, such a dilution facilitates the rapid calculations and administration of KCl to the patient based on his body weight and serum potassium concentration according to the British National Formulary recommendations.⁶ Thus, the maximum daily dose is 50 mEq⁶ (equivalent to 50 mL of the freshly prepared KCl solution) that has not been reached as shown in Table 1. However, the KCl IV solution was initially mixed with oral rehydration solution, and such intervention led to gastritis and diarrhoea. Diarrhoea caused further loss of potassium, which was reflected in the fluctuating level of serum potassium concentration. If diarrhoea is not resolved in BS patients, hypokalaemia may be aggravated, leading to QT prolongation and sudden death.⁴ The use of oral rehydration solution as a diluent for concentrated potassium chloride led to the formation of a hyperosmotic solution that exerted an osmotic laxative effect and hence diarrhoea.⁷ Such an effect was observed in a small number of patients who received hypertonic nasogastric tube solutions.⁸ Moreover, hyperosmotic solutions are known irritants to the gastric mucosa and hence lead to gastritis.^{9,10} In addition to diarrhoea, gastritis-induced vomiting is considered another route of ion loss, including potassium ions.⁴ Therefore, the main problem was

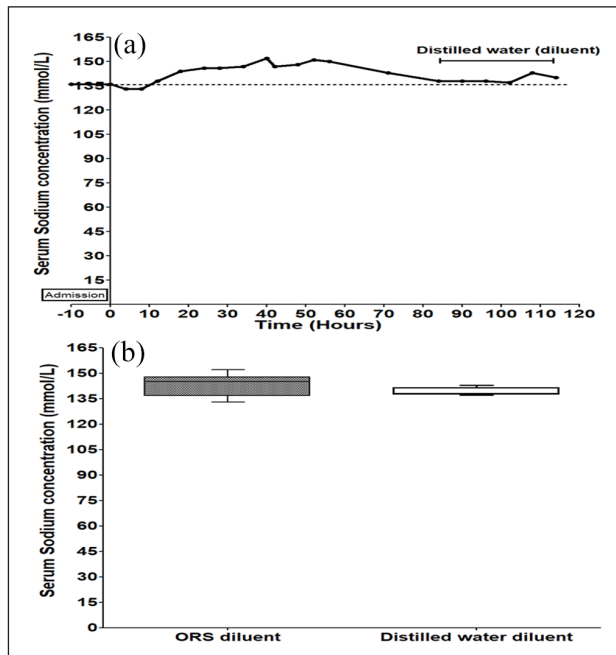


Figure 3. Serum sodium concentration and the effect of using distilled water as a diluent for the concentrated intravenous solution of potassium chloride. (a) Timescale graph showing stabilized and normalized sodium concentration when diluting concentrated intravenous potassium chloride with distilled water after it was diluted with oral rehydration solution (ORS). (b) The mean serum concentration of sodium did not show significant difference when concentrated intravenous potassium chloride was diluted in distilled water when compared with concentrated intravenous potassium chloride diluted in ORS. The dash-line represents minimum normal concentration. Data presented as mean \pm SEM analysed through paired Student's t-test (CI = 95%). Normalized potassium, chloride, and sodium concentrations culminated in recovery and patient discharge from the hospital. The mother of the patient was counselled to prepare KCl IV solution for oral administration.

the osmolarity of the solution, which was solved by diluting the KCl IV solution with distilled water. Once the IV KCl solution was diluted with distilled water, diarrhoea and gastritis symptoms were resolved, and the patient was well recovered after 24 h and discharged after 6 days at potassium concentration 4.2 mmol/L. Such a normal, high and stable serum potassium concentration provides a novel finding in managing paediatric patients with BS. Thus, a previous study conducted on 20 paediatric patients with BS in Costa Rica revealed an average serum potassium concentration of 3.05 mmol/L,¹¹ which is less than the normal concentration (3.5–5 mmol/L). In addition, serum potassium concentration was not corrected through a readily made oral KCl solution, whereas a significant improvement and difference were achieved through administering a freshly prepared KCl solution using distilled water (Figure 1 and Table 1). These findings may suggest the importance of preparing KCl solution freshly rather than storing it diluted in plastic bottles.

The restricted and limited ability to administer drugs intravenously is considered a major obstacle in managing neonates

with BS. Shifting the route of administration from IV to oral (or NGT) is a vital strategy to overcome such a pathological obstacle. However, the optimal benefit should be obtained through careful calculations and other considerations before shifting the route of administration. These considerations include understanding the physicochemical properties and pharmacokinetic and pharmacodynamic factors of the administered drugs. Thus, to provide equivalent benefit from shifting the route of administration, the barriers to reducing the bioavailability of orally administered drugs should be overcome to yield 100% bioavailability that is equivalent to the bioavailability if drugs were administered intravenously. Therefore, it is essential to improve the bioavailability of oral drugs, mainly through enhancing the rate and percentage of absorption as well as reducing the intestinal and hepatic metabolism (first-pass effect).¹² Shifting the route of administration from the IV to oral route provides a wide range of benefits based on the purpose of such an intervention. This may include replacing a drug with its oral counterpart, such as replacing IV omeprazole with oral omeprazole (20–40 mg), which is called sequential therapy.¹²

Furthermore, when an IV drug is replaced with a different oral drug that belongs to the same pharmacological class that is expected to impose an equivalent therapeutic outcome, such a shift in the route of administration is called switch therapy. This is exemplified by orally administered cefuroxime (500 mg) twice daily instead of IV ceftriaxone (1 g) once daily.¹³ However, when an IV drug such as heparin is replaced with another drug such as warfarin that belongs to a different pharmacological class and administered through different doses and intervals but provides a similar effect, such an intervention is called step-down therapy.¹⁴

In our case of BS, sequential therapy was applied through shifting the route of administration of potassium chloride from IV to NGT. Such an intervention was associated with rapid and convenient normalization of serum potassium and chloride concentrations, as shown in Figures 1 and 2, respectively. The main advantage of such a shift in the route of administration is minimizing the risk of cannula-related infections.¹² In addition, shifting the route of administration from IV to NGT (or oral) reduces the workload on nurses. A previous study revealed that an IV administration of antibiotics takes approximately 10 min of supervision; therefore, switching to the oral route reduces the nurses' workload by approximately 350 h per year.¹⁵ In addition, this case reveals the importance of hospital pharmacists as members of a multidisciplinary clinical team, providing important and vital recommendations that culminate in optimal quality of health-care through recruiting the available therapeutic resources.¹⁶

Conclusion

In conclusion, BS is a genetic disease characterized mainly by hypokalaemia. Correcting hypokalaemia in neonates with BS is challenging since IV cannulation is extremely difficult because of compromised body size and weight. Therefore,

shifting the route of administration from IV to oral provides a prompt and essential solution for severe hypokalaemia, hence efficiently managing BS patients.

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Author contributions

S.A. conducted patient supervision and drug administration. Y.A.S. and H.S.A. provided drug opinion and calculations. S.A. and Y.A.S. wrote the manuscript.

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Ethics approval

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Informed consent

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